Research article ISSN 2639-9512

Stem Cell & Regenerative Medicine

DCS -Il2 Necessary for Glucocorticoids Which Necessary for Interferons Synthesis and Serotonin Synthesis Then Promote Ang2-At2 and VEGF-A for Anti-Inflammatory Growth

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Received: 20 Nov 2022; **Accepted:** 19 Dec 2022; **Published:** 30 Dec 2022

Citation: Marzouk El Tantawi. DCS -Il2 Necessary for Glucocorticoids Which Necessary for Interferons Synthesis and Serotonin Synthesis Then Promote Ang2-At2 and VEGF-A for Anti-Inflammatory Growth. Stem Cells Regen Med. 2022; 6(1): 1-27.

Porpoise of study

Understanding the Diffuse large B-cell lymphoma (DLBCL), bone cancer, brain cancer, Psoriatic arthritis (PsA), and Bladder Cancer Diseases. Where glucocorticoids and Estrogen are necessary for regulating self-renewal in cancer stem cell population in B-lineage acute lymphoblastic leukemia mediated by Ang2-AT2 synthesis upon ACE functions followed by VEGF-A productions necessary for anti-inflammatory growth including Increasing in circulating memory B cells.

Highlight

_IL2 is the basic regulator for both GCs-gamma and IFN-gamma regulated firstly by pro-inflammatory cytokines which produced by pyrimidine kinases and ATPase effect on primary pro-inflammatory molecules which produced upon Cox2 functions on inflammatory sources, then will be subject to synthase for IFN-beta productions necessary for anti-inflammatory processes. The mutation in thymine kinase production (may due to mutation in both S6K and in ATPase, or due to deficiency in thymine nucleotides) will induce mutated cytokines kinases production (may due to inhibition in synthetase functions) can induce mutated B-estradiol that can cause mutations in IL2 productions by DCs that will cause inhibition or mutation in estrogen followed by mutations in both glucocorticoid-beta and IFN-beta productions that will be the result of causing the Diffuse large B-cell lymphoma (DLBCL), where the mutation in IL2 can induce IL30 and IL40 productions which characterized autoimmune disorders.

_ PLCs synthesis promoted by Src kinase, Syk, and by adopter protein which promoted by B-arrestins regulation (that regulated by GCs synthesis and Estrogen), that also PLCs synthesis are Regulated by GCs functions where both are having a critical roles in Thromboxane-A synthesis. That deficiency in PLCγ2 synthesis can lead to Bone cancer, osteoporosis, and arthritis.

_ The activation of glucocorticoids are the basis for increasing glutamine upon suppression of immune activities for production of cytokines, macrophages, phagocytic, and neutrophil to kill the bacteria through activating Interferons productions.

_ Pro-inflammatory cytokines accumulation due to inhibition in glutamine followed by inhibition in Proline (which is imp for amino acids synthesis) then followed by inhibition in hydrophobic acids synthesis, then followed by inhibition or deficiency in OPA1 enzymes then followed by inhibition in IL2 which produced upon synthetase on cytokines kinases (on pro-inflammatory cytokines) followed by accumulation in pro-inflammation and decreasing in glucocorticoids synthesis and in PLCγ2 production.

_The activation of GCs-beta synthesis will decrease IL-12-induced STAT4 phosphorylation and IFN-gamma production then will enhances IFN-beta-induced STAT4 activation.

Abstract

Dendritic cells (DCs) play an important role in improving and adapting immune responses, and development of chronic inflammation through producing Interleukin-2 which stimulate beta oxidation processes by OPA1 synthase for promoting both IFN-beta and GC-beta production followed by alpha oxidations for TLR4 and SIRPα1 production and for nucleocytosolic acetyl-CoA alpha production which considered as signature of a “growth specifically for anti-inflammatory growth. Glucocorticoids and glutamine are the basic tools for increasing immune efficiency (regulated by OPA1 enzymes) and the main for regulating the adopted Interferons, that the deficiency in glucocorticoids synthesis and glutamine will suppress immune activities and will lead to deficiency in Interferons productions followed by decreasing in macrophages and T-cells functions.

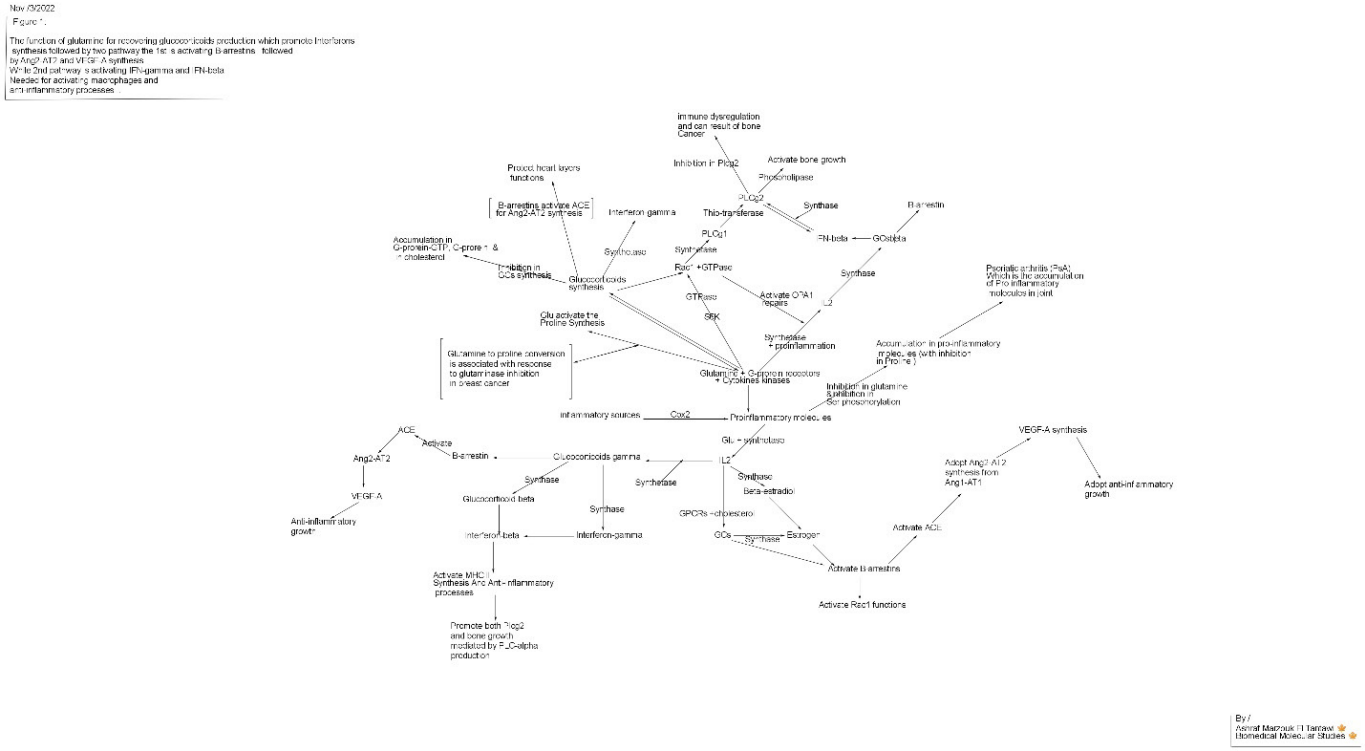

Figure 1

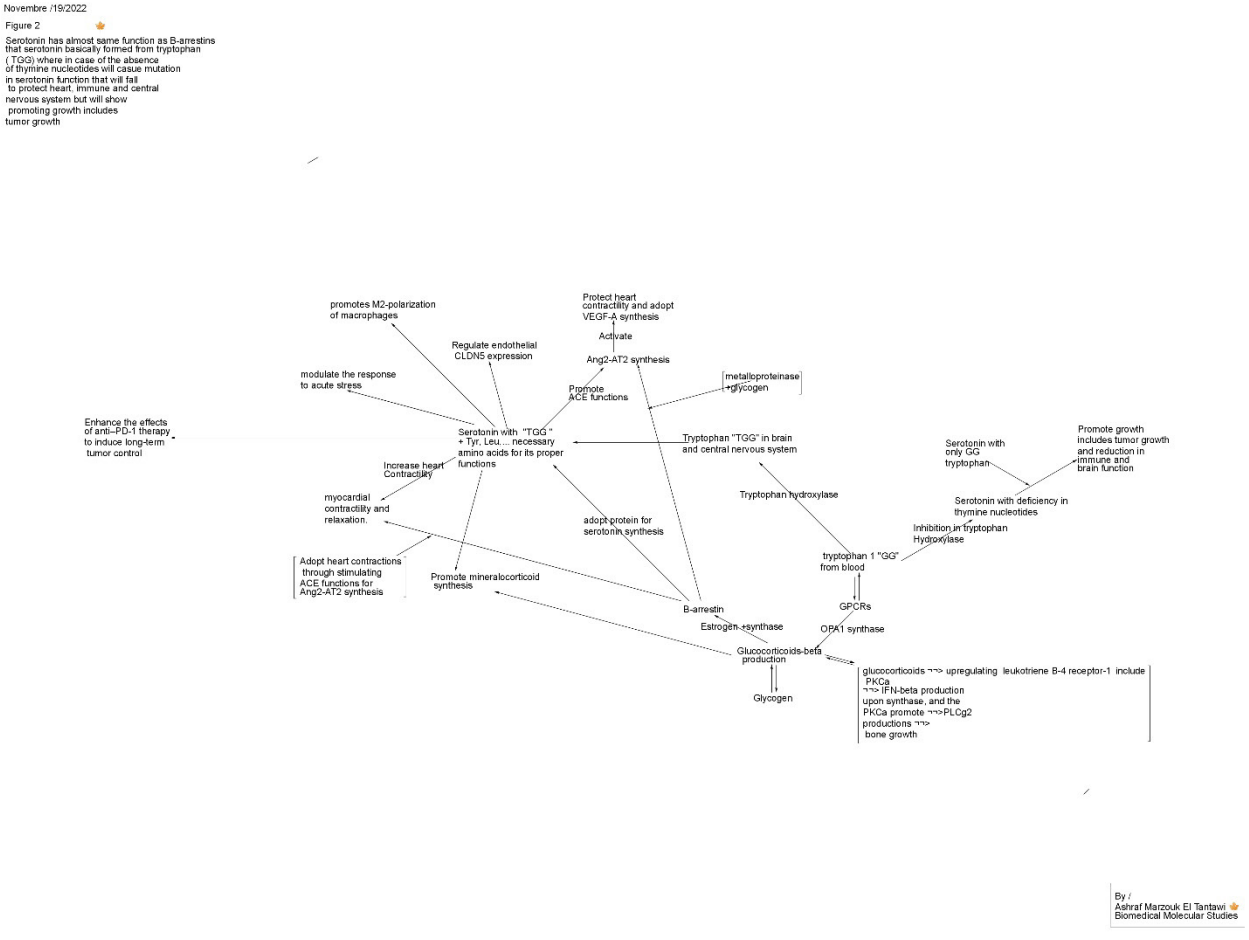

Figure 2

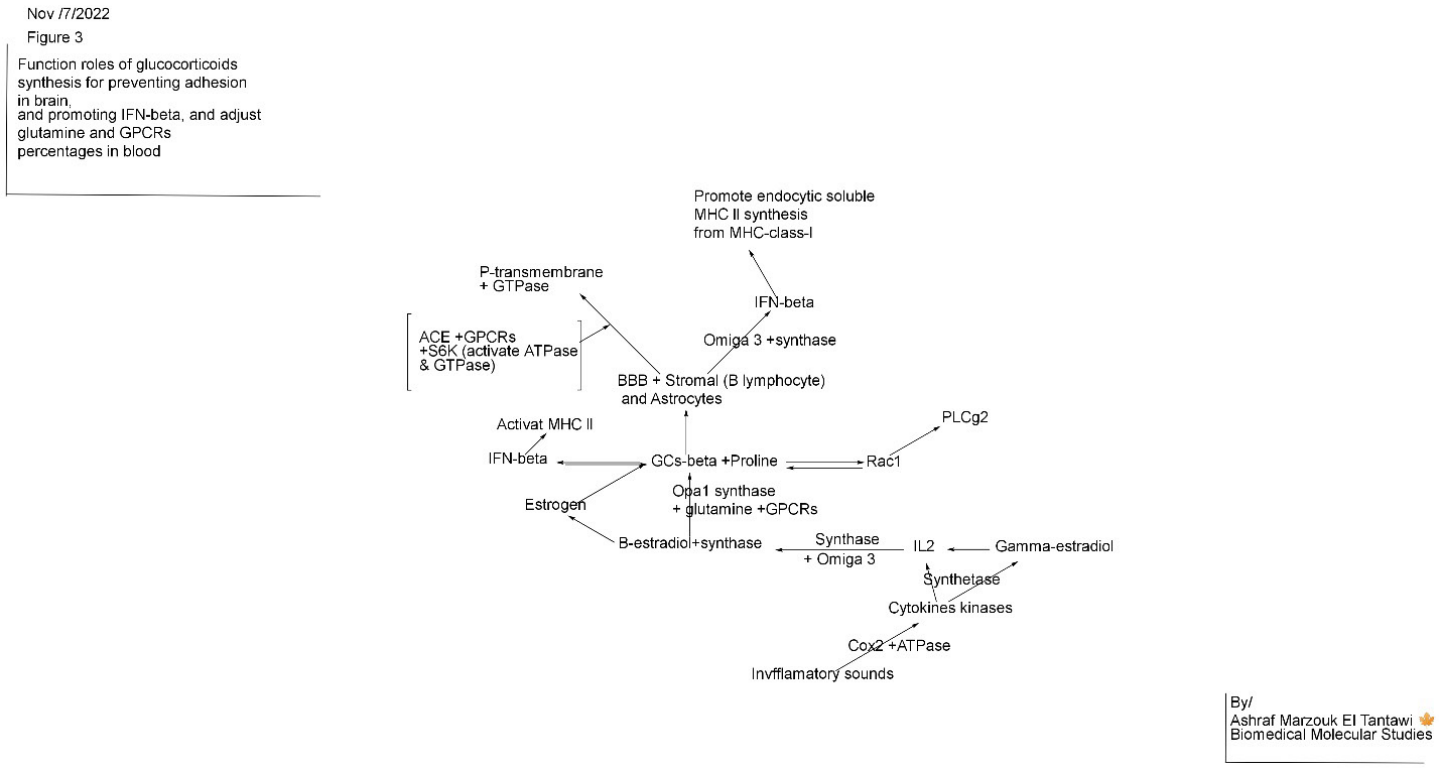

Figure 3

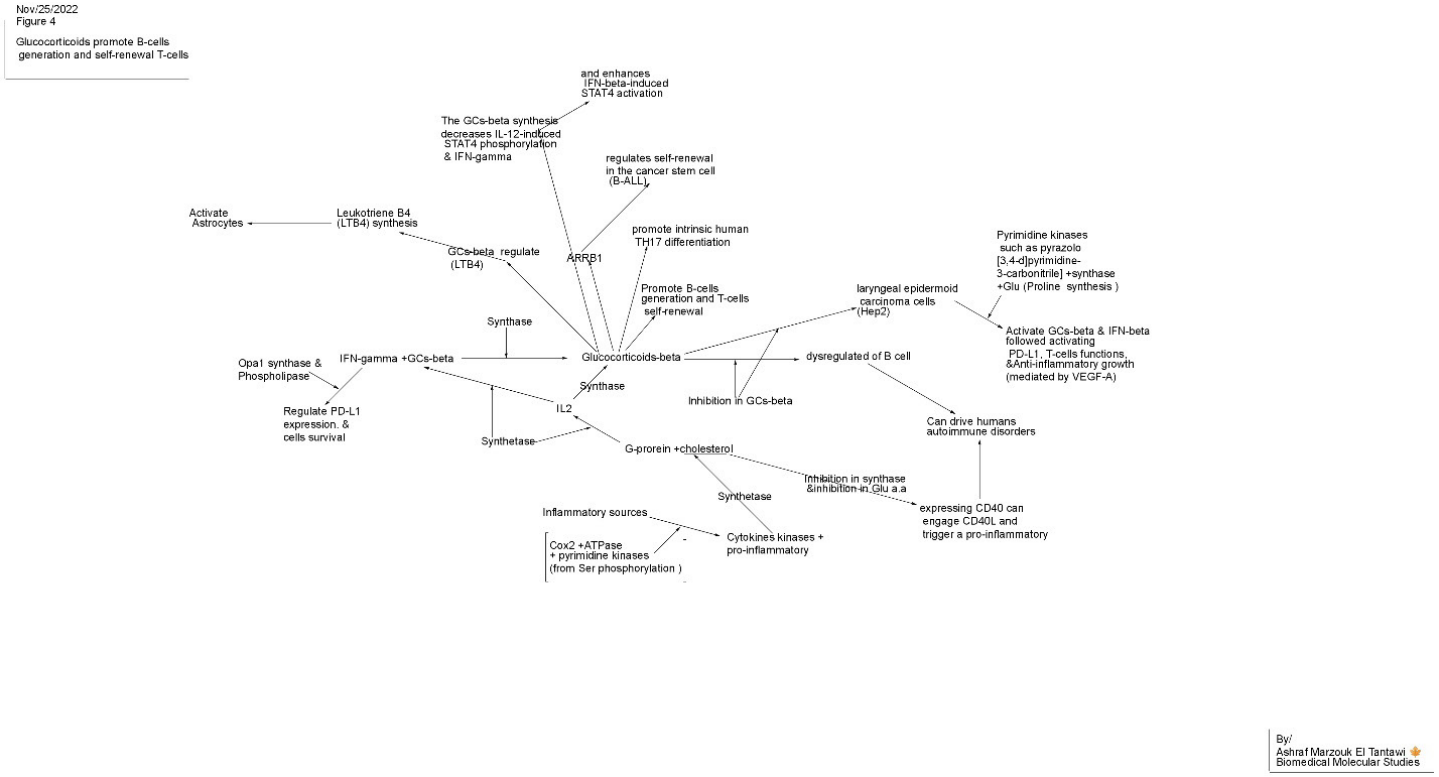

Figure 4

The formation of Glucocorticoid-gamma and IFN-gamma started by the effects of Cox2 on inflammatory sources followed by cytokine kinases production for IL2 synthesis upon synthetase functions followed by synthase for glucocorticoid-beta and IFN-beta productions which followed by phospholipase effect for producing PD-L1 synthesis which promote the progression of ovarian cancer. The effects of ATPase and Cox2 on inflammatory source will produce long fatty chains and degraded molecules which will be subject to the ATPase function for producing cytokines kinases which will be Subject to the influences of synthetase functions for producing Acyl-COA-gamma which are the basis for Interleukin-2 composition and production by DCs and vice versa.

The unsaturated fatty acids {arachidonic acid (AA)} are the effective necessary toole for accelerating GCs-beta and IFN-beta synthesis upon the activity of OPA1 membrane functions for accelerating the activities of DCs functions for producing Interleukin-2 (mediated by Leukotriene B4 production) which will be modified by synthase for activating GCs-beta followed by interferon-beta (IFN-beta) productions which accelerate anti-inflammatory processes and growth mediated by GCs-beta synthesis which accelerate both Ang2-AT2 and VEGF-A productions upon B-arrestins and ACE functions which adopt and filter glycoprotein and glycopeptides percentages for running angiotensin active pathway.

Arachidonic acid (AA) has strong roles in accelerating synthase function and beta oxidation, where Glucocorticoids-beta regulate Leukotriene B4 (LTB4) Productions that cooperate in anti-inflammatory processes through promoting IFN-beta synthesis followed by activating PLCγ2 for bone growth .

Deficiency in glucocorticoids synthesis (which depends on GPCRs and on cholesterol) will be result of accumulation of GPCRs and cholesterol (with increasing in fibroblast synthesis which depends on GPCRs synthesis) that have high affinity to bind to K and Na salts and cause toxicity in heart layers and will be result of decreasing in Interferons productions that will cause down regulation in anti-inflammatory processes.

The Diffuse large B-cell lymphoma (DLBCL) are characterized histologically by sheets of large transformed B, and show accumulation in PKC and can show as accumulation of their diagnostic levels because PKC have been mutated due to deficiency in thymine nucleotides (deficiency in Ser “TCT &TCA” codons with availability of only this codons Ser TCC which accelerate PKC productiond) , where thymine kinases (TK) and PKC together in their proper composition are necessary for building beta estradiol synthesis followed by proper building the IL2 productions then followed by proper synthesis of both GCs-beta and IFN-beta respectively followed by VEGF-A productions for anti-inflammatory growth. It's cleared that B-arrestins and serotonin are having almost same origin, almost same function, that may B-arrestins promote and regulate the serotonin productions , but serotonin basically originated from tryptophanTph1 (TGG) which originated and can be regulated by Ser (AGT) in blood where thymine bind with guanine are important for tryptophan synthesis *in vivo*) , that Tph2 responsible for serotonin synthesis in brain (the binding of thymine T with guanine “GG” is so necessary" to form proper serotonin molecule in brain upon tryptophan hydroxylase (Tph). function) , that serotonin can be boosted and enhancement by more necessary amino acids for Enhancement its functions such as tryptophan (TGG) , Leu “TTG“, Tyr, Gly, Ser “AGT”, and methionine “ATG“ for activating both Leu and Met-pentapeptides in enkephalin tissue in brain, .that as the thymine nucleotides missed in serotonin molecules (so missed in tryptophan TGG) as serotonin will show mutations in its structure and functions but will still promote growth through its purines kinases (GG) which can promote tumor growth with deficiency in enkephalin functions that can enhance brain cancer.

The deficiency in PLCs synthesis which regulated by Src kinase, Syk, and by adopter protein which regulated by B-arrestins (regulated by GCs synthesis and Estrogen), can lead to Bone cancer, osteoporosis, and arthritis. That both thymine kinases “TK” and cytosine “PKC” kinases are so important for estrogen synthesis mediated by estradiol beta production for activating GCs-beta which promote the programmed IFN-beta and for VEGF-A synthesis necessary for the progression of anti-inflammatory growth.

Materials

-Leukotriene B4 Receptors (LTB4)
- Dendritic cells (DCs)
- interleukin-2 (IL2) , IL8, IL23
-OPA1 synthetase, synthase, and phospholipase
-Estradiol beta, and Estrogen
-Glucocorticoids-beta
-Interferons-gamma and beta
-Rac1 and Plcγ2
-Proline, glutamine, tyrosine, and tryptophan
-tryptophan hydroxylase
-serotonin
- B-lineage acute lymphoblastic leukemia cells (B-ALL).
-OPA1 oxydative enzymes
-beta-estradiol & Estrogen
- Leukotriene B4 (LTB4
-nucleocytosolic acetyl-CoA alpha

Introduction

Interferons (IFNs) promoted firstly by cytokines kinases and DCs followed by glucocorticoids productions that IFN-gamma firstly produced upon synthetase functions followed by IFN-beta synthesis (upon synthase effect on IFN-gamma) then followed by IFN-alpha synthesis (upon phospholipase functions) that plays a necessary role in antitumor host immunity and in anti-inflammatory growth.

The Dysregulation of glucocorticoids and interferons have been implicated in cancer, autoimmune disorders, and pathogenesis of chronic viral infections. Fibroblast growth factor receptors (FGFRs) belong to a family of four transmembrane receptor

tyrosine kinases (FGFR1–4) that help regulate multiple irregular physiological processes. They are highly conserved, widely distributed receptors due to their roles in promoting ATPase function pathway which activate numerous physiological processes started by long fatty chains and inflammation productions which supposed to be followed by gamma then followed by beta oxidation for functioning inflammation molecules through synthetase and synthase oxidative functions respectively for producing gamma then beta active subunits which normally contains active promoter in their molecules which are built and regulated by pyrimidine kinases which produced from hydrophobic acids and from the hydrophobic domain in TAM active receptors kinases, where Ser phosphorylation in mTOR pathway and Proline functions promote hydrophobic amino acids synthesis regulated by synthetase followed by synthase oxidative function, where reactivating OPA1 will be done through S6K which promote both ATPase and GTPase which activate the OPA1 repair.

The FGFRS Are Activated and Promoted By Either of These Two Ways

1st by GPCRs followed by CTGF productions which can promote FGFRs productions (without GCs-beta followed by angiotensin adoptions), 2nd through angiogenesis pathway which can promote VEGF-A productions which can promote FGFR growth (but in adopted pathway), where VEGF-A synthesis pathway can inhibit irregular CTGF growth then promote adopted growth through B-arrestins functions followed by Ang2-AT2 synthesis and then followed by VEGF-A synthesis which activate anti-inflammatory growth.

That deficiency in glucocorticoids synthesis (which depends on and regulated by GPCRs and on cholesterol) will be result of accumulation of GPCRs and cholesterol that can bind to K and Na salts and cause toxicity in heart layers and will be result of decreasing in Interferons productions that will cause down regulation in anti-inflammatory processes. DCs activated firstly by Cox2 which produce long fatty chains followed by cytokines kinases production which stimulate the IL2, IL8, and IL15 production (upon OPA1 synthetase and synthase respectively) for promoting GCs beta and IFN-beta where both are cooperating together for running anti-inflammatory processes.

The effect of Interferons-beta on T cells also prevent adhesion of the blood–brain barrier. Astrocytes functions have a key role in regulating and protecting the activities and function of neurons, through their roles in neurotransmission, metabolite and electrolyte homeostasis, functioning inflammation through producing I GCs-beta, FN-beta (regulated by IFN-gamma synthesis), and synapse modulation.

The GCs-beta regulated by pyrimidine kinases and by cytokines kinases (CK) which activate DCs for producing IL2 upon synthetase functions which followed by synthase effect on IL2 for producing GCs-beta and IFN-beta respectively followed by activating angiotensin pathway for producing both Ang2-AT2 and VEGF-A for running B-cells maturations and anti-inflammatory growth. Where Diffuse large B-cell lymphoma (DLBCL) starts in white blood cells called lymphocytes due to decreasing or deficiency in thymine kinases which produced upon Ser phosphorylation pathway that thymine kinases are necessary to regulate PKC through Glucocorticoids-beta synthesis which regulated and promoted by GPCRs and Estrogen upon synthase function.

Methods and Results

Dendritic cells (DCs) play an important role in improving and adapting immune responses, and in the development the chronic inflammation through producing Interleukin-2 which stimulate beta oxidation regulated by OPA1 synthase for promoting both GC-beta and IFN-beta productions followed by alpha oxidations for TLR4 and SIRPα1 production and for nucleocytosolic acetyl-CoA alpha production which considered as signature of a "growth specifically anti-inflammatory growth. Dendritic cells (DCs) are antigen presenting cells that release cytokines and considered as the central for the activation and innate the acquired immune responses [1].

The cytokines kinases activate DCs function through stimulating IL2, IL8, and IL15 production (by OPA1 synthetase and synthase function respectively) for promoting TLR4 functions (that mediated by GCs followed by IFNs synthesis for activating MHC-class-I and MHC-class-2 functions respectively), that also proliferation can be activated by either irregular un adopted CTGF functions or by the adopted and programmed VEGF-A productions by GCs and by Ang2-AT2 productions. That, DCs have important roles in maintenance immunological homeostasis, and the development of promising DC-based therapeutic strategies will give more effective and safer prevention and treatment for an increasing number of autoimmune disorders [2].

As Dendritic cells "DCs" improve immune to be more safer and protected from auto immune as DCs is adopted by an specific adopter sequenced orders based on ribosomes and chromosomes functions which promoted by pyrimidine kinases synthesis and by Acyl-COA-beta production upon Beta-Oxidation based on hydrophobic effective domains MerTK synthesis which can convert inflammations molecules (which produced firstly by the Cox2 and by ATPase effects on inflammatory sources) to Interleukin-2 upon synthetase on inflammation to produce Acyl-COA-gamma which promote interleukin-2 production and then followed by active beta subunits productions upon synthase function which activate T-cells function mediated by GCs-beta and IFN-beta synthesis. That DCs protroduce Interleukin-2 "IL-2" that coregulated the expression of IL-15 upon immune cells stimulei, that the IL-2 production is regulated DCs resulted in a migratory profile and T cell stimulation capacity [3].

DCs are activated firstly by Cox2 which produce long fatty chains followed by cytokines kinases production which stimulate the IL2, IL8, and IL15 production (upon OPA1 synthetase followed by synthase respectively) for promoting GCs beta and IFN-beta where both are cooperating together for running anti-inflammatory

processes in cooperated different pathways for the final result of running anti-inflammatory growth (which mediated by activating MHC-class-I and MHC-class-2 functions respectively) which also can be activated by either CTGF or by the VEGF-A productions necessary pathway. The IL2 synthesis is regulated by Acyl-COA-gamma synthesis upon synthetase functions for digesting lipid followed by synthase function necessary for beta oxidation for activating GCs-beta and IFN-beta followed by adopting anti-inflammatory processes. That Intracellular acetyl CoA levels enhanced histone acetylation, lipid synthesis, and IFNγ production for improving the metabolic and functional fitness of CD8+ T cells in tumors [4].

The Role of IFNS in Activating T-Cells and Angiogenesis Active Pathways by Promoting Anti-Inflammatory Growth

Several studies suggesting that IFN-gamma in response to various stimuli of, which led to the idea of autocrine myeloid-cell activation in innate immunity. Mechanistically IFN-γ binds to its receptor and then activates JAK2 (regulated by synthetase) to phosphorylate STAT1, and then followed by IFN-beta productions. That, SIRP-gamma (promoted by IFN-gamma) productions from myeloid is the first SIRP molecular structure that produced and then promote MHC-I synthesis regulated firstly by IFN-gamma for endocytic soluble MHC class II synthesis then for SIRPα1 and for TLR4 Biosynthesis [5].

The IFN-beta produced by nuclear orphan pathway upon synthase function which are so important for T-cells re-functions. That ROR beta synthesis are main basic roots for both GC-beta and IFN-beta productions which consequently are the basis for the SIRPα1 synthesis followed by TLR4 synthesis and anti-inflammatory growth. That, the effect of Interferons-beta on T cells also prevent adhesion of the blood–brain barrier, and also facilitates the induction of regulatory T cells [6].

The Endothelial cells "ECs" in brain capillaries are the site of the blood—brain barrier productions (where G-protein activate GPCRs which necessary for glucocorticoids synthesis regulated by estrogen too) that indicated the ECs are the site of filtering blood through their ACE functions which placed on their surface for producing BBB and Ang2-AT2 (the Ang2-AT2 synthesis from the excess of Ang1-AT1 where the remain of Ang1-AT1 is appear in the form of BBB) for running brain function and protecting heart activities through the production of active signals necessary for producing the adopted VEGF-A necessary for anti-inflammatory growth for brain, for heart layers functions, and for central nerve cells. The T-cells and macrophages depends mainly on pyrimidine kinases and on hydrophobic domain in the TAM three domains functions.

The dysfunction in endothelial ACE will lead to dysfunction in angiotensin pathway that will lead to increasing in Ang1-AT1 and BBB with increasing in adhesion chsracter and will the dysfunction in ACE will promote the accumulation of glycoprotein and long fatty fatty chains. P-glycoproteins are transmembranous ATP-dependent pumps, originally discovered for their ability to confer multi drug resistance to neoplastic cells [7].

The activation of P-glycoproteins which are transmembranous ATP-dependent and cytokines kinases that can activate ATPase function to break tumors contents for producing long fatty chains which will be improved to both Acyl-COA-gamma and the Acyl-COA-beta upon synthetase and synthase respectively, where polyunsaturated fatty acids accelerate beta oxidation for both GCs-beta and IFN-beta productions (including Omiga 3) which are necessary for activating T-cells and anti-inflammatory growth.

IFN-beta has the direct roles to regulate and adopt T-cells functions (that allow T-cells to pass through brain endothelial cells capillaries that prevent blood barrier adhesion) that IFN-beta activate MHC-class-I productions followed by MHC class II Biosynthesis mediated by angiotensin Biosynthesis pathway. Where it has been reported that: the Interferon-β promotes the survival and function of induced regulatory T cells [8].

The role of IFN-gamma and IFN-beta in suppressing Diffuse large B-cell lymphoma, or DLBCL

Diffuse large B-cell lymphoma, or DLBCL starts in white blood cells called lymphocytes. B lymphocytes is a population of cells that express clonally diverse cell surface immunoglobulin (Ig) receptors recognizing specific antigenic epitopes. That GCs were identified as the main site for high-affinity antibody-secreting plasma cell and memory B-cell generation [9].

The previous study indicate that GCs regulated by pyrimidine kinases and by cytokines kinases (CK) which activate DCs for producing IL2 upon synthetase functions which followed by synthase effect on IL2 for producing GCs-beta and IFN-beta which followed by activating angiotensin process for producing both Ang2-AT2 and VEGF-A for running B-cells maturations and anti-inflammatory growth. That any mutation in Interleukins productions will reflect mutations in the GCs-beta followed by mutations in B-cells production where the mutation in GCs-beta can appear in the B-cell surface membranes which promote CD40 productions and will give the autoimmune disorders Symptoms. Where the dysregulated B cell signalling can drive many of human autoimmune diseases [10].

In autoimmune disorders the Non-hematopoietic cells expressing CD40 can also engage CD40L and trigger a pro-inflammatory response [11]. And, IL-2 induces expression and secretion of IFN-gamma in murine peritoneal macrophages [12]. And, the stimulation with IL-2 will induce IFN gamma in a time and in a dose-dependent manner [13].

IL-2 regulate the expression of IFN-gamma mediated by GCs synthesis and followed by angiotensin activation and T-cells activation. Also, Ser /Thr kinases (Stk24) plays an important role in controlling IL-17-triggered inflammation and autoimmune diseases through producing (pyrimidine kinases cytokines kinases) and provides new insight into the therapeutic targets of IL-17-mediated inflammatory disease [14].

That Ser (TCT, TCC, TCA, TCG) produce mostly thymine kinases and cytosine kinases upon ATPase function while Thr

(ACT, ACC, ACA, ACT) kinases produce mostly purine kinases that promote ATPase function through S6K synthesis, where the inhibition in one of those kinases will cause mutation in GCs-beta which has the roles of regulating B-cells activity and has the roles of antibody-secreting plasma cell and memory B-cell generations. But, the accumulations of PKC is due to the deficiency or inhibition in thymine kinases followed by inhibition or mutation in cytokines kinases will be result in mutation in IL2 that can be accumulated and can be improved to IL30 and IL40 *in vivo* that can be the result of pathogenic diseases such as autoimmune disorders disease.

The IL2 is the basic regulator for both GCs-gamma and IFN-gamma regulated firstly by pro-inflammatory cytokines which produced by pyrimidine kinases and ATPase effect on primary pro-inflammatory molecules which produced upon Cox2 functions on inflammatory sources, then IL2 will be subjected to synthase function for producing GCs-gamma followed by synthase function for glucocorticoid-beta synthesis and IFN-beta productions.

Inhibition in pro-inflammation cytokines due to inhibition or deficiency in one of pyrimidine kinases: thymine kinase (TK) or PKC (CK) will be result in accumulation in IL2 that will be improved due to their accumulation for producing IL40 which will form mutated B-cells and their activities will be characterized by producing pro-inflammatory molecules.

The Interleukin-2 which produced by Cox2 effects on inflammatory sources followed by the effect of pyrimidine kinases and synthetase functions for IL2 productions which are necessary for glucocorticoids beta synthesis and IFN-beta productions (upon synthase function) for running anti-inflammatory processes (mediated by activating MHC ll) during viral infections. That it has been reported that: Endogenous IL-2 contributes to T cell expansion and IFN-gamma production during lymphocytic choriomeningitis virus infection [15]. Where, the Growth and maturation of other cell types and leukocyte migration are mediated by proper IFN-γ production. And, IFN-γ activates macrophages that promote them to be able to mount an effective immune response, such as enhance antigen processing and presentation through upregulation of class II MHC, [16]. And, the effects of IFN-γ as anti-tumor comprise the development, recruitment, and activation of innate immune cells as well as the activation and maintenance of the effector T cells [17] that have proper roles to suppress cancer tumors. As I mentioned previously IFN-gamma upon synthase function will activate IFN-beta productions followed by activating T-cells proper functions through activating MHC class II from MHC class I and then followed by CTLA-4 reactivation mediated by SIRPα1 and PD-L1 synthesis which are necessary for living cells survival.

Diffuse large B-cell lymphoma (DLBCL) is characterized by sheets of large transformed B cells that efface the normal lymph node architecture 1. However tumor samples contain variety proportions of admixed benign cells with defect in their phospholipids membranes that include various subsets of T cells, macrophages, mast cells and stromal cells and collectively define the microenvironment of tissue tumor.

What the role of pyrimidine kinases thymine kinases and PKC (cytosine kinases) in that kind of tumor growth? PKC-beta II expression has prognostic significance not only for CHOP therapy in low-risk IPI disease, [18]. Previous studies reported that overexpressed. PKC delta promoted apoptosis. However, recently data showed inhibition of PKC delta blocked proliferation and survival of cancer stem cells [19].

That in case of Deficiency in pyrimidine TAT AT kinases which responsible for building promoter within IFN-gamma and beta molecules will cause dysregulation to IFNs and GCs functions and will be result of increasing the tumors growth in spite of availability of PKC with absence of thymine kinases (TAT kinases).

That, deficiency in Ser amino acids and deficiency in proline will Lead to decreasing in pyrimidine synthesis (TAT and TAC) [20]. And, pyrimidine TAT and TAC kinases synthesis are having the responsibility for building promoters within active beta subunits. That Glucocorticoid-beta and mineralocorticoids are basically regulated by tyrosine TAT and TAC kinases (Pyrimidine kinases) for protecting heart [21]. Where also it's necessary to note that the percentage of pyrimidine kinases TATAT related to PkC (TATAC or TAC) has to be equal for proper activated functions for all IFNs molecules.

PKC and Src family are regulated by pyrimidine kinases which are thymine kinases and cytosine kinases or just cytosine kinase (note, both kinases are produced from the Ser phosphorylation in mTOR pathway) where thymine kinases necessary for building thymine within the IFN-gamma and beta promoters, but cytosine kinases "TAC" necessary for building active sequence within promoters sequence which necessary for regulating the migrating IFN-gamma and IFN-beta molecules through involvement in anti-inflammatory processes, that deficiency in cytosine kinases synthesis will be result of defect in migrating molecules with un movement of their configuration , which leads to their stability and accumulation within defective cells and the formation of a tumor contents. Also, the mutation in PKC molecules with inhibition in thymine kinases will effect on GCs-beta synthesis and by decreasing in their functions that lead to Diffuse large B-cell lymphoma (DLBCL) due to over availability of the mutated PKC delta.

Where it has been reported that Pyrazolo [3,4-d]pyrimidine-3-carbonitrile and pyrazolo [3,4-b] pyridine-3-carbonitrile derivatives was synthesized and Have been evaluated for their potential cytotoxicity against human laryngeal epidermoid carcinoma cells (Hep2) [22]. That, pyrazolo [3,4-d] pyrimidine-3-carbonitrile will perform and plays the role of thymine and repair the deficiency of thymine in the IFN-gamma and in IFN-beta molecules that can suppress cytotoxicity and tumors contents and promote the modulation of main original cells. So my conclusion is : DLBCL tumors due to deficiency in thymine kinases (TAT) which necessary for building promoters TATATC within PKC and within both IFN-beta and GCs-beta to guide and direct their migration and functions for running both anti-inflammatory processes and growth mediated by IFN-beta synthesis followed

by activating two pathways first activating both T-cells and beta-cells while second pathway is activating both B-arrestins and ACE functions fir activating Ang2-AT2 followed by VEGF-A synthesis which necessary for activating anti-inflammatory.

The IL2 is considered as the basic regulator for GCs-gamma and IFN-gamma regulated by pro-inflammatory cytokines (and adopted by both pyrimidine TAT and TAC kinases) which produced by pyrimidine kinases and ATPase effect on primary pro-inflammatory molecules which produced upon Cox2 functions on inflammatory sources, then will be subject to synthase for IFN-beta productions necessary for anti-inflammatory processes.

It has been indicated that the necessity of IFN-gamma and intertukins (Interleukin-2) synthesis which produced by JAK signaling for cells survivals through producing PD-L1 instead of accumulation of PD1. That, interferon-gamma-JAK1/JAK2-STAT1/STAT2/STAT3-IRF1 axis primarily regulates PD-L1 expression [23]. Actually JAK1/JAK2-STAT1/STAT2/STAT3-IRF1axis stimulate and promote firstly DCs function to activate IFN-Gamma synthesis (upon synthetase functions) which will activate IFN-beta (upon synthase function) followed by MHC class ll production within cells followed by SIRPα1 and TLR4 synthesis (upon phospholipase functions) necessary for for anti-inflammatory growth.

Where PD-1 will stimulate IFN-gamma and promote MHC class l synthesis (promoted and regulated by proper OPA1 and by pyrimidine kinases) followed by MHC II synthesis and then followed by activating PD-L1, SIRPα1, and TLR4 Synthesis (upon phospholioase functions) "respectively" necessary for anti-inflammatory growth and cells survivals. That, it has been reported that: Interferon-α Up-Regulates the Expression of PD-L1 Molecules on Immune Cells through STAT3 and p38 Signaling [24]. So the roles of IFNs regulated firstly by Ser /Thr phosphorylation and by JAK signaling (for producing purines and pyrimidine kinases) are having wide functions in activating anti-inflammatory processes including anti-inflammatory growth, but we've to don't neglect that the roles of IFNs for running anti-inflammatory pathways are basically regulated by both thymine kinases and PKC (TAT and TAC kinases) which produced firstly by Ser phosphorylation in mTOR pathway for fully running and protecting the IFNs (gamma, beta, and alpha respectively) proper functions for strengthen immune efficiency and central nerve cells functions that widely protect from autoimmune disorder diseases.

The IFN-alpha are produced upon the effect of Phospholipase on IFN-beta which are the main basic for promoting PD-L1 synthesis that followed by TLR4 functions and mediated by Ang2-AT2 synthesis and VEGF-A productions which necessary for anti-inflammatory growth , where in case of inhibition in OPA1 synthase and phospholipase functions will lead to accumulation of inflammatory molecules that have high affinity to bind to K salts which lead to toxicity in heart layers and in Central nerve cells that can be main reason for tumor cancer and can induce cells death with increasing in PD-1.

The Role of Astrocytes in Anti-Inflammatory Processes and Growth

Astrocytes regulated by pyrimidine kinases followed by glucocorticoid-beta and B-arrestins which involved in K+ ion homeostasis through protecting tissues from the k binding toxicity, and also regulate extracellular Ca2+. VGCCs, and promote the created signals needed for Vascoconstructions that can run connective cells functions in central nerve cells, where the decreasing in created signals by beta oxidation can lead to isolation to specific cells and accumulation of long fatty chains and cholesterol that can lead to toxicity if bind to K and Na salts and can lead to tumor cancer.

Astrocytes not only regulate blood flow through adopting fibrinolysis, but also transfer mitochondria to neurons, and supply the fuel for neuronal metabolism. That, astrocytes can phagocytose synapses, alter neurotrophin secretion, and clear debris [25]. Also it has been reported that astrocyte dysfunction involved in the pathophysiology of neurological disorders, including neurodegenerative disease, stroke, epilepsy, migraine, and neuroinflammatory diseases [26]. That astrocytes functions confirm not only to activate and protect immune cells and heart function but also have a key role in regulating and protecting the activities and function of neurons, through their roles in neurotransmission, metabolite and electrolyte homeostasis, functioning inflammation through producing IFN-beta and GCs-beta, and synapse modulation. That astrocytes can alter neurotrophin secretion through its function in adopting and modulating both Ang2-AT2 and VEGF-A (the vascular permeability factor) productions. That, astrocytes have angiotensin-converting enzyme 1, that convert angiotensin I (Ang1-AT1) to angiotensin II (Ang2-AT2), and act on the type 1 angiotensin receptor (AT1) expressed by(or can be represented) BBB to induce vasoconstriction through ACE functions and Ang2-AT2 Biosynthesis.

VEGF Biosynthesis also known as a vascular permeability factor in which is a multifunctional active protein structure that is involved in angiogenesis, inflammation, cancer [27], Astrocytes functions to facilitate and accelerate the proliferation and neural differentiation of BMSCs, through changing and improve inflammatory molecules for producing Beta-subunit upon synthase function which activate astrocytes at different phase after CNS injuries. That it has been reported that astrocyte-derived IL-6 participates in the proliferation and neural differentiation of BMSCs [28]. Actually the IL2 and IL6 are derived from DCs not from astrocytes that stimulate beta-Oxidation by OPA1 synthase for Beta-subunits (GCs-beta and IFN-beta synthesis). Which activate astrocytes for adopting Ang2-AT2 synthesis from the glycoprotein Ang1-AT1 which therefore activate VEGF-A productions which promote anti-inflammatory growth in one just outline pathway but in clear pathway which upon phospholipase effects will activate MHC class ll synthesis from MHC class l followed by SIRPα1 and TLR4 productive which promote and adopt the anti-inflammatory growth, so basically DCs has the basics roles in modulating and stimulating the IFN-beta and glucocorticoid-beta productions needed for B-arrestins synthesis which activate astrocytes for Ang2-AT2 followed by

VEGF-A productions which promote anti-inflammatory growth in several direct and indirect pathways. That, the delaying in synthase function for Beta-subunit synthesis will lead to more improvement in IL2 and IL6 to IL30 or other that can be harmful for immune functions and can be the main source for causing tumor cancer. That, certain scenarios create disparity of IL-6 production that are detrimental to the cellular immune response [29].

DCs are producing IL2 upon viral stimulation which upon synthetase and BTK that will be improved to IL6 then to IL23 which upon synthase will improve the Beta-subunit production (Acyl-COA-beta or GCs-beta and IFN-beta) {{imp notice as synthase functions will be delayed as the IL6 will implicate and improved to IL 30 and IL40 which characterized autoimmune disorders}}.

So in conclusion in this section

Both stromal and Astrocytes are regulated and activated by GCs-beta production followed by interferon beta productions , where the first activate angiotensin II synthesis (mediated by GCs-beta and B-arrestins) from the type 1 angiotensin receptor (Ang1 AT1) which expressed by BBB ECs to induce vasoconstriction, hile the IFN-beta activate T-cells and macrophages for improving anti-inflammatory processes. Where, Endothelial cells in brain capillaries are the site of the blood—brain barrier (BBB) that the Leu main amino acids are necessary for BBB which activated in the form of Leu-pentapeptides in enkephalin tissue that promote and improve the BBB functions in brain increasing Ang2-AT2 productions to prevent the adhesion and facilitate the T-cells and macrophages passing through for proper activities. P-glycoproteins are transmembranous, ATP-dependent, that BBB produced upon ACE functions for confer Ang2-AT2 synthesis in one side while the other is the Ang1-AT1 or BBB which protected and adopted by ACE functions. Where, MHC-I synthesis regulated are by IFN-gamma (which improved by astrocytes and stromal cells for producing IFN-beta which necessary for improving T-cells functions) for endocytic soluble MHC class II synthesis then for SIRPα1 and for TLR4 Biosynthesis which mediate anti-inflammatory growth. And both the astrocytes and stromal are regulating and promoting each other through the DCs stimulation to both of them (which improve inflammatory molecules for producing IL2 and IL6) through its IL2 production which improve to IL6 then to IL23 upon synthase function and pyrimidine kinases functions mediated by Acyl-COA-beta. That Beta-subunits Acyl-COA-beta will promote GCs followed by B-arrestins which will adopt Ang2-AT2 synthesis (upon ACE functions) promote the VEGF-A productions for improving anti-inflammatory growth and for T-cells production. That the delay in previous pathway will give the priority to IL2 and IL6 to be improved to IL 30 and IL40 (upon deficiency in synthase function) which are the sign of autoimmune diseases and the sign of some cancers diseases. So, development of immune by DCs function are followed by OPA1 synthase function which will prevent the increasing in the autoimmune disorders regulated by OPA1 synthase.

The improvements in DCs activities will lead to improve stromal and astrocytes functional activities for improving the anti-inflammatory growth by stromal and astrocytes mediated by B-arrestins and Ang2-AT2 synthesis followed by VEGF-A productions for anti-inflammatory growth.

The role of IFN-gamma and IFN-beta in suppressing cancer tumors

IFN-γ (regulated by beta-estradiol followed by IL2 productions) influences tumor cells directly and indirectly by promoting the IFN-beta productions for activating anti-inflammatory processes. The anti-tumor effects of IFN-γ comprise the development, recruitment, and activation of innate immune cells as well as the activation and maintenance of effector T cells [30] which their proper functions are to suppress cancer tumors. As I mentioned previously IFN-gamma upon synthase function will activate IFN-beta followed by activating T-cells proper functions through activating MHC class II from MHC class I and then followed by CTLA-4 ractivation.

Diffuse large B-cell lymphoma (DLBCL) is characterized histologically by sheets of large transformed B cells that efface the normal lymph node architecture 1. However tumor samples contain variety proportions of admixed benign cells with defect in their phospholipids membranes that include various subsets of T cells, macrophages, mast cells and stromal cells and collectively define the microenvironment of tissue tumor.

What the role of pyrimidine kinases thymine kinases and PKC (cytosine kinases) in that kind of tumor growth?. PKC-beta II expression has prognostic significance not only for CHOP therapy in low-risk IPI disease [31]. Other previous studies reported that overexpressed. PKC delta promoted apoptosis. However, recently data showed inhibition of PKC delta blocked proliferation and survival of cancer stem cells [32].

Firstly, it is right that the Protein kinase C-beta II (PKC-beta II) expression has been reported to indicate inferior prognosis in diffuse large B-cell lymphoma (DLBCL) but that in case of Deficiency in pyrimidine TAT kinases which responsible for building promoter which regulate all GCs-beta and IFN-gamma and beta molecules and regulate their migration, that it's necessary to report that the percentage of pyrimidine kinases TATAT related to PkC TATAC or TATATC has to be equal for running proper functions for anti-inflammatory functions.

PKC and Src family are regulated by pyrimidine kinases which are thymine kinases and cytosine kinases 1 (note, both kinases are produced from the Ser phosphorylation in mTOR pathway) where thymine kinases necessary for building TATAT promoters within and GC-beta and IFN-beta , but cytosine kinases "TAT TAC" necessary for building active sequence which necessary for regulating the migrating IFN-gamma and IFN-beta molecules through involvement in anti-inflammatory processes , that deficiency in cytosine kinases synthesis (through Thr phosphorylation in mTOR pathway) will be result of defect in migrating molecules with un movement of their configuration

, which leads to their stability and accumulation within defective cells and the formation of a tumor. Also, the mutation in PKC molecules with inhibition in thymine kinases will lead to diffuse large B-cell lymphoma (DLBCL) due to overexpressed the mutated PKC delta.

Where It Has Been Reported That

Pyrazolo [3,4-d] pyrimidine-3-carbonitrile and pyrazolo[3,4-b] pyridine-3-carbonitrile derivatives was synthesized and Have been evaluated for their potential cytotoxicity against human laryngeal epidermoid carcinoma cells (Hep2) [33]. That the pyridozolol plays so important role of replacing the deficiency in thymine kinase and rebuilds GCs and interferons to run anti-inflammatory processes, as indicated the importanty of pyrazolo pyrimidine for running anti-inflammatory processes. So: DLBCL tumors due to deficiency in thymine kinases which necessary for building promoters TATA within PKC and IFN-beta to guide and regulate the migration and movement of their molecules.

Interferon-β increases the stimulatory capacity of monocyte-derived dendritic cells to induce IL-13, IL-5 and IL-10 in autologous T-cells [34]. Where the decreasing or inhibition in glucocorticoid-beta followed by inhibition in interferon beta (can be due to inhibition in glu and Pro) can reflect accumulation of DCs products "IL2" that can be mutated due to their accumulation and can be improved to produce nearly IL30 or IL40 (due to several irregular reactions which will not be recognized by IL2 family) and identify some pathogenic cases such as cause cancer and autoimmune disorder diseases. Also I prefer to say in previous study that: Interferon-β increase the improvements capacity of monocyte-derived from dendritic cells to induce IL-5, IL-10, and IL-13, (synthase regulation) which can improve to IL23 which followed by phospholipase effects for VEGF-A productions (mediated by Ang2-AT2 synthesis) for anti-inflammatory growth and mediated by MHC class ll followed by SIRPα1 production and TLR4 production necessary for adopted anti-inflammatory growth "or proliferation". Where, in other pathway Interferon-β increases the improvements capacity of monocyte-derived from dendritic cells to induce IL-5, IL-10, and IL-13, to IL23 which promote MHC class ll synthesis from MHC class l then will activate PD-L1 from PD1 fo'owef by SIRPα1 production within cells and then followed by TLR4 production for anti-inflammatory growth and cells survival. That, IFN-beta *in vitro* can induce the development of DC2, which provide a permissive environment for Th2 differentiation [35]. And, IFN-α/β, among other "DCs" innate cytokines that is considered as an important 'third signal that shapes the effector and memory T-cell pool. Moreover, IFN-α/β also serves as a counter-regulator of T helper type 2 and type 17 responses [36]. So we can confirm that IFN-beta, GCs-beta, and nucleocytosolic CoA alpha are having strong roles in regulating and shaping the effector memory T-cells pool of functions and have the strong roles in the increasing and adopting the improvements capacity of monocyte-derived from dendritic cells to induce IL-5, IL-10, and IL-13, to IL23 which promote MHC class ll synthesis from MHC class l then will activate PD-L1 from PD1 followed by SIRPα1 production within cells and then followed by TLR4 production for anti-inflammatory growth and cells survival. Also, IFNγ (regulated firstly by Cox2 functions and by cytokines kinases followed by IL2 synthesis) is an important activator of macrophages and inducer of Class I major histocompatibility complex (MHC class l) molecule expression which upon IFN-beta synthesis will promote the MHC ll synthesis, which has the effective roles in adopting heart function and protect immune with central nerve cells from autoimmune disorders and from cancer diseases. Where, IFN-γ-induced expression of the MHC class Il transactivation (CIITA), a transcriptional coactivator essential for MHC-II expression, was inhibited in DN PKC-α-overexpressing cells [37].

Where the PKC-α-overexpression

Will start from first point to activate directly the DCs-IFNs-anti-inflammatory pathway "DIFAN" that will lead to affect on MHC ll to be attenuated in their function activities for a while till DIFAN be done from MHC ll activation. But over expression of IFN-gamma and synthetase enzyme will increase firstly MHC class l then will be followed by activating IFN-beta synthesis (upon synthase function) then followed by MHC class ll productions which will activate SIRPα1 and TLR4 productions which will promote anti-inflammatory growth respectively. Where, IFN-gamma and programmed death-1 (PD-1) expression are fully connected to and regulated by pyrimidines kinases in order to activate both MHC-class-I followed by MHC class II (upon synthase function) followed by PD-L1 production (upon synthase and phospholipase function respectively) then followed by SIRPα1, and TLR4 productions (upon phospholipase functions) which also mediated by Ang2-AT2 and VEGF-A productions too for adopting the previous MHC class I and MHC-II bio-functional Pathway and at the same time protect heart functions. That, It has been reported that the interferon-gamma-JAK1/JAK2-STAT1/STAT2/STAT3-IRF1 axis primarily regulates PD-L1 expression [38]. Actually JAK1/JAK2-STAT1/STAT2/STAT3-IRF1 axis stimulate and promote firstly the DCs function to activate IFN-Gamma synthesis and MHC class I synthesis (upon synthetase functions) which will activate IFN-beta (upon synthase function) followed by MHC class ll production within cells followed by SIRPα1 and TLR4 synthesis (upon phospholipase functions) necessary for anti-inflammatory growth.

Where PD-1 can (in availability of proper cellular activities) stimulate T-cells mediated by synthetase followed by synthase function for MHC II synthesis from MHC class l which followed by activating PD-L1, SIRPα1, and TLR4 synthesis upon phospholipase functions "respectively" for running anti-inflammatory growth. And it has been reported that: Interferon-α Up-Regulates the Expression of PD-L1 Molecules on Immune Cells through STAT3 and p38 Signaling [39]. So the IFNs synthesis are regulated firstly by Ser /Thr phosphorylation and by JAK signaling that are having wide functions for activating anti-inflammatory processes including anti-inflammatory growth, but we've to don't neglect that the roles of IFNs are basically regulated by thymine kinases which produced from Ser phosphorylation in mTOR pathway followed by cytosine kinases (protein kinases

C) for fully completing and protecting the IFNs proper synthesis and functions and protecting immune and central nerve cells from disorder diseases and from autoimmune diseases that will be discussed later.

The IFN-alpha are produced upon the effect of Phospholipase on IFN-beta followed by TLR4 functions and mediated by Ang2-AT2 synthesis and VEGF-A productions which necessary for anti-inflammatory growth (mainly regulated by Glucocorticoids-beta), where in case of inhibition in OPA1 synthase and phospholipase functions will lead to accumulation of inflammatory molecules (including cholesterol and G-protein) which have high affinity to bind to K salts which lead to toxicity in heart layers and in Central nerve cells that can be main reason for tumor cancer and can induce cells death due to increasing in PD-1 with inhibition in PD-L1 synthesis. Actually, the IFN-gamma synthesis started by the effects of Cox2 on inflammatory sources followed by cytokine kinases production for IL2 synthesis upon synthetase functions followed by synthase for glucocorticoid-beta and IFN-beta productions which followed by phospholipase effect for producing PD-L1 synthesis which promote the progression of ovarian cancers [40].

Glucocorticoids Are the Basis for Upregulating Leukotriene B-4 Receptor-1 for Interferons Expression and T-Cells Differentiation

Pro-inflammatory molecules produced upon Cox enzymes effects on inflammatory sources followed by ATPase and GTPase (regulated by S6K synthesis from Ser/Thr phosphorylation pathway) for producing pro-inflammatory cytokines which will be Subject to the influences of mitochondria OPA1 membrane functional effects for producing firstly IL2 (fatty Acyl-COA-gamma) upon synthetase functions followed by synthase effect for improving the IL2 for producing IL8, IL17 and IL23 (but not IL30 and not IL40 which are not recognized by IL2 family and they are the signs of autoimmune disorders that will discussed later) which will be improved for activating GCs-beta and FN-beta synthesis respectively then followed by phospholipase effects for Acyl-COA-alpha productions respectively for running the adopted proliferation and anti-inflammatory growth mediated by Ang2-AT2 and VEGF-A productions regulated by ACE functions. Where, the effects of ATPase and Cox2 on inflammatory source will produce long fatty chains and degraded molecules which will be subject to the influences of synthetase effects for producing Acyl-COA-gamma which will be the basis of Interleukin-2 production by DCs. That it has been reported that:

Interleukin-2 (IL-2) stimulates the induction of this gene expression and Met synthetase activity in G1 lymphoblasts, in part by an increase in the transcription rate of the gene [41]. So OPA1 synthetase effects mediate Interleukin-2 synthesis by Dendritic cells "DCs" function followed by synthase function for producing Acyl-COA-beta "IL8" and more in IL-beta family eg IL23 (but not IL30 and IL40 which are not recognized by IL2 and by IL23 family). But note the necessity of the availability of Methionine (ATG) in both GCs-beta and in IFN-beta are so required for reactivating Met-pentapeptides and Leu-pentapeptides in the brain enkephalin tissue for activating full brain function that deficiency in those two amino acids with deficiency in proline and Tyr can be the reason for enhancing brain cancer.

The Unsaturated fatty acids {arachidonic acid (AA)} are necessary for accelerate the activity of OPA1 functions for activating DCs functions for producing Interleukin-2 (mediated by Leukotriene B4 production) which will be modified by synthase for activating interferon-beta (IFN-beta) productions which accelerate anti-inflammatory processes and growth mediated by GCs-beta synthesis which accelerate both Ang2-AT2 and VEGF-A productions upon B-arrestins and ACE functions which adopt and filter glycoprotein and glycopeptides percentages for running angiotensin active pathway. That, arachidonic acid (AA)is a strong activator to OPA1 synthase enzymes (regulated by pyrimidine kinases) that accelerate the effects of OPA1 synthase on inflammatory molecules for producing Leukotriene B4 which can reactivate CDs for adopt the IL2 synthesis which upon synthase will be improved to Acyl-COA-beta synthesis (for IL8 ¬¬> IL23 synthesis) which will promote GCs-beta and IFN-beta synthesis respectively followed by promoting angiogenesis for both Ang2-AT2 and VEGF-A productions (mediated by B-arrestins synthesis and ACE functions), where VEGF-A are necessary for adopting anti-inflammatory growth and T-cells activation mediated by MHC ll productions and followed by SIRPα1, PD-L1 and TLR4 production for running the adopted proliferations through anti-inflammatory growth pathways. The Leukotriene B4 are produced from arachidonic acid (AA) augments interleukin-2 receptor-beta (IL-2R beta) expression. That, Leukotriene B4 (LTB4) is a potent lipid inflammatory mediator which induces IL-2 and interferon-gamma (IFN-gamma) production [42]. But, Glucocorticoids up-regulate leukotriene B-4 receptor-1 expression during neutrophilic differentiation of HL-60 cells [43]. So, glucocorticoids are the basic source for upregulating the leukotriene B-4 receptor-1 for the Interferon-gamma and IFN-beta expression productions. And in clear the glucocorticoid-bets synthesis are the main basis for adopting and regulating IFN-beta productions for ensuring the adoption of B-cell and T-cells functions. And, glucocorticoids-beta are the active regulator for leukotriene B-4 receptor for IFN-beta production upon synthase function for treating Kaposi's Sarcoma which is a type of cancer that forms in the lining of blood and lymph vessels. Where, Arachidonic Acid "AA" Derive Lipid Mediators Influence Kaposi's Sarcoma [44]. And also, AA can appear as anti-inflammatory effects due to its regulations to accelerate glucocorticoid-beta expression for accelerating both Interferons production and mineralocorticoid (which prevent cytotoxicity) for activating B-arrestins productions which activate ACE for Ang2-AT2 followed by VEGF-A synthesis which necessary for running anti-inflammatory growth. That it has been reported that: Arachidonic acid (AA) has potent anti-inflammatory actions and prevents the cytotoxic actions of alloxan and streptozotocin (STZ) against pancreatic β [45]. So AA has strong roles in accelerating the synthase function for GCs-beta synthesis mediated by the productions of IL2 (acyl-CoA gamma) which accelerate Leukotriene B4 (LTB4) Productions for promoting Interferon-beta that cooperate in the running anti-inflammatory processes, while at the same time GCs-beta activate T-cells differentiation and astrocytes functions through activating angiogenesis by producing Ang2-AT2 and VEGF-A which necessary for activating anti-inflammatory growth (regulated by B-arrestins synthesis which activate ACE).

Osteoarthritis "OA" is characterized by a sharp expression in Gamma-Phospholipase C-1 "PLCγ1", with decreasing "or inhibition" in PLCγ2 "PLC beta" productions (means inhibition in pyrimidine kinases followed by inhibition in synthase and followed by inhibition in both GCs-beta and IFN-beta respectively) which can reflect increasing in DCs activities without improving to their IL2 productions (where IL2 supposed to be subject to the influences of synthase effect for IL8… IL23 productions). It's important to note that the increasing and accumulation in inflammatory molecules including cholesterol in Osteoarthritis "OA" can be considered as due to deficiency or inhibition in glucocorticoids-beta synthesis where GCs synthesis depends on the cholesterol and GPCRs as a main activator for its synthesis regulated by OPA1 synthase function, that later in this study will be discussed clearly.

That glucocorticoids beta has strong role in recruitment of leucocytes to the inflammatory sites throughout regulating LTB4 (regulated by GCs-beta) and its receptors. That it has been reported that LTB4 and its receptors play a critical role in the recruitment of leucocytes to the inflammatory sites [46]. That in normal cases the CD14 Induces a Syk/PLCγ2-Dependent Endocytosis Pathway that Promotes the Internalization of TLR4 [47]. That cd14 productions mediated by Leukotriene B4 (LTB4) which regulated by GCs-beta for activating astrocytes (through activating angiotensin pathway for VEGF-A productions) and for activating PLCγ2 productions (mediated by synthase effect for IFNs-beta synthesis) for normal bone growth and for T-cells differentiation. And, PKC-alpha activation by arachidonic acid, involving a sequential model of activation in which an increase in intracytosolic Ca (2+) leads to the interaction of arachidonic acid with the Ca (2+)-binding région [48]. And, PKCα regulates ERα activity in osteoblast-like cells and inhibits Wnt/β-catenin signaling, [49]. So the role of GCs-beta are widely increased to activate estrogen receptors-a (ERα) in osteoblast-like cells (that estrogen necessary for B-arrestin synthesis by GCs-beta) through PKC-alpha activation by arachidonic acids (where GCs-beta activate arachidonic acids function. So, in brief the pyrimidine kinases adopt & promote¬¬> Glucocorticoids-beta ¬¬> upregulating leukotriene B-4 receptor-1 (include PKCa in its composition) ¬¬> IFN-beta production upon synthase, and the PKCa promote (through GCs-beta and IFN-beta) ¬¬>PLCγ2 productions ¬¬> bone growth. Where, deficiency in one of the two pyrimidine kinases will be result of mutation in estrogen followed by mutation and down regulation in GCs-beta and in leukotriene B-4 followed by mutated PLCγ2 and accumulation in mutated PLCγ1 that can improve to bone cancer. Also its important to note that Ser/Thr phosphorylation pathway are labeling the structure and the activités of Wnt/B-catenin pathway that inhibition in one of the two kinases produced from Ser/Thr phosphorylation will alter the Wnt/B-catenin cellular pathway to produce mutated pathogenic pathway. Where, Protein kinase D (PKD) is a member of the Ca (2+)/calmodulin-dependent kinase superfamily of serine/threonine kinases and has been described as the crossroads for the bone morphogenetic protein (BMP)-IGF-I signaling axis. That it has been reported that: PKD1 action contributes to the regulation of osteoblast genesis [50]. So protein kinases (both purines and pyrimidine kinases) contribute, and regulate DCs, GCs, IFNs, and PLCs functional pathways. Where it has been reported that: the activation of Protein Kinase A in Mature Osteoblasts Promotes a Major Bone Anabolic Response [51]. The activation of Protein Kinase A in Mature Osteoblast can be done through glucocorticoids-beta activities which regulate Leukotriene B4 Receptors (LTB4) expression that can activate PLCγ2 productions (Upton synthase and phospholipase functions) and promote bone growth. So in conclusion the pyrimidine kinases are firstly regulated by Ser phosphorylation pathway (while purines kinases produced by Thr phosphorylation through mTOR pathway) for producing the both types of pyrimidine kinases (thymine and cytosine kinases "PKC") which are so necessary for regulating glucocorticoids synthesis (which regulated and activated by G-protein and GPCRs) and regulating cellular activities including IFN-beta which necessary for running anti-inflammatory processes, where inhibition of one of those kinases will lead to inhibition or mutation in their own pathways that will be result of running mutated pathogenic pathway that can cause cancer, autoimmune disorders, and some other diseases.

Serine Phosphorylation Necessary for Pyrimidine Kinases Synthesis Which Promote Inflammatory Cytokines and Il2 Proper Synthesis

The estradiol gamma regulated by pyrimidine kinases (thymine and cytosine kinases) is the primary structure of IL2 and considered as the step of binding cytokines kinases with cholesterol for producing estrogen and IL2 upon synthetase functions in RORs pathway followed by synthase effect for producing estradiol-beta followed by estrogen production and ROR beta systems which responsible for reactivating GCs-beta and IFN-beta productions.

The mutation in cytokines kinases or inhibition in thymine kinases "TK" can induce mutated B-estradiol synthesis and can cause inhibition or mutation in estrogen followed by mutation in GCs-beta and in IFN-beta that can be results of availability of PKC without thymine in both GCs and in IFNs that will cause Diffuse large B-cell lymphoma (DLBCL) and can be associated with mutation in IL2 which can accumulated and can induce IL30 and IL40 which characterized autoimmune disorders.

The Diffuse large B-cell lymphoma (DLBCL) are characterized histologically by sheets of large transformed B, and show accumulation in PKC which can show as accumulation of their diagnostic levels because PKC have been mutated and lose their functions due to deficiency in TK (that pyrimidine necessary for regulating and protecting purines functions within genes molecules) where TK and PKC together in their proper composition are necessary for building beta estradiol molecules followed by proper building the IL2 then followed by proper producing both GCs-beta and IFN-beta followed by IFN-alpha synthesis and VEGF-A productions (which promoted by Ang2-AT2 productions by ACE functions) for anti-inflammatory growth.

It has been concluded and reported that: sex steroids modulate the production of B-lineage cells by influencing the differentiation, proliferation, and survival of early B-cell precursors [52]. And,

17β-Estradiol enhances the activation of IFN-α signaling in B cells [53]. And, in other study concluded that Receptors estrogen promotes B cell [54]. So, Ser/Thr phosphorylation pathway are labeling the structure and the activités of Wnt/B-catenin pathway through pyrimidine and purines kinases production which directly promotes the β estradiol productions which directly promote glucocorticoid-beta which influences B lymphocyte in stromal cell. That it has been reported that: 17-β estradiol directly influences B lymphocyte precursors in stromal cell [55]. Also, Estradiol (E2) treated mice express high-affinity, unmutated anti-DNA antibodies, indicating that naïve B cells that are normally deleted or anergized are rescued from tolerance induction [56]. And, it has been reported that Interferon-γ levels are upregulated by 17-β-estradiol and diethylstilbestrol [57]. Also, 17β-estradiol participates in the induction of influences interferon genes and pathways, that, further studies revealed that 17β-estradiol significantly increased the percentage of CD3+CD69+ and CD3+IFNγ+ T cells [58]. So, it is clear that pyrimidines kinases (thymine kinases "TK" and cytosine kinases "PKC") are the basic regulator for estrogen synthesis mediated by estradiol beta production for activating GCs-beta followed by IFN-beta synthesis then followed by both IFN-alpha and VEGF-A synthesis in the progression of anti-inflammatory growth.

Inhibition in thymine kinases reflect inhibition in synthase & in hydrophobic domain "MerTK domain" followed by inhibition in estradiol-beta, then can be followed by increasing and accumulation in estradiol-gamma have high affinity to bind with k and Na salts that can cause mutation in their molecules that can produce toxicity and mutation in their produced mRNA that can cause mutated tumor growth.

The accumulation of mutated estradiol gamma can produce mutated primary structure of IL2 which will lead to the IL30 and IL40 productions which characterized autoimmune disorder diseases and can be associated with accumulated cholesterol too which can lead to increasing in oxygen rich carbon molecules and in oligomycin that can promise high binding affinity and stability with k and Na salts for producing toxicity in the tissues. However, despite the importance of pyrimidine kinases (TK and CK) in estrogen synthesis and then in the formation of B-arrestins , the importance of estrogen is not limited to the formation of B-arrestins only, but also includes the activations of anti-inflammatory growth by activating interferon pathways started by GCs gamma and IFN-gamma synthesis followed by activating both GC-beta and IFN-beta synthesis and MHC class II which followed by activating SIRPα1 and TLR4 mediated by VEGF-A functions for activating anti-inflammatory growth. As estrogen synthesis (mediated by estradiol-beta or beta-estradiol) are the main regulations for GCs and for B-arrestins synthesis followed by VEGF-A productions for anti-inflammatory growth, as beta-estradiol are necessary for both GCs-beta and IFN beta productions (mediated by pyrimidine kinases synthesis) which necessary for the adopter B-arrestins synthesis which adopt VEGF-A production mediated by Ang2-AT2 functions for anti-inflammatory growth.

Beta-estradiol, estrogen, GCs, and IFNs Biosynthesis, (mediated by B-arrestins and VEGF-A synthesis) are so important for improving and adopting anti-inflammatory growth and protect heart function.

The inhibition in Beta-estradiol will cause reduction in heart layers activities due to reduction in GCs-beta and in mineralocorticoid synthesis that will reflect heart diseases including causing toxicity in heart layers.

The DCs roles are described as the axis of receiving signals in the form of oxidative enzymes functions such as Cox2 followed by phosphorylation effects by S6K and pyrimidine kinases (which produce by Ser phosphorylation) for cytokines kinases productions which stimulate DCs function for IL2 production (upon synthetase functions) followed by synthase oxidative function for Estrogen, and for both GCs-beta and IFN-beta synthesis which followed by activating angiogenesis functions for VEGF-A productions which mediated by Ang2-AT2 synthesis which promote anti-inflammatory growth .

ATPase (activated by S6K production through Ser/Thr phosphorylation) can produce large amounts of inflammatory chemokines that contribute to the recruitment of DC precursors in inflamed tissues [59].

The development of immune efficiency by improving DCs functions through improving pro-inflammatory molecules by OPA1 proper functions will lead to safer prevention from autoimmune disorders where DCs has strong roles for improvements glucocorticoid-beta and interferon-beta production respectivily upon synthase function followed by VEGF-A productions (which mediated by B-arrestins for stimulating the ACE for both Ang2-AT2 and VEGF-A synthesis. Where the most essential step for activating DCs function is the availability of glutamine which important for Proline synthesis and necessary for amino acids synthesis which will be involved in IL2 molecules production, where Glu and Pro systems regulated by Ser Thr phosphorylation and by synthetase functions (which has the function of pyrimidine synthesis).

Interleukin-2 produced by dendritic cells and has the roles of activating firstly B-estradiol followed by GCs-beta and IFN-beta synthesis then followed by Rac1 production (in other pathway) which promote Plcγ2 Synthesis which necessary for bone growth through activating anti-inflammatory growth mediated by PLC-alpha productions. The anti-inflammatory growth are mainly mediated by activating angiogenesis for producing Ang2-AT2 which firstly adopted by ACE functions (which stimulated by B-arrestins) which then followed by VEGF-A synthesis for adopting vascular functions and anti-inflammatory growth. Also, inhibition or mutation in the Interleukin-2 production by dendritic cells (which basically regulated by pyrimidine kinases) will reflect Inhibition or mutation in both glucocorticoid-beta and IFN-beta followed by reduction in PLCγ2 and in ca+ transport that will be the result of increasing in the CTGF activities instead of in VEGF-A activity (regulated by Ang2-AT2 productions) that will

be the result of running mutated tumor growth (instead of normal anti-inflammatory growth) and will be the result of the IL30 and IL40 which reflect running Pathogenic pathways *in vivo*. Some patients with osteoporosis and arthritis are having the risk of bone cancer in the joints due to inhibition or mutation in MerTK domain (due to reduction in pyrimidine kinases synthesis) associated with increasing in TYRO3 domain, that arthritis, osteoporosis, or injury associated with inhibition or mutation in angiotensin pathway with increasing in CTGF activities for irregular growth processes.

The deficiency in MerTK domestic with increasing in TYRO3 will inhibit or will decrease DCs function followed by decreasing in both GCs-beta and IFN-beta followed by decreasing in PLCγ2 activities with increasing and accumulation in mutated PLCγ1 production (that carry pro-inflammatory characters) which can lead to osteoporosis and arthritis and can lead to increasing in the risk of other tumor cancer such as leukemia. That it has been reported that: IL-2 contributed to an increased susceptibility to cancer [60], that as I mentioned mutation in IL2 due to deficiency in pyrimidine kinases with availability of purines can increase tumor growth through activating CTGF functions, But in proper IL2 protection by DCs, the powerful action of IL2 compound has the ability to induce a pro-inflammatory reaction and a tumor influx of lymphocytes together with an IFN-γ response and NK and/or T cell Responses [61]. So in brief , the inhibition in pyrimidine kinases can reflect mutation in IL2 and reflects inhibitiin MerTK productions and accumulation to GPCRs with accumulation to cholesterol too that can cause accumulation to the mutated IL2 which will be improved to other irregular mutated molecules such as IL30 or IL40 which characterized the autoimmune disorders diseases.

The Oxidations by Cox2 and by ATPase on inflammatory sources in order to create the largest amount of oxygen Rapture with analyzing inflammatory sources followed by producing both pyrimidine and purines kinases by Ser Thr phosphorylation pathway (and mediated by pyrimidine nucleotides synthesis upon synthetase functions) then followed by activating IL2 productions (where IL2 can be stimulated and activated by Acyl-COA-gamma productions which important for GCs-gamma and for IFN-gamma synthesis) followed by Acyl-COA-beta production upon synthase function which activate both glucocorticoid-beta and interferon-beta productions respectively. Where the accumulation in cholesterol with long fatty chains which produced due to reductions in OPA1 function and due to deficiency in some necessary amino acids such as Proline can be the result of the accumulation of cholesterol and the formation of IL2 mutation and can form more mutations such as IL30 and IL40 production. Also the GTPase (which has important roles in activating OPA1 repairs) has a necessary roles in activating DCs function and support IL2 synthesis through the role of GTPase in activating synthetase, synthase, and phospholipase functions that synthetase will promote the producing IL2 followed by beta subunits Acyl-COA-beta (IL23) production upon synthase function which promote glucocorticoid-beta and interferon-beta productions followed by Rac1 productions (in another pathways) PLCγ2 synthesis followed by PLC-alpha for bone growth.

The proper IFN-α/β synthesis has the direct and indirect effects in regulating the development of T-cell effector responses and its role in promoting T-cell memory IFN-α/β among other cytokines is considered an important 'third signal' that shapes the effector and memory T-cell pool [62]. And, pyrimidines kinases are so necessary roles for activating Rac1 functions, where, the p21-Activated kinase 1 (PAK1) (a member of serine-threonine kinases family) plays a role in the regulation of autophagy via direct or indirect mechanism [63]. And the T lymphocytes (that regulated by pyrimidine kinases) originate from haematopoietic stem cells within the bone marrow that activated by PLCγ2 synthesis. That PLCγ2 participates in TCR signal transduction and plays a role in T-cell selection [64]. So Rac1 which basically regulated by pyrimidine kinases (PAK1) has the regulation roles in promoting PLCγ2 Synthesis that hse an important role in participating in TCR signal transduction and in T-cell selection.

Lymphocyte is a type of white blood cell (leukocyte) in the immune system are firstly improved by Interleukin-2 production which improved by synthase enzymes functions for activating GCs-beta followed by IFN-beta productions respectively that improve "leucocytes" lemphocyte anti-inflammatory functions.

The DCs functions represent the interface between the universe of foreign and tissue-specific antigens and T lymphocytes that have the roles of function in the regulation of anti-inflammatory processes mediated by B-estradiol, GCs-beta, and IFN-beta synthesis respectively that mutation in IL2 productions will reflect running mutated GCs and IFNs that will effect on T lymphocyte synthesis for irregular composition and activities which will cause decreasing in anti-inflammatory processes. That Dendritic cells (DCs) are known to be for professional antigen-presenting cells (APC), as these cells are capable of presenting processed peptides from various antigens, initiating and modulating the adaptive immune response by activating both T and B lymphocytes.and mediated by glucocorticoids and interferons synthesis respectively followed by Ang2-AT2 and VEGF-A productions. That it has been reported that: TCR-γδ cells activated by the synthetic phosphoantigen bromohydrin Pyro phosphate (promoted by ATPase activities) induce the production of IL-12 by DC, an effect involving IFN-γ production [65]. That phospho-membrane which regulated by glucocorticoids productions (from GPCRs upon synthase function and mediated by B-estradiol synthesis which regulated by py kinases) are regulating T-cells through GCs-beta functions followed by IFN-beta productions and activating the angiotensin pathway for producing Ang2-AT2 and VEGF-A for promoting anti-inflammatory growth. And it has been reported that: DCs able to kill tumor cells have also been described in rat models [66]. So through previous pathway for producing GCs-beta and IFN-beta for activating both T-cells and B-cells the DCs can considered as the main tools for improving anti-inflammatory processes. That firstly DCs stimulated and promoted by Cox2 and ATPase oxidations which followed directly by synthetase functions for Interleukin-2 production which can analyze inflammatory tumor contents for producing glucocorticoid-beta and IFN-beta upon synthase function (mediated by IL8, IL23 productions)

followed by activating and MHC ll products then followed by SIRPα1 and TLR4 productions for anti-inflammatory growth mediated by VEGF-A productions. As PLCγ1 can form complex with NDRG1 for PLCγ2 synthesis upon synthase function which can activate IFN-beta and GCs-beta productions in where each can run own pathway for activating anti-inflammatory growth. That it has been reported that: NDRG1 can form a complex, that the inhibition of PLCγ1 dramatically suppressed VEGF-A-induced angiogenesis [67].

Mutation in cytokine kinases will be result of mutation in both estrogen and glucocorticoids and can be result of bone cancer (with decreasing in Thio-transferase). Both glucocorticoids and Rac1 are basically Regulated by, S6K, and by pyrimidine kinases (thymine kinases and cytosine kinases (PKC) production, where S6K synthesis with pyrimidine are involved in Rac1 synthesis, that Rac1 has the function of contributing the PLCs synthesis upon thiotransferase enzymes functions for rebuilding bones growth through activating anti-anti-inflammatory growth, where inhibition in one of previous kinases will effect on the followed cellular pathways that can lead to mutations followed by tumor growth and cancers. KPNA2 (which have the glutamatergic effect necessary for Proline synthesis from glutamate that prevents the accumulation of glutamate and protect the availability of Proline synthesis. That it has been reported that: PLCγ2 dysfunction is associated with a variety of diseases including cancer, and PLCγ2-associated antibody deficiency and immune dysregulation, in some cases with autoinflammation [68]. That as there are dysregulation in PLCγ2 associated with pro-inflammation as indicated there are dysregulation in estrogen and in GCs synthesis which can be the result of accumulation of cholesterol and in pro-inflammation, which need to be functioned by effort of synthase for Rac1 GCs, and IFNs synthesis. And, it has proven that to inhibit RANKL-mediated osteoclastogenesis via modulating PLCγ signaling pathways [69]. So the modulating PLCγ1 by activating Plcγ2 production by synthase effect via GCs-beta and IFN-beta proper expression will functioned RANKL-mediated osteoclastogenesis to be enrolled in PLCγ2 synthesis followed by anti-inflammatory growth which represented in bone growth. That the PLCs signaling can improved by Rac1 to activate firstly PLCγ1 followed by PLCγ2 productions (mediated by Thio-transferase enzyme function) then followed by PLC-alpha synthesis mediated by VEGF-A, where PLCs are so important signaling that can improve immune effectiveness and anti-inflammatory growth. Also, Ang2-AT2 synthesis (mediated by GCs-beta and B-arrestins synthesis "ARRB1") can activate PLCγ2, where GCs-beta are necessary for improving heart function and pulses (regulated by pyrimidine kinases synthesis) and necessary for improving VEGF-A productions which necessary for adopting anti-inflammatory growth for both heart and bones growth, and important for adopting mineralocorticoid synthesis and functions for get rid of Na and K salts and protect heart and all immune from hyper Molecular toxicity that can be the main reason for pathogenic cases. That, ARRB1 also regulates self-renewal in the cancer stem cell population in B-lineage acute lymphoblastic leukemia (B-ALL), which predominantly affects B cell. And many cancers are driven from CSCs and both ARRB1 and ARRB2 were shown to be crucial in regulating CSC self-renewal [70]. And some studies have attempted to identify the cell type/cellular compartment involved in β-arrestin-mediated inflammatory regulation [71]. While, GCs regulate B-arrestins synthesis and redricte GPCRs signaling [72]. So the conclusion of previous studies : the glucocorticoids which are the basic regulator for B-arrestins expression are now considered as the basic regulator for anti-inflammatory processes that are crucial in regulating CSC self-renewal and mediate anti-inflammatory processes as effective for adopting self-renewal in stem cell population. Notice that GPCRs and glutamate are necessary for glucocorticoids productions that as I mentioned the GCs synthesis reflect adjustment to GPCRs percentages that while the B-arrestins promoted and regulated by both glucocorticoid-beta and Estrogen productions for running its role of anti-inflammatory growth includes self-renewal in the cancer stem cell populations.

Estrogen plays an important role in the growth and maturation by its stimulation and regulation to GCs-beta synthesis which stimulate and activate both B-arrestins and both Ang2-AT2 and VEGF-A (regulated by ACE) synthesis for modulating anti-inflammatory growth. That, Estrogen regulates the expression of IL-6 in bone marrow cells by a so far unknown mechanism [73]. Estrogen promote the B-arrestins production which will adopt and activate the self-renewal in T-cells population which will reactivate DCs (Via feedback) for producing IL2 which upon synthase will promote IL6, IL8 and IL23 productions which will reactivate the Glucocorticoid-beta synthesis for readopt and prevent GPCRs accumulations.

Inhibition in estrogen reflect increasing in cholesterol and consequently in inflammations and inhibition in both glucocorticoids and in synthase, and will lead to increasing in irregular TNFα activities via Activating CTGF functions. Where, TNFα promoted an up to 2 folds increase in cellular cholesterol, which was resistant to ACAT inhibition [74]. But estrogen synthesis reflect GCs-beta and IFN-beta synthesis respectively followed by B-arrestins synthesis and Ang2-AT2 and VEGF-A synthesis which are the basis for running and adopting anti-inflammatory growth and protect the heart layers functions from accumulated cholesterol and GPCRs.

The inhibition in estrogen synthesis reflect Inhibition in glucocorticoids - beta synthesis (and inhibition in glutamine and in Proline associated with decreasing in amino acids synthesis) followed by inhibition in Interferons-beta synthesis and associated with increasing in cholesterol and in inflammations that will show increasing in TNF-a activities via increasing in CTGF functions. That, Deregulation of ER is involved in tumorigenesis in multiple organ sites [75]. And in conclusion the Dysregulation in estrogen receptor (ER) productions are associated with accumulation of cholesterol and Gamma-estradiol and can be associated with IL30 or IL40 (due inhibition in B-estradiol) can consider as the main reasons for tumorigenesis. And it is so imp to note that, Inhibition of the Rho GTPase, Rac1, decreases estrogen receptor levels [76]. That previous study concluded that decreasing in S6K

reflects decreasing in GTPase (which imp for OPA1 repairs for activating OPA1 function) that will associated with the decreasing in Rac1 which depend on S6K (that can reflect decreasing in B-estradiol due decreasing in OPA1 synthase) that will reflect decreasing in both B-estradiol and Estrogen productions (which promoted by cholesterol as a substrate for its Biosynthesis) that will reflect decreasing in glucocorticoids productions which can reflect accumulations in cholesterol and in GPCRs (that can be the basis for increasing in left vertical size associated with decreasing in mineralocorticoid synthesis which associated with high binding affinity to K and Na that will be results of toxicities and followed by tumor cancer growth). Also, the Loss of PLCγ2 led to broad changes in expression of several macrophage surface markers and phenotype, including reduced phagocytic activity and survival, while pluripotent stem cell LPS-induced secretion of the inflammatory cytokines TNFα and IL-6 was unaffected [77].

Glutamine Necessary for Proline Synthesis and Necessary for Protection from Psoriatic Arthritis (PsA) and Cancer through Glucocorticoids Synthesis

Glutamine as we mentioned are necessary for proper IL2 productions (which regulated by Ser/Thr phosphorylation functions) followed by glucocorticoids synthesis followed by Interferons productions for activating T-cells, B-cells and macrophages functions and at the same time are protecting heart functions through activating Ang2-AT2 synthesis followed by VEGF-A productions for anti-inflammatory growth.

Rac1 GTPase Promotes Interaction of Hematopoietic Stem/Progenitor Cell with Niche and Participates in Leukemia Initiation and Maintenance [78].

Psoriatic arthritis (PsA) is an inflammatory joint disease characterized by extensive bone resorption. Pro-inflammatory cytokines which produced in inflamed joints (which firstly formed upon the Cox2 effects on inflammatory sources “signals”) that generated and released from bone marrow due to deficiency in glutamine followed by deficiency in Proline then followed by deficiency in pyrimidine kinases production and in hoth Glucocorticoids-beta and IFN-beta synthesis.

The accumulation of Pro-inflammatory cytokines are due to inhibition in glutamine followed by inhibition in Proline (which is imp for hydrophobic amino acids synthesis) then followed by inhibition in hydrophobic acids synthesis (including inhibition in tyrosine kinases synthesis) then followed by inhibition or deficiency in OPA1 enzymes then followed by inhibition or mutation in IL2 which produced upon synthetase effects on cytokines kinases (on the pro-inflammatory cytokines) followed by decreasing in GCs-beta synthesis and associated with accumulation in pro-inflammation with accumulation in cholesterol and then will be the result of decreasing or inhibition in PLCγ2 production regulated by Rac1 functions.

Inhibition in glutamine will lead to accumulation in pro-inflammatory oxidized molecules which produced by Cox2 oxidative functions due to inhibition in hydrophobic acids synthesis including Tyr which necessary for activating synthase enzymes. Where endogenous proline is synthesized mainly from glutamine and can play an important role in cell signaling throughout promoting pyrimidine kinases synthesis followed by proper IL2 productions then followed by GCs-beta and IFN-beta productions which activate the adopted anti-inflammatory growth and processes. Where inhibition in glutamine will be result of accumulation of oxygen species with inhibition in Proline synthesis *in vivo* which is so important for promoting Rac1 functions that will lead to mutation and dysfunction in Rac1 activities. That, Glutamine to proline conversion is associated with response to glutaminase inhibition in breast cancer [79]. And, Proline oxidase, the first enzyme in proline catabolism, is a mitochondrial tumor suppressor that inhibits proliferation and induces apoptosis [80]. So, proline is a mitochondrial tumor suppressor through promoting Tyr, Leu, Ser, Thr… etc synthesis which activate firstly both kinases followed by IL2 productions and both GCs-beta (which activate B-cells functions and promote angiotensin pathway for VEGF-A productions which activate adopted anti-inflammatory growth) and IFN-beta productions which accelerate anti-inflammatory processes, that finally improve the mitochondrial membrane repair for accelerating OPA1 enzymes proper functions. And, the glutamine–proline regulatory axis plays an important role in the aggressive subclass of luminal BC and is therefore a potential therapeutic target [81]. And, the asparaginase has been approved for treating acute lymphoblastic leukemia. Targeting glutamine and arginine starvations are in various stages of clinical trials, and targeting proline starvation is in preclinical development [82]. And, Glutamine Is Essential for Stemness of Bone Marrow Mesenchymal Stem Cells and Bone Homeostasis [83]. And also, glutamine-derived glutathione prevents accumulation of reactive oxygen species and thereby safeguards cell viability [84]. So, now it is clear that inhibition in glutamine will positively lead to accumulation in the pro-inflammation (which produced by Cox2 functions) ¬¬> that will be the main reasons for Psoriatic arthritis (PsA), and bone cancer.

It’s clear also to note that Psoriatic arthritis (PsA) associated with liver fibrosis because Glu is necessary for Leu synthesis and migration that

Glu “GAG, GAA” ¬¬¬> Leu “CTC, CTT” (upon translations processes), where Leu is so necessary for sestrin synthesis and functions, that the reductions in Glu will reflect reduction in Leu which is necessary for live and brain functions.

Glutamine has the function of improving pro-inflammation which due to Cox2 functions for activating Proline synthesis and activating OPA1 synthetase for producing IL2 which activate IL8 and IL23 productions (upon synthase function) for both GCs-beta and IFN-beta productions followed by promoting MHC ll synthesis then followed by SIRPα1 and TLR4 synthesis mediated by VEGF-A synthesis for adopting anti-inflammatory growth. Where, the Glucocorticoid deficiency causes transcriptional and post-transcriptional reprogramming of glutamine metabolism [85]. So the necessity of Glu is enrolled for glucocorticoids synthesis that the GCs synthesis can adopt the Glu percentages,

and decrease the cholesterol G-protein in blood (where G-protein and cholesterol promote glucocorticoids synthesis) and also the necessity of the Glu is enrolled in promoting Leu synthesis and migrations upon translation for activating brain function through activating Leu pentapeptides in enkephalin tissue.

The Role of Serotonin in Activating T-Cells, And Promoting Ang2-At2 for VEGF-A for Protecting Heart Function Anti-Inflammatory Growth

5-HT-stimulated ERK1/2 phosphorylation in this cellular background requires phospholipase D, protein kinase C, and activation of the Raf/MEK/ERK module [86].

The actions of 5-HTI-like receptors may include inhibition of release and smooth muscle contraction. That serotonin looks as depending on the the availability of Leu, Tyr Gly, Ser, tryptophan, Glu, Asp, & Thr which are important for activating brain enkephalin tissue through activating Leu and methionine-pentapeptides. Glucocorticoids play a critical role in the modulation of stress responses by controlling the function of the serotonin (5-HT) system. Glucocorticoids control the excitability of DR 5-HT neurons [87].

And, the absence of serotonin within the brain interferes with the ability of the HPA axis to correctly modulate the response to acute stress, by altering the nuclear mechanisms of the GR [88].

The activation of serotonin 5-HT2C receptors, which engage Erk1/2 pathway via a β-arrestin-dependent mechanism, and MEK-dependent promotes the β-arrestin phosphorylation function at Thr383, which is necessary step for Erk recruitment to the receptor/β-arrestin complex [89]. And, previous studies indicate that 5-HT stimulated angiogenesis through activation of Akt in ECs [90]. And, Serotonin/5-HT1A Signaling in the Neurovascular Unit Regulates Endothelial CLDN5 Expression [91]. And, serotonin 5-HT regulates the balance of Th17/Tregs and promotes M2-polarization of macrophages and has a direct or indirect regulatory effect on traditional immunocytes such as T cells, macrophages, DC cells, and NK cells [92]. And the expression of 5-HT4 is markedly upregulated, and stimulation of 5-HT4 receptor increases myocardial contractility and relaxation [93]. And, Serotonin Is Associated with Coronary Artery Disease and Cardiac Events [94]. And, it has been proven that glycogen when is a G-protein coupled receptor through synthase oxidative function will activate Glucocorticoid-beta synthesis (upon pyrimidine kinases regulation) which had the roles of regulating serotonin functions. Where Glycogen synthase kinase-3ß supports serotonin transporter function, that glycogen synthase kinase-3ß (GSK3ß) regulates Serotonin (5-HT) transporter (Sert) [95]. Also, serotonin (regulated by thymine kinases) has the role of activating mineralocorticoid indicating its origin synthesis regulated by glucocorticoid-beta, and indicated that serotonin has the same origin as B-arrestins regulated by glucocorticoids (or may serotonin regulated by B-arrestins), that serotonin having the role of protecting muscles and heart from K and Na binding that cause toxicity. And it has been reported that: 5-HT modulates the synthesis of MR protein [96].

Now It's clear that B-arrestins and serotonin are having almost same origin, almost same function, that may B-arrestins promote and regulate the serotonin productions, but serotonin basically originated from tryptophanTph1 (TGG) which originated and can be regulated by Ser (AGT) in blood where thymine bind with guanine are important for tryptophan synthesis *in vivo*), that Tph2 responsible for serotonin synthesis in brain (the binding of thymine T with guanine "GG" is so necessary" to form proper serotonin molecule in brain upon tryptophan hydroxylase (Tph). Function, that serotonin can be boosted and enhancement by more necessary amino acids for Enhancement its functions such as tryptophan (TGG), Leu "TTG", Tyr, Gly, Ser "AGT", and methionine "ATG" for activating both Leu and Met-pentapeptides in enkephalin tissue in brain, that as the thymine nucleotides missed In serotonin molecules (so missed in tryptophan TGG) as serotonin will show mutations in its structure and functions but will still promote growth through its purines kinases (GG) which can promote tumor growth with deficiency in enkephalin functions that can enhance brain cancer.

The serotonin and serotonin receptors modulate the phenotype and function of various immune cells and peripheral nervous system. That immune cells and cancer cells also can release, and respond to serotonin through the contradictory roles of serotonin in regulating the functions of different immune cells [97]. That the contradictory roles of serotonin in regulate the functions of different immune cells are depending on the presence of thymine nucleotides in tryptophan (TGG) which is the sole of serotonin, that if thymine will disappeared (threaded and connected with guanine) will affect on the direction of serotonin functional pathway (exact as I noted that B-arrestins function depend on pyrimidine kinases (TAT and TAC [98]). So the serotonin will enhance CD8+ T cell accumulation in tumors and reduced tumor growth (but in deficiency in the TGG threatening the serotonin will enhance tumor growth) and will enhance the PD1 accumulation (but will not enhance PD-L1 synthesis).

Where it has been reported that the serotonin were able to enhance the effects of anti–PD-1 therapy to induce long-term tumor control in mice [99]. So in brief serotonin are dependent on Thymine availability (connected to guanine nucleotide) and have almost the same functional pathway as B-arrestins that thymine kinases are playing important roles in adopting both hormones for protecting heart functions, and for activating M2-polarization of macrophages and has a direct or indirect regulatory effect on traditional immunocytes such as T cells that can promote self-renewal functions. And it's clear that serotonin playing important roles in activating angiotensin more similar as B-arrestins that both can activate ACE for Ang2-AT2 productions which activate VEGF-A synthesis in which necessary for anti-inflammatory growth, that serotonin modulate the response to acute stress by modulating the altering nuclear pathway and through promoting angiotensin pathway for Ang2-AT2 which protect heart pulses and functions and for VEGF-A productions for running anti-inflammatory growth.

Diffuse B-cell lymphoma linked to Deficiency in Serotonin which depends on thymine in tryptophan TGG

Diffuse large B-cell lymphoma (DLBCL) characterized by sheets of large transformed B cells, and decreasing or inhibition in GCs-beta (which necessary for regulating B-cells) and the DLBCL include various subsets of T cells, macrophages, mast cells. That DLBCL positivity linked to the deficiency in Serotonin which depends on the availability of thymine in tryptophan (TGG) , that both are depend on the availability of thymine kinases (T) production (promote by Ser phosphorylation) to regulate the purines kinases (GG) through tryptophan synthesis.

Psoriatic arthritis (PsA) is an inflammatory joint disease also characterized by extensive bone resorption.

The accumulations of Pro-inflammatory cytokines which produced in inflamed joints and in other cancer diseases such DLBCL is due to deficiency in glutamine followed by deficiency in Proline then followed by deficiency in both hydrophobic amino acids synthesis and glucocorticoids synthesis.

Serotonin has necessary roles in activating B-cells, that the Growth-inhibition of cell lines derived from B cell lymphomas through antagonism of serotonin receptor signaling [100]. And it has been reported that neutrophil recruitment and T-cell activation can both be mediated by serotonin [101]. And, serotonin plays a fundamental role in arthritis through the regulation of the Th17/T-regulatory cell balance and osteoclastogenesis [102]. And, it has been reported that 5-Hydroxytryptamine drives apoptosis in biopsylike Burkitt lymphoma cells: reversal by selective serotonin reuptake inhibitors [103]. That it's clear that deficiency in thymine kinase will inhibit serotonin which mediate neutrophil recruitment and T-cell activation. That basically the deficiency in Ser phosphorylation will reflect deficiency in thymine kinases production that will result of decreasing in serotonin and cause B-cell lymphoma cells and can be the result of the arthritis (PsA). Where the proper serotonin originated from tryptophanTph1 (TGG) and has important role in activating B-cell and T-cells directly and indirectly and is so imp for beating cancers and arthritis OPA.

The Role of Glucocorticoids in Increasing Anti-Inflammatory Growth Mediated By B-Arrestins Synthesis

Glucocorticoids are formed by cholesterol upon synthetase and synthase function for producing GCs gamma and GCs-beta respectively upon orphan nuclear pathway.

Glucocorticoids are the basis of life in the development of the fetus and therefore in humans. It is the basis for strengthening immunity, and it is the first hormone formed in decisiveness at the beginning of facing allergic and immune problems and confronting the invasion of viruses and diseases. The glucocorticoids function are regulating the Rac1, the Interferons,the Plcγ2, Ang2-AT2, and VEGF-A synthesis, that also regulate the adopted anti-inflammatory growth (immune growth).

That the necessity of GCs synthesis can be confined or concluded the B-arrestins synthesis which is the adopter protein that regulate and adopt running several cellular pathways according to the stimulated immune signals. That it has been reported that: Increase of circulating memory B cells after 6 months of glucocorticoid treatment [104]. And, Glucocorticoids promote intrinsic human TH17 differentiation [105] (mediated by Ang2-AT2 and VEGF-A synthesis, where angiotensin are important for adopting anti-inflammatory growth through promoting TH17 differentiation). That, GCs play imp roles in activating B-cells maturation and promote intrinsic human TH17 differentiation mediated by B-arrestins synthesis wh3is si active adopter protein nécessary for adopting B-cells maturation, necessary for stem cells renewal and necessary for protecting myocardial functions. And, B-arrestins (ARRBs) are implicated in regulating stem cell maintenance. Where, ARRB1 regulates self-renewal in the cancer stem cell population in B-lineage acute lymphoblastic leukemia (B-ALL) [106]. Glucocorticoids increase the synthesis of immunoglobulin E by interleukin 4-stimulated human lymphocytes [107]. And, glucocorticoid dexamethasone is the first trial-proven drug that reduces COVID-19 mortality by suppressing immune system [108]. And, glutamine are so necessary for activating glucocorticoids and Rac1 synthesis that deficiency in glutamine are consequently inhibit IFN-gamma that Immunosuppression Induced by Glutamine Deprivation Occurs via Activating PD-L1 Transcription in Bladder Cancer [109]. Where activation the glucocorticoids functions will increase glutamine utilisation in blood [110]. And, Glucocorticoid deficiency causes transcriptional and post-transcriptional reprogramming of glutamine Metabolism [111]. And, plays a crucial role in the production of cytokines, macrophages, phagocytic, and neutrophil to kill the bacteria [112]. And, Glutamine metabolism is essential for the production of IL-17A in γδ T cells and skin inflammation [113]. So, previous studies revealed that the activation of glucocorticoids are the basis for increasing glutamine for the production of cytokines, macrophages, phagocytic, and neutrophil to kill the bacteria through activating Interferons productions. And then we can conclude that deficiency in glucocorticoids synthesis and glutamine will suppress immune activities and will lead to deficiency in Interferons productions followed by decreasing in macrophages and T-cells functions. That availability of vit D and glutamine will activate glucocorticoids synthesis which activate Interferons productions for suppressing viral effects.

Where it has been reported that :, in spite of the SARS-CoV-2, are known to suppress and evade the antiviral responses of the host organism mediated by interferon (IFN), a family of cytokines that plays an important role in antiviral, the vitamin D, zinc and glutamine, nutrients have been shown to facilitate immune functions [114]. And it's more important to conclude the role of GCs in B-arrestins synthesis for stimulating ACE for activating Ang2-AT2 synthesis which activate monocyte cells, where the Stimulation of the Angiotensin II AT2 Receptor is Anti-inflammatory in Human Lipopolysaccharide-Activated Monocytic Cells [115]. And the glial cells are able to produce and process Ang II. Ang receptors were localized in the blood vessels and neural cells. Local Ang II signaling may thus allow for autoregulation of neurovascular activity [116]. So, B-arrestins which regulated by glucocorticoids

and Estrogen are necessary for regulating self-renewal in cancer stem cell population in B-lineage acute lymphoblastic leukemia mediated by Ang2-AT2 synthesis upon ACE functions followed by VEGF-A productions necessary for anti-inflammatory growth including Increasing in circulating memory B cells. Where, due to inflammatory sources signals the cytokines kinases will be produced upon Cox2 and ATPase followed by estradiol gamma productions which will activate DCs to produce IL2 which will be activated by synthase for GCs synthesis and B-estradiol synthesis which activate Beta-arrestins which will activate ACE for Ang2-AT2 synthesis followed by VEGF-A productions for anti-inflammatory processes and for anti-inflammatory growth. Also it has been reported that: DCs can readily produce VEGF-A in response to a large variety of PAMPs and DAMPs if PGE2 is present in the local microenvironment [117].

The formation of that GCs-beta active gene are the basis for improving, for increasing and for protecting immunity including anti-inflammatory growth, that GCs synthesis will be result of consuming cholesterol and GPCRs for their biosynthesis and preventing and preventing their accumulation in blood , that means GCs synthesis protects the body from cholesterol accumulations, from GPCRs accumulation and from their binding with salts such K and Na that their binding can produce toxicity in blood. Remember adrenalin in embryo are large enough to run all immune activities and protecting heart functions that indicate GCs are the basis for adopting and running immune functions and protect heart function manner mediated by B-arrestins synthesis and activating anti-inflammatory growth mediated by Ang2-AT2 and VEGF-A synthesis. Glucocorticoids synthesis are carrying the critical role for adopting both cholesterol and GPCRs percentage in blood and consequently functioning the inflammatory molecules which produced by Cox2 functions which modified by DCs for producing gamma-subunits (IL2) then upon OPA1 synthase function will produce GCs-beta which promote B-arrestins for adopting and running the increasing in anti-inflammatory processes through activating ACE for promoting the Ang2-AT2 synthesis followed by VEGF-A synthesis for running anti-inflammatory growth. That GCs synthesis can be defined as the challenge pathway for converting GPCRs and cholesterol to adopter active driven protein (B-arristin) regulated by OPA1 synthase enzymes (and firstly by JAK signaling) for protecting myocardial layer and immune from increasing in GPCRs and from cholesterol accumulations through producing both mineralocorticoid and B-arrestins in Myocardial layer for protecting from salts binding and then strengthen heart functions through activating ACE functions for Ang2-AT2 synthesis and VEGF-A synthesis for anti-inflammatory growth then for strengthen best proper condition for heart layers. Where it has been reported that: GCs induce proteins with anti-inflammatory activities, including glucocorticoid-induced leucine zipper (GILZ) which mediate several actions of GCs, including inhibition of the NF-κB. (The NF-KB which activated by irregular cellular activities). The GILZ play a regulatory role in many tissues including the cardiovascular tissues [118]. And, GCs synthesis are important challenge for activating angiotensin Ang2-AT2 synthesis which followed by VEGF-A synthesis for running anti-inflammatory growth. And, As the synthesis of Acyl-COAs In embryo are promoting the nucleocytosolic acetyl-CoA-alpha productions as the nucleocytosolic alpha (NSO-alpha) is the main important improved steps for anti-inflammatory growth started in early activity in embryo, that the NO-alpha firstly regulated by GC-beta followed by B-arrestins productions then followed by Ang2-AT2 synthesis and VEGF-A which necessary for anti-inflammatory growth [119]. So the synthesis of Acyl-COAs as playing the major roles in anti-inflammatory growth In embryo indicate that are necessary for nucleocytosolic alpha (NSO-alpha) which regulated firstly by GCs-beta synthesis for improving the anti-inflammatory growth mediated by Ang2-AT2 synthesis and by VEGF-A synthesis for embryo development and for protecting heart layers from salts binding and from cholesterol accumulations, And So, the endothelial functions which responsible for gcs synthesis are having the basic roles responsible for adopting the inflammation and cholesterol percentage through GCs-beta synthesis and prevent cholesterol accumulations and GPCRs accumulation too through activating ACE functions for activating angiotensin active pathway which are important for running the "adopted" anti-inflammatory processes which are the basis for "adopting" the anti-inflammatory growth too through VEGF-A synthesis which regulated by Ang2-AT2 synthesis. where many Biomedical studies have proven and indicated to me that Cox2 and ATPase are the necessary basis for producing cholesterol and inflammation (as their functions for acting on inflammatory source) which then stimulate OPA1 synthetase for activating DCs to induce IL2 for inducing IL10, and IL17 (upon synthase function) for running two pathways: the 1st / is for running GCs synthesis for B-arrestins synthesis which stimulate ACE functions for activating angiotensin pathways by Ang2-AT2 synthesis followed by and VEGF-A synthesis, but the 2nd pathway / is for activating IFN-beta productions for reactivating anti-inflammatory processes mediated by MHC class l, MHC ll synthesis followed by SIRPα1 and TLR4 synthesis for proliferation. That, GCs synthesis are potential for Interferons synthesis for increasing the pool of anti-inflammatory processes but it can appear that GCs suppress IFN-gamma but the synthesis of IFN-gamma by GCs are having short life time "steps" followed fastly by IFN-beta synthesis which then followed by IFN-alpha synthesis which promote nucleocytosolic alpha synthesis. Where, GCs have been shown to potentiate IFN-γ induction of FcγRI gene expression in myeloid cells [120]. That The decreasing or inhibition in GCs-beta and in synthase function can reflect Inhibition in interferon beta (due to inhibition in pyrimidine kinases) that will be the result of accumulation of DCs products IL2 which can be mutated due to their accumulation and improved to produce nearly IL30 or IL40 which aren't recognized by IL2 family that will characterized the autoimmune disorder diseases (that as I mentioned firstly is due to inhibition in GCs-beta due to synthase inhibition). And, the IFN-beta which activated by GCs-beta can improve environment for Th2 differentiation *in vivo.* That IFN-beta *in vitro* can induce the development to DC2, which provide a permissive environment for Th2 differentiation [121]. And, IFN-α/β, among other "DCs" innate cytokines that is considered as an important 'third signal that shapes the effector and memory T-cell pool. Moreover, IFN-α/β also serves as a

counter-regulator of T helper type 2 and type 17 responses [122]. Note that, IFN-α/β, among other "DCs" innate cytokines that is considered as'third signal that shapes the effector and memory T-cell pool has a clear meaning that IFN-α/β, among "DCs" which innate proper cytokines contain proper TAT and TAC promoter are involved in GCs-beta synthesis which necessary for memories functions. That it's important to clarify that due to glucocorticoidsbeta (dexamethasone) synthesis will enhances IFN-beta-induced STAT4 activation and consequently will show decreaseing in IL-12-induced STAT4 phosphorylation which used for GCs-beta synthesis followed by IFN-beta synthesis. That it has been reported that, glucocorticoids (dexamethasone) decreases IL-12-induced STAT4 phosphorylation and IFN-gamma production and enhances IFN-beta-induced STAT4 activation [123]. So, We can confirm and concluded that IFN-beta are potentiated and promoted by GCs-beta synthesis which adopted cholesterol and GPCRs percentage *in vivo* and can promote nucleocytosolic CoA alpha which regulating and shape the effector memory T-cells functions (mediated by Ang2-AT2 synthesis and VEGF-A synthesis for running anti-inflammatory growth). That, O-GlcNAcylation is clearly formed from GCs-beta Biosynthesis pathways which has a strong roles in increasing the T-cells and B-cells functions. That, O-GlcNAcylation promotes the development, proliferation, and activation of T and B cells. O-GlcNAcylation regulates inflammatory and antiviral responses of macrophages [124]. That GCs are having strong roles in regulating and shape the effector memory T-cells pool of functions and have strong roles in the increasing the adopting improvements capacity of monocyte-derived from dendritic cells to induce IL-5, IL-10, and IL-13, to IL23 which promote MHC class ll synthesis from MHC class l then will activate PD-L1 from PD1 fo'owef by SIRPα1 production within cells and then followed by TLR4 production for anti-inflammatory growth and cells sevival. Also, IFNγ (regulated by estradiol gamma and by GCs-gamma) is an important activator of macrophages and inducer of Class I major histocompatibility complex (MHC) molecule expression which upon IFN-beta synthesis and functions (IFN-beta potentiated by GCs-beta upon synthase function) will promote the MHC ll synthesis, but depending firstly on proper Protein-Kinase-Cs (PKCs) expression where it's expression depends on pyrimidine kinases (TAT and TAC kinases) synthesis which has the effective roles in adopting heart function and protect immune with central nerve cells from autoimmune disorders and from cancer diseases. Where, IFN-γ-induced expression of the MHC class Il transactivator (CIITA), a transcriptional coactivator essential for MHC-II expression, was inhibited in DN PKC-α-overexpressing cells [125]. Where the PKC-α-overexpression (regulated and promoted by Ser phosphorylation pathway for thymine promoters TATATA kinases productions), will reactivate firstly the cholesterol and S6K synthesis in mTOR pathway which followed by synthetase effects for activating DCs for producing their IL2 followed by the Glucocorticoid-gamma synthesis which activate GC-beta synthesis which by itself will promote the IFN-beta (which I identify it as the DCs-GCs -IFNs-anti-inflammatory growth pathway followed by proliferation processes. But over expression of IFN-gamma by synthetase function in will delay only the starting function of DCs-GCs -IFNs-anti-inflammatory growth pathway (but not inhibition) till will start the first point of the synthesis of DCs-GCs -IFNs-anti-inflammatory growth pathway again for refunctioning the extra of the DN PKC-α-overexpressing. But, the decreasing in thymine kinases synthesis (TAT kinases) with continuing DN PKC-overexpressing will lead to accumulation in both GCs gamma and IFN-gamma with decreasing in synthase function that will lead to dysregulation in immune functions and will be the main reasons for autoimmune disorders diseases.

PLCγ2, GCs-beta, IFN-beta, and Ang2-AT2 necessary to beat osteoporosis, arthritis and bone cancer with the importance of estrogen synthesis:

Thymine and cytosine kinases which produced from Ser phosphorylation in mTOR pathway are the basic for activating estrogen synthesis upon synthase effect on cholesterol molecules.

Rac1 basically contain S6K rich Proline and hydrophobic amino acids that each amino acid especificslly the Proline amino acids are characterized Rac1 functions and activities for contributing the anti-inflammatory processes and anti-inflammatory growth, that Rac1 has the roles of acting on inflammatory sources through analyzing their contents by oxidation for producing long fatty chains (that firstly Rac1 activate ATPase and GTPase by S6K which act on inflammatory molecules producing long fatty chains) which will subject to the influences of OPA1 oxidative function (which repaired by GTPase and promoted by Rac1) for producing fatty Acyl-COAs isoforms which can be considered as GP-GTP isoforms (upon binding with GTP), Gp-GTP gamma (upon synthetase functions) , GP-GTP beta (upon synthase effect on Gp-GTP), and GP-GTP alpha (upon phospholipase effects on GP-GTP) where some considered that GTPase has been analyzed to give Gp isoforms but GTPase which promoted by S6K will activate OPA1 enzymes that will act on inflammations and on long fatty chains for producing Gp-GTP nuclear isoforms (gamma, beta, and alpha) which activate GCs synthesis, and GP-GTP beta which have the roles of promoting PLCγ1, PLC-beta, and PLC-alpha upon thiotransferase functions followed by IFN-gamma, IFN-beta, and IFN-alpha synthesis respectively for anti-inflammatory processes and growth [126].

The Rac1 are Regulated by thymine kinases and cytosine kinases (PKC) production and by S6K production from Ser/ Thr mTOR phosphorylation pathway, where Rac1 has the function of contributing in PLCs synthesis for rebuilding bones growth and contributing in anti-inflammatory processes, where inhibition in one of previous kinases will effect on the next cellular pathways that can lead to cancers and pathogenic symptoms. And, Studies of PLCγ1-deficient fibroblasts have shown that epidermal growth factor failed to mobilizeintracellular Ca2+. That Among signal transduction pathway components, Src family kinases, Syk kinase and the adapter protein LAT have all been shown to play critical roles in FcγR-regulated phagocytosis (through activating Plcγ2 production). Where, PLCγ2 is essential for FcRγ-containing

collagen receptor-mediated release of ATP/ADP and thromboxin A2 in platelets [127].

Plcγ2 play critical roles in anti-inflammatory processes as revealed before and are recovered by GCs-beta and by VEGF-A which promoted by Ang2-AT2 synthesis that both Plcγ2 and VEGF-A are recovering TXA2 synthesis and collagen synthesis. That it has been reported that: PLCγ2 dysfunction is associated with a variety of diseases including cancer, and PLCγ2-associated antibody deficiency and immune dysregulation, in some cases with autoinflammation [128]. And, it has proven that to inhibit RANKL-mediated osteoclastogenesis via modulating PLCγ signaling pathways [129]. So PLCs synthesis are promoted by Src kinase, Syk, and by adopter protein which promoted by B-arrestins regulation which regulated by GCs synthesis and Estrogen, that PLCs synthesis are promoted by GCs functions where both are having a critical roles in Thromboxane-A synthesis. That deficiency in PLCγ2 synthesis can lead to Bone cancer, osteoporosis, and arthritis. Note that Plcγ2 can activate Ang2-AT2 synthesis (mediated by GCs-beta and B-arrestins synthesis) which is necessary for improving heart function and pulses (regulated by pyrimidine kinases synthesis) and necessary for improving VEGF-A productions which necessary for adopting anti-inflammatory growth for both heart and bones growth, and important for adopting mineralocorticoid synthesis and functions for get rid of Na and K salts and protect heart and all immune from hyper Molecular toxicity that can be the main reason for pathogenic cases.

The Inhibition in estrogen reflect increasing in cholesterol and consequently in inflammations with inhibition in synthase function that the accumulation in inflammations will promote TNF a. Where, TNFα promoted an up to 2 folds increase in cellular cholesterol, which was resistant to ACAT inhibition [130].

But estrogen synthesis reflect IFN-beta and GCs-beta synthesis followed by B-arrestins synthesis and followed by Ang2-AT2 and VEGF-A synthesis which are the basis for running and adopting anti-inflammatory growth and protect the heart layers functions. It is reasonable that the expression of ER and the activity of ER must be tightly regulated. Deregulation of ER is involved in tumorigenesis in multiple organ sites. Progression from an ER-positive phenotype to an ER-negative phenotype typically involves the constitutive activation of growth-promoting signals, thereby leading to a loss of estrogen dependence and resistance to anti-estrogens [131]. And it is so imp to note that, Inhibition of the Rho GTPase, Rac1, decreases estrogen receptor levels [132].

The effect on microglia function in the brain might be accompanied by a dysregulation of other immune cells' function and other tissues/organs, such as bones and liver [133]. Triggering receptor expressed on myeloid cells-2 (TREM2) is an innate immune receptor that promotes phagocytosis by myeloid cells such as microglia and macrophages [134].

Loss of PLCγ2 led to broad changes in expression of several macrophage surface markers and phenotype, including reduced phagocytic activity and survival, while pluripotent stem cell LPS-induced secretion of the inflammatory cytokines TNFα and IL-6 was unaffected [135]. Stem cells residing in alveoli and terminal bronchioles that can self-renew and differentiate into alveolar type (AT)-1 cells, AT-2 cells [136].

The Conclusion

The glucocorticoids which are the basic regulator for B-arrestins expression are now considered as the basic regulator for anti-inflammatory processes that are crucial in regulating "CSC" self-renewal stem cells and mediate anti-inflammatory processes as effective for adopting self-renewal in stem cell population and effective for starting the running anti-inflammatory growth and processes mediated by Interferon-beta synthesis (in one pathway) and VEGF-A synthesis mediated by Ang2-AT2 synthesis (in secondly pathway).

The GPCRs and glutamate are necessary for glucocorticoids productions "synthesis" , that the GCs synthesis prevent the GPCRs accumulation, while the B-arrestins promoted and regulated by both glucocorticoid-beta and Estrogen productions for running its basic functions for anti-inflammatory growth and processes (mediated by IFN-beta synthesis which continuing running anti-inflammatory processes) includes self-renewal in the cancer stem cell populations. Estrogen promote the B-arrestins production which adopt and activate the self-renewal in T-cells population (through activating GCs-beta synthesis) where estrogen synthesis pathway (regulated by both purines and pyrimidine kinases synthesis) will reactivate DCs for producing IL2 which upon synthase will promote IL6, IL8 and IL23 productions which will reactivate the Glucocorticoid synthesis for readopt and prevent GPCRs accumulations followed by starting running the anti-inflammatory growth and processes . The Deregulation in ER productions are associated with accumulation of Gamma-estradiol "followed by decreasing or inhibition in GCs-beta synthesis" and may associated with IL30 or IL40 (due to inhibition in B-estradiol) are the main reasons for tumorigenesis . The decreasing in S6K reflects decreasing in GTPase (which imp for OPA1 repairs for activating OPA1 function) that will associated with decreasing in Rac1 which depend on S6K (that can reflect decreasing in B-estradiol due decreasing in OPA1 synthase) that will reflect decreasing in both B-estradiol and Estrogen productions (which promoted by cholesterol which considered as substrate for estrogen Biosynthesis) that will reflect decreasing in glucocorticoids productions and can reflect accumulations in cholesterol and in GPCRs (that can be the basis for increasing in left vertical size associated with decreasing in mineralocorticoid synthesis which associated with high binding affinity to K and Na that will be results of toxicities and followed by tumor cancer growth).

Pyrimidines kinases (thymine kinases "TK" and cytosine "PKC" kinases) are necessary for estrogen synthesis mediated by B-estradiol production for activating GCs-beta, for IFN-beta and

for both IFN-alpha and VEGF-A synthesis in the progression of anti-inflammatory growth.

The decreasing or inhibition in purines and in pyrimidine kinases can cause decreasing in S6K that will .reflects decreasing in both ATPase and GTPase (where GTPase improves the OPA1 repairs for activating OPA1 functions) that will associated with the decreasing in Rac1 which depend on S6K (that can reflect decreasing in B-estradiol due to decreasing in OPA1 synthase) that will reflect decreasing in both B-estradiol and Estrogen productions (which promoted by cholesterol as a substrate for estrogen Biosynthesis) that will be the result of decreasing in glucocorticoids-beta and IFN-beta productions with accumulations in cholesterol and in GPCRs (that can be the basis for increasing in left vertical size associated with decreasing in mineralocorticoid synthesis) and can be the result of decreasing in T-cells self-renewal and in B cells functions that can be associated with decreasing in PLCγ2 synthesis and in brief can lead to several cases of cancers and heart diseases.

The accumulations of PKC due to the deficiency or inhibition in thymine kinases followed by inhibition or mutation in cytokines kinases will be result in mutation in IL2 that can be accumulate and can be improved to IL30 and IL40 due to irregular processes in vivo that can be result in pathogenic diseases such as causing autoimmune disorders disease. Proinflammatory cytokines produced in inflamed joints (upon Cox2 effects on inflammatory sources) promote the generation and released from bone marrow. That the accumulation of Proinflammatory cytokines which characterized several diseases including tumor growth can be due to inhibition in glutamine followed by inhibition in Proline (which is imp for amino acids synthesis) then followed by inhibition in GCs-beta and in IFN-beta associated with deficiency in OPA1 synthase.

It's cleared to me that B-arrestins and serotonin are having almost same origin, almost same function, with same pathways that may B-arrestins promote and regulate the serotonin productions , but serotonin originated from tryptophanTph1 which originate from blood, while Tph2 responsive for serotonin synthesis in brain (the binding of thymine T "which is so necessary" to GG in serotonin molecule in brain upon tryptophan hydroxylase (Tph) function), that serotonin can be boosted and enhancement by more necessary amino acids for Enhancement its functions such as tryptophan (TGG), Leu, Tyr, Gly, and methionine for activating both Leu and Met-pentapeptides in enkephalin tissue in brain, .that as the thymine missed in serotonin (missed in tryptophan TGG) as will show mutations in its structure and functions but will still promote growth through its purines kinases (GG) which can promote tumor growth.

Case Reports

60-year-old woman presented with a persistent dry cough, extreme fatigue, and a decrease in appetite following a diagnosis of streptococcal pharyngitis and tonsillitis 3 weeks prior. Diagnostic tests. Results of laboratory investigations revealed anemia, with a ferritin level of 1607 ng/mL (reference range, 11-307 ng/mL), a low transferrin level, a low iron level, and a hemoglobin of 8.6 g/dL (13.6 g/dL 2 months previously) [137].

Diffuse Large B Cell Lymphomas (DLBCL) encompasses a heterogeneous group of tumors that together constitute the commonest of all Non Hodgkin Lymphoma (NHL) [138]. Lymphomas are a group of malignant blood cell tumors that develop from lymphocytes representing 2.2% of all malignant neoplasms of the head and neck. Two main categories of lymphomas are Hodgkin's lymphoma and non-Hodgkin's lymphoma [139].

The Case Report: of A Psoriatic Arthritis Patient with Dactylitis & Enthesitis

Dactylitis is characterized by generalized swelling of a finger or toe. Though it is commonly seen, the literature on psoriatic dactylitis is scant, with the majority consisting of solitary case reports [140].

A 36-year-old woman presented at the Johns Hopkins Arthritis Center for a second opinion regarding a diagnosis of psoriatic arthritis (PsA).She had developed pain and stiffness in her hands, feet, knees, ankles, elbows and shoulders. She had mild plaque psoriasis of the scalp and base of the neck, as well as inverse psoriasis of the perianal and genital areas. She had psoriatic nail onycholysis, hyperkeratosis and pitting [141].

Conflict of Interest

The Author declare that the research work has been conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Vinish M, Cui W, Stafford E, et al. Dendritic cells modulate burn wound healing by enhancing early proliferation. Wound Repair Regen. 2016; 24: 6-13.
2. Jacques Mbongue, Dequina Nicholas, William Langridge, et al. The Role of Dendritic Cells in Tissue-Specific Autoimmunity. J Immunol Res. 2014; 2014: 857143.
3. Anguille S, Smits EL, Cools N, et al. Short-term cultured, interleukin-15 differentiated dendritic cells have potent immunostimulatory properties. J Transl Med. 2009; 7: 109.
4. Snehanshu Chowdhury, Anwesha Kar, Sandip Paul, et al. Intracellular Acetyl CoA Potentiates the Therapeutic Efficacy of Antitumor CD8+ T Cells. Cancer Res. 2022; 82: 2640-2655.
5. Ashraf M El T. An In-Depth Study of TCA cycles, OPA, S6K1, ATPase, TLR4, MHC-class-I, GCs, and IFNs Biosynthesis and Their Roles of Deficiency in Diabetes, Asthma, Cancer, etc. and the NAD Roles in their Activities. J Bio Sci. 2021; 3: 1194-1205.
6. Lloyd H Kasper, Anthony T Reder. Immunomodulatory activity of interferon-beta. Ann Clin Transl Neurol. 2014; 1: 622-631.

7. George J Siegel, Bernard W Agranoff, R Wayne Albers, et al. Molecular, Cellular and Medical Aspects. Basic Neurochemistry. 1999.
8. Nanako Nishiyama, Akira Shibuya, Chigusa Nakahashi-Oda. Interferon-β promotes the survival and function of induced regulatory T cells. Cytokine. 2022; 158: 156009.
9. Tucker W LeBien, Thomas F Tedder. B lymphocytes: how they develop and function. Blood. 2008; 112: 1570-1580.
10. David J Rawlings, Genita Metzler, Shaun W Jackson, et al. Altered B cell signalling in autoimmunity. Nature reviews immunology. 2017; 17: 421-436.
11. Jodi L Karnell, Roland Kolbeck, Rachel Ettinger, et al. Targeting the CD40-CD40L pathway in autoimmune diseases Humoral immunity and beyond. Advanced Drug Delivery Reviews. 2019; 141: 92-103.
12. Puddu P, Carollo M, Pietraforte I, et al. IL-2 induces expression and secretion of IFN-gamma in murine peritoneal macrophages. J Leukoc Biol. 2005; 78: 686-695.
13. Bosco MC, Espinoza-Delgado I, Schwabe M, et al. Regulation by interleukin-2 (IL-2) and interferon gamma of IL-2 receptor gamma chain gene expression in human monocytes. Blood. 1994; 83: 2995-3002.
14. Yu Jiang, Miao Tian, Wenlong Lin, et al. Protein Kinase Serine Threonine Kinase 24 Positively Regulates Interleukin 17 Induced Inflammation by Promoting IKK Complex Activation. Frontiers in Immunology. 2018; 9: 921.
15. Cousens LP, Orange JS, Biron CA. Endogenous IL-2 contributes to T cell expansion and IFN-gamma production during lymphocytic choriomeningitis virus infection. J Immunol. 1995; 155: 5690-5699.
16. Gunjan Kak, Mohsin Raza, Brijendra KT. Interferon-gamma IFN-γ Exploring its implications in infectious diseases. j Biomolecular Concepts. 2018; 9: 64-79.
17. Flávia Castro, Ana Patrícia Cardoso, Maria José Oliveira, et al. Interferon-Gamma at the Crossroads of Tumor Immune Surveillance or Evasion. Front Immunol. 2018; 9: 847.
18. Chaiwatanatorn K, Stamaratis G, Opeskin K, et al. Protein kinase C-beta II expression in diffuse large B-cell lymphoma predicts for inferior outcome of anthracycline-based chemotherapy with and without rituximab. Leuk Lymphoma. 2009; 50: 1666-1675.
19. Qunling Zhang, Juan Gu, Kai Xue, et al. Protein Kinase C Delta in Diffuse Large B-Cell Lymphoma Post-Rituximab Era Potential Prognostic Marker in Germinal Center B-Cell Lymphoma. Blood. 2017; 130: 2839.
20. Ashraf Marzouk El Tantawi. Toll-Like Receptor-4 Synthesis is Regulated by JNK Signaling, by Three Glucocorticoids Isoforms and by Three Interferons Isoforms, also its Advantages in Activities Depending on the Containment from Arg Proline and Hydrophobic Amino Acids in its Compositions. J Bio Sci. 2021; 3: 1125-1133.
21. Ashraf Marzouk El Tantawi. Inhibition in Proper Ser and In Plcγ2 Synthesis Are the Main for Causing Osteoarthritis, Diabetes and C-Lymphocytic Leukemia Diseases. Japan Journal of Clinical and Medical Research. 2022; 2: 1-10.
22. Abdel-latif E, Abdel-fattah S, Etman HA, et al. Synthesis and antitumor activity of some new pyrazolo 3,4-d pyrimidine and pyrazolo 3,4-b pyridine derivatives. Egyptian Journal of Basic and Applied Sciences. 2019; 3: 118-124.
23. Angel Garcia-Diaz, Daniel Sanghoon Shin, Blanca Homet Moreno, et al. Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression. Cell Rep. 2017; 19: 1189-1201.
24. Alexandr V Bazhin, Katharina von Ahn, Jasmin Fritz, et al. Interferon-α Up-Regulates the Expression of PD-L1 Molecules on Immune Cells Through STAT3 and p38 Signaling. 2018; 9: 2129.
25. Yonghee Kim, Jinhong Park, Yoon Kyung Choi. The Role of Astrocytes in the Central Nervous System Focused on BK Channel and Heme Oxygenase Metabolites. 2019; 8: 121.
26. Ricci G, Volpi L, Siciliano G, et al. Astrocyte neuron interactions in neurological disorders. J Biol Phys. 2009; 35: 317-336.
27. Zhang S, Shang D, Shi H, et al. Function of Astrocytes in Neuroprotection and Repair after Ischemic Stroke. 2021; 84: 426-434.
28. Wang FW, Jia DY, Du ZH, et al. Roles of activated astrocytes in bone marrow stromal cell proliferation and differentiation. Neuroscience. 2009; 160: 319-329.
29. Lauro Velazquez-Salinas, Antonio Verdugo-Rodriguez, Luis L Rodriguez, et al. The Role of Interleukin 6 During Viral Infections. Front Microbiol. 2019; 10: 1057.
30. Flávia Castro, Ana Patrícia Cardoso, Maria José Oliveira, et al. Interferon-Gamma at the Crossroads of Tumor Immune Surveillance or Evasion. Front Immunol. 2018; 9: 847.
31. Chaiwatanatorn K, Stamaratis G, Opeskin K, et al. Protein kinase C-beta II expression in diffuse large B-cell lymphoma predicts for inferior outcome of anthracycline-based chemotherapy with and without rituximab. Leuk Lymphoma. 2009; 50: 1666-1675.
32. Qunling Zhang, Juan Gu, Kai Xue, et al. Protein Kinase C Delta in Diffuse Large B-Cell Lymphoma Post-Rituximab Era Potential Prognostic Marker in Germinal Center B-Cell Lymphoma. Blood. 2017; 130: 2839.
33. Abdel-latif E, Abdel-fattah S, Gaffer HE, et al. Synthesis and antitumor activity of some new pyrazolo 3,4-dpyrimidine and pyrazolo 3,4-b pyridine derivatives. Egyptian Journal of Basic and Applied Sciences. 2019; 3: 118-124.
34. Elke Wiesemann, Daniela Sönmez, Fedor Heidenreich, et al. Interferon-β increases the stimulatory capacity of monocyte-derived dendritic cells to induce IL-13, IL-5 and IL-10 in autologous T cells. J Neuroimmunology. 2022; 123: 160-169.

35. Yassir Hussien, Dmitry Yarilin, Beini Xiao, et al. Interferon-beta induces the development of type 2 dendritic cells. Cytokine. 2001; 13: 264-271.

36. Jonathan P Huber, J David Farrar. Regulation of effector and memory T-cell functions by type I interferon. Immunology. 2011; 132: 466-474.

37. Mélanie Giroux, Manuel Schmidt, Albert Descoteaux. IFN-γ-Induced MHC Class II Expression: Transactivation of Class II Transactivator Promoter IV by IFN Regulatory Factor-1 is Regulated by Protein Kinase C-α. J Immunol. 2003; 171: 4187-4194.

38. Angel Garcia-Diaz, Daniel Sanghoon Shin, Antoni Ribas, et al. Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression. Cell Rep. 2017; 19: 1189-1201.

39. Alexandr V Bazhin, Katharina von Ahn, Svetlana Karakhanova, et al. Interferon-α Up-Regulates the Expression of PD-L1 Molecules on Immune Cells Through STAT3 and p38 Signaling. Front Immunol. 2018; 9: 2129.

40. Abiko K, Matsumura N, Hamanishi J, et al. IFN-γ from lymphocytes induces PD-L1 expression and promotes progression of ovarian cancer. Br J Cancer. 2015; 112: 1501-1509.

41. Rafael TOBENNA, Saburo HORIKAWA, Victor CALVO, et al. Interleukin-2 induces ??-S-adenosyl-L-methionine synthetase gene expression during T-lymphocyte activation. Biochem J. 1996; 319: 929-933.

42. Stanková J, Gagnon N, Rola-Pleszczynski M. Leukotriene B4 augments interleukin-2 receptor-beta IL-2R beta expression and IL-2R beta-mediated cytotoxic response in human peripheral blood lymphocytes. Immunology. 1992; 76: 258-263.

43. HideruObinata, TakehikoYokomizo, TakaoShimizu, et al. Glucocorticoids up-regulate leukotriene B-4 receptor-1 expression during neutrophilic differentiation of HL-60 cells. Biochemical and Biophysical Research Communications. 2003; 309: 114-119.

44. Jayashree A Chandrasekharan, Neelam Sharma-Walia. Arachidonic Acid Derived Lipid Mediators Influence Kaposi's Sarcoma-Associated Herpesvirus Infection and Pathogenesis. Front Microbiol. 2019; 10: 358.

45. Undurti N Das. Syntaxin interacts with arachidonic acid to prevent diabetes mellitus. Lipids in Health and Disease. 2022; 21: 73.

46. Steven Mathis, Venkatakrishna R Jala, Bodduluri Haribabu. Role of Leukotriene B4 Receptors in Rheumatoid Arthritis. Autoimmun Rev. 2007; 7: 12-17.

47. Ivan Zanoni, Renato Ostuni, Lorri R Marek, et al. CD14 Controls the LPS-Induced Endocytosis of Toll-like Receptor 4. Cell. 2011; 147: P868-880.

48. Rubén López-Nicolás, Senena Corbalán-García, Juan C Gómez-Fernández, et al. Molecular Mechanisms of PKC?? Localization and Activation by Arachidonic Acid. The C2 Domain also Plays a Role. Journal of Molecular Biology. 2006; 357: 1105-1120.

49. Gabriel L Galea, Lee B Meakin, Joanna S Price. Protein Kinase Cα PKCα Regulates Bone Architecture and Osteoblast Activity. J Biol Chem. 2014; 289: 25509-25522.

50. Jeffery J Ford, Lee-Chuan C, John C Lee, et al. Protein Kinase D1 Is Essential for Bone Acquisition during Pubertal Growth. Endocrinology. 2013; 154: 4182-4191.

51. Liana Tascau, Thomas Gardner, Francis Y Lee, et al. Activation of Protein Kinase A in Mature Osteoblasts Promotes a Major Bone Anabolic Response. Endocrinology. 2016; 157: 112-126.

52. Kay L Medina, Andreas Strasser, Paul W Kincade. Estrogen influences the differentiation, proliferation and survival of early B-lineage precursors. Blood. 2000; 95: 2059-2067.

53. Guanjun Dong, Hongye Fan, Yonghong Yang, et al. 17β-Estradiol enhances the activation of IFN-α signaling in B cells by down-regulating the expression of let-7e-5p, miR-98-5p and miR-145a-5p that target IKKε. Biochimica et Biophysica Acta BBA-Molecular Basis of Disease. 2015; 1852: 1585-1598.

54. Yibing Fu, Li Li, Xiaowen Liu, et al. Estrogen promotes B cell activation *in vitro* through down-regulating CD80 molecule expression. Gynecological Endocrinology. 2011; 17: 593-596.

55. Medina KL, Kincade PW. 17-β estradiol directly influences B lymphocyte precursors in stromal cell free cultures. FASEB Journal. 1998; 12: A1071.

56. Margaret S Bynoe, Christine M Grimaldi, Betty Diamond. Estrogen up-regulates Bcl-2 and blocks tolerance induction of naïve B cells. Biological sciences. 2000; 97: 2703-2708.

57. Karpuzoglu-Sahin E, Hissong BD, Ansar Ahmed S. Interferon-γ levels are upregulated by 17-β-estradiol and diethylstilbestrol. Journal of Reproductive Immunology. 2001; 52: 113-127.

58. Ram P Singh, Bevra H Hahn, David Bischoff. Type 1 Interferon in Pathologies, Autoimmune Diseases, and Chronic Viral Infections Interferon Genes Are Influenced by 17β-Estradiol in SLE. Front Immunol. 2021; 12: 725325.

59. Federica Sallusto, Antonio Lanzavecchia. The instructive role of dendritic cells on T-cell responses. Arthritis Res. 2002; 4: S127-S132.

60. Authors Zhang M, Tan X, Huang J, et al. Association between two interleukin-2 gene polymorphisms and cancer susceptibility: a meta-analysis. OncoTargets and Therapy. 2016; 9: 2181-2192.

61. Lorenzo Mortara, Enrica Balza, Antonino Bruno, et al. Anti-cancer Therapies Employing IL-2 Cytokine Tumor Targeting: Contribution of Innate, Adaptive and Immunosuppressive Cells in the Anti-tumor Efficacy. Front Immunol. 2018; 9: 2905.

62. Jonathan P Huber, David Farrar J. Regulation of effector and memory T-cell functions by type I interferon. Immunology. 2011; 132: 466-474.

63. Dahong Yao, Chenyang Li, Muhammad Shahid Riaz Rajoka, et al. P21-Activated Kinase 1: Emerging biological functions and potential therapeutic targets in Cancer. Theranostics. 2020; 10: 9741-9766.

64. Guoping Fu, Yuhong Chen, Renren Wen, et al. Phospholipase Cγ2 plays a role in T-cell receptor signal transduction and T-cell selection. J Immunol. 2012; 189: 2326-2332.

65. Reschner A, Hubert P, Jacobs N, et al. Innate lymphocyte and dendritic cell cross-talk: a key factor in the regulation of the immune response. Clin Exp Immunol. 2008; 152: 219-226.

66. Trinite B, Chauvin C, Peche H, et al. Immature CD4- CD103+ rat dendritic cells induce rapid caspase-independent apoptosis-like cell death in various tumor and nontumor cells and phagocytose their victims. J Immunol. 2005; 175: 2408-2417.

67. Watari K, Shibata T, Fujita H, et al. NDRG1 activates VEGF-A-induced angiogenesis through PLCγ1/ERK signaling in mouse vascular endothelial cells. Commun Biol. 2020; 3: 107.

68. Jacob T Jackson, Elisabeth Mulazzani, Stephen L Nutt, et al. The role of PLCγ2 in immunological disorders, cancer and neurodegeneration. JBC. 2021; 297: 100905.

69. Chang Liu, Yuan He, Xiaobing Xu, et al. Phospholipase Cγ Signaling in Bone Marrow Stem Cell and Relevant Natural Compounds Therapy. Curr Stem Cell Res Ther. 2020; 15: 579-587.

70. Georgios Kallifatidis, Kenza Mamouni, Bal L Lokeshwar. The Role of β-Arrestins in Regulating Stem Cell Phenotypes in Normal and Tumorigenic Cells. J Mol Sci. 2020; 21: 9310.

71. Deepika Sharma, Narayanan Parameswaran. Multifaceted role of β-arrestins in inflammation and disease. Genes Immunity. 2015; 16: 499-513.

72. Robert H Oakley, Javier Revollo, John A Cidlowski. Glucocorticoids regulate arrestin gene expression and redirect the signaling profile of G protein-coupled receptors. National Academy of Sciences. 2012; 109: 17591-1796.

73. Väänänen HK, Härkönen PL. Estrogen and bone metabolism. Maturitas. 1996; 23: S65-69.

74. Okoro EU. TNFα-Induced LDL Cholesterol Accumulation Involve Elevated LDLR Cell Surface Levels and SR-B1 Downregulation in Human Arterial Endothelial Cells. Int J Mol Sci. 2021; 22: 6236.

75. Hua H, Zhang H, Kong Q, et al. Mechanisms for estrogen receptor expression in human cancer. Exp Hematol Oncol. 2018; 7: 24.

76. Adena E Rosenblatt, Maria Ines Garcia, Leah Lyons, et al. Inhibition of the Rho GTPase, Rac1, decreases estrogen receptor levels and is a novel therapeutic strategy in breast cancer. Endocr Relat Cancer. 2011; 18: 207-219.

77. Juliane Obst, Hazel L Hall-Roberts, Thomas B Smith, et al. PLCγ2 regulates TREM2 signalling and integrin-mediated adhesion and migration of human iPSC-derived macrophages. Scientific Reports. 2021; 11: 19842.

78. Shuying Chen, Huan Li, Shouyun Li, et al. Rac1 GTPase Promotes Interaction of Hematopoietic Stem/Progenitor Cell with Niche and Participates in Leukemia Initiation and Maintenance in Mouse. Stem Cells. 2016; 34: 1730-1741.

79. Maria T Grinder, Bylgja Hilmarsdottir, Siver A Moestue, et al. Glutamine to proline conversion is associated with response to glutaminase inhibition in breast cancer. Breast Cancer Res. 2019; 21: 61.

80. Wei Liu, Anne Le, Chad Hancock, et al. Reprogramming of proline and glutamine metabolism contributes to the proliferative and metabolic. Biological Sciences. 2012; 109: 8983-8988.

81. Madeleine L Craze, Hayley Cheung, Andrew R Green, et al. MYC regulation of glutamine-proline regulatory axis is key in luminal B breast cancer. Br J Cancer. 2018; 118: 258-265.

82. Helen HW Chen, Lynn G Feun, Niramol Savaraj, et al. Targeting the Proline-Glutamine-Asparagine-Arginine Metabolic Axis in Amino Acid Starvation Cancer Therapy. Pharmaceuticals. 2021; 14: 72.

83. Tao Zhou, Yuqing Yang, Liang Xie, et al. Glutamine Metabolism Is Essential for Stemness of Bone Marrow Mesenchymal Stem Cells and Bone Homeostasis. Stem Cells Int. 2019; 2019: 8928934.

84. Steve Stegen, Peter Carmeliet, Geert Carmeliet, et al. Glutamine Metabolism in Osteoprogenitors Is Required for Bone Mass Accrual and PTH-Induced Bone Anabolism in Male Mice. JBMR. 2020; 36: 604-616.

85. Meltem Weger, Benjamin D Weger, Nils Krone, et al. Glucocorticoid deficiency causes transcriptional and post-transcriptional reprogramming of glutamine metabolism. E BioMedicine. 2018; 36: 376-389.

86. Tim D Werry, Karen J Gregory, Patrick M Sexton, et al. Characterization of serotonin 5-HT2C receptor signaling to extracellular signal-regulated kinases 1 and 2. Journal of Neurochemistry. 2005; 93: 1603-1615.

87. Jue Wang, Roh-Yu Shen, Samir Haj-Dahmane. Endocannabinoids mediate the glucocorticoid-induced inhibition of excitatory synaptic transmission to dorsal raphe serotonin neurons. J Physiol. 2012; 590: 5795-5808.

88. Giulia Sbrini, Paola Brivio, Francesca Calabrese, et al. The Absence of Serotonin in the Brain Alters Acute Stress Responsiveness by Interfering With the Genomic Function of the Glucocorticoid Receptors. Front Cell Neurosci. 2020; 14: 128.

89. Elisabeth Cassier, Nathalie Gallay, Thomas Bourquard, et al. Phosphorylation of β-arrestin2 at Thr383 by MEK underlies β-arrestin-dependent activation of Erk1/2 by GPCRs. eLife. 2017; 6: e23777.

90. Iwabayashi M, Taniyama Y, Sanada F, et al. Role of serotonin in angiogenesis: induction of angiogenesis by sarpogrelate via endothelial 5-HT1B/Akt/eNOS pathway in diabetic mice. Atherosclerosis. 2012; 220: 337-342.

91. Kotaro Sugimoto, Naoki Ichikawa-Tomikawa, Hideki Chiba, et al. Serotonin/5-HT1A Signaling in the Neurovascular Unit Regulates Endothelial CLDN5 Expression. J Mol Sci. 2021; 22: 254.
92. Minjie Wan, Lili Ding, Dong Wang, et al. Serotonin: A Potent Immune Cell Modulator in Autoimmune Diseases. Front Immunol. 2020; 11: 186.
93. Marina Rieder, Nadine Gauchel, Daniel Duerschmied, et al. Serotonin: a platelet hormone modulating cardiovascular disease. J Thromb Thrombolysis. 2021; 52: 42-47.
94. Kjell Vikenes, Mikael Farstad, Jan Erik Nordrehaug. Serotonin Is Associated with Coronary Artery Disease and Cardiac Events. Circulation. 1999; 100: 483-489.
95. Ragu Varman D, Jayanthi LD, Ramamoorthy S. Glycogen synthase kinase-3ß supports serotonin transporter function and trafficking in a phosphorylation-dependent manner. J Neurochem. 2021; 156: 445-464.
96. Semont A, Fache M, Ouafik L, et al. Effect of serotonin inhibition on glucocorticoid and mineralocorticoid expression in various brain structures. Neuroendocrinology. 1999; 69: 121-128.
97. Surojit Karmakar, Girdhari Lal. Role of serotonin receptor signaling in cancer cells and anti-tumor immunity. Theranostics. 2021; 11: 5296-5312.
98. Ashraf Marzouk El Tantawi. Rac1 Rich Proline are OPA1 Flux Influencer for PLCs and IFNs Synthesis where Immune and Toxicity Due Deficiency in Synthetase and in Proline Synthesis. Jap J Clin Med Res. 2022; 2: 2-14.
99. Marcel André Schneider, Laura Heeb, Michal Mateusz Beffinger, et al. Attenuation of peripheral serotonin inhibits tumor growth and enhances immune checkpoint block-ade therapy in murine tumor models. Sci Transl Med. 2021; 13: eabc8188.
100. Shrikant S Kolan, Tommy Lidström, Mattias NE Forsell, et al. Growth-inhibition of cell lines derived from B cell lymphomas through antagonism of serotonin receptor signalling. Scientific reports. 2019; 9: 4276.
101. Nadine Herr, Christoph Bode, Daniel Duerschmied. The Effects of Serotonin in Immune Cells. Front Cardiovasc Med. 2017; 4: 48.
102. Yasmine Chabbi-Achengli, Tereza Coman, Corinne Collet, et al. Serotonin Is Involved in Autoimmune Arthritis through Th17 Immunity and Bone Resorption. 2016; 186; 927-937.
103. Adamantios Serafeim, Gillian Grafton, Anita Chamba, et al. 5-Hydroxytryptamine drives apoptosis in biopsylike Burkitt lymphoma cells: reversal by selective serotonin reuptake inhibitors. Blood. 2002; 99: 2545-2553.
104. Lanzillotta M, Della-Torre E, Milani R, et al. Increase of circulating memory B cells after glucocorticoid-induced remission identifies patients at risk of IgG4-related disease relapse. Arthritis Res Ther. 2018; 20: 222.
105. Juliana de Castro Kroner, Kristin Knoke, David M Kofler, et al. Glucocorticoids promote intrinsic human TH17 differentiation. J ALLERGY CLIN IMMUNOL. 2018; 142: 1669-1673.
106. Georgios Kallifatidis, Kenza Mamouni, Bal L Lokeshwar, et al. The Role of β-Arrestins in Regulating Stem Cell Phenotypes in Normal and Tumorigenic Cells. Int J Mol Sci. 2020; 21: 9310.
107. Wu CY, Sarfati M, Heusser C, et al. Glucocorticoids increase the synthesis of immunoglobulin E by interleukin 4-stimulated human lymphocytes. JCI. 1991; 87: 870-877.
108. Lu Y, Liu F, Tong G, et al. Clinical evidence of an interferon-glucocorticoid therapeutic synergy in COVID-19. Sig Transduct Target Ther. 2021; 6: 107.
109. Liping Wang, Ting Xu, Haitao Niu, et al. Immunosuppression Induced by Glutamine Deprivation Occurs via Activating PD-L1 Transcription in Bladder Cancer. Front Mol Biosci. 2021; 8: 687305.
110. Ronan Thibault, Susan Welch, Nelly Mauras, et al. Corticosteroids increase glutamine utilization in human splanchnic bed. Am J Physiol Gastrointest Liver Physiol. 2008; 294: G548-553.
111. Meltem Weger, Benjamin D Weger, Benjamin Görling, et al. Glucocorticoid deficiency causes transcriptional and post-transcriptional reprogramming of glutamine metabolism. E BioMedicine. 2018; 36: 376-389.
112. Ali Mujtaba Shah, Zhisheng Wang, Jian MA. Glutamine Metabolism and Its Role in Immunity a Comprehensive. Animals. 2020; 10: 326.
113. Guanhua Li, Lu Liu, Zhihua Yin, et al. Glutamine metabolism is essential for the production of IL-17A in γδ T cells and skin inflammation. Tissue and Cell. 2021; 71: 101569.
114. José João Name, Andrea Rodrigues Vasconcelos, Wagner José Fávaro, et al. Vitamin D, zinc and glutamine: Synergistic action with OncoTherad immunomodulator in interferon signaling and COVID-19. Int J Mol Med. 2021; 47: 11.
115. Mario Menk, Jan Adriaan Graw, Clarissa von Haefen, et al. Stimulation of the Angiotensin II AT2 Receptor is Anti-inflammatory in Human Lipopolysaccharide-Activated Monocytic Cells. Inflammation. 2015; 38: 1690-1699.
116. Preenie de S. Senanayake, Judy Drazba, Karen Shadrach, et al. Angiotensin II and Its Receptor Subtypes in the Human Retina. Investigative Ophthalmology Visual Science. 2007; 48: 3301-3311.
117. Valentina Salvi, William Vermi, Veronica Gianello, et al. Dendritic cell-derived VEGF-A plays a role in inflammatory angiogenesis of human secondary lymphoid organs and is driven by the coordinated activation of multiple transcription factors. Oncotarget. 2016; 7: 39256-39269.
118. Asma Ahmed, Christian Schmidt, Thomas Brunner, et al. Extra-Adrenal Glucocorticoid Synthesis in the Intestinal Mucosa: Between Immune Homeostasis and Immune Escape. Front Immunol. 2019; 10: 1438.

119. Ashraf Marzouk El Tantawi. Inhibition in Proper Ser and In Plcγ2 Synthesis Are the Main for Causing Osteoarthritis, Diabetes and C-Lymphocytic Leukemia Diseases. Japan Journal of Clinical Medical Research. 2022; 2: 127.

120. Xiaoyu Hu, Wai-Ping Li, Charis Meng, et al. Inhibition of IFN-γ Signaling by Glucocorticoids. J Immunol. 2003; 170: 4833-4839.

121. Yu-Min Huang-Link, Yassir Hussien, Dmitry Yarilin, et al. Interferon-beta induces the development of type 2 dendritic cells. Cytokine. 2001; 13: 264-271.

122. Jonathan P Huber, J David Farrar. Regulation of effector and memory T-cell functions by type I interferon. Immunology. 2011; 132: 466-474.

123. Angela J Fahey, Adrian Robins R, Karin B Kindle, et al. Effects of glucocorticoids on STAT4 activation in human T cells are stimulus-dependent. Journal of Leukocyte Biology. 2006; 80: 133-144.

124. Yi-Hsuan Chang, Chia-Lin Weng, Kuo-I Lin. O-GlcNAcylation and its role in the immune system. J Biomed Sci. 2020; 27: 57.

125. Mélanie Giroux, Manuel Schmidt. Albert Descoteaux. IFN-γ-Induced MHC Class II Expression: Transactivation of Class II Transactivator Promoter IV by IFN Regulatory Factor-1 is Regulated by Protein Kinase C-α. J Immunol. 2003; 171: 4187-4194.

126. Ashraf Marzouk El Tantawi. Rac1 Rich Proline are OPA1 Flux Influencer for PLCs, GCs, and IFNs Synthesis where Immune and Toxicity Due Deficiency in Synthetase and in Proline Synthesis. Japan Journal of Clinical Medical Research. 2022; 2: 132.

127. Renren Wen, Shiann-Tarng Jou, Yuhong Chen, et al. Phospholipase Cγ2 Is Essential for Specific Functions of FcεR and FcγR. J Immunol. 2002; 169: 6743-6752.

128. Jacob T Jackson, Seth L Masters, Stephen L Nutt, et al. The role of PLCγ2 in immunological disorders, cancer and neurodegeneration. JBC. 2021; 297: 100905.

129. Chang Liu, Yuan He, Xiaobing Xu, et al. Phospholipase Cγ Signaling in Bone Marrow Stem Cell and Relevant Natural Compounds Therapy. Curr Stem Cell Res Ther. 2020; 15: 579-587.

130. Okoro EU. TNFα-Induced LDL Cholesterol Accumulation Involve Elevated LDLR Cell Surface Levels and SR-B1 Downregulation in Human Arterial Endothelial Cells. Int J Mol Sci. 2021; 22: 6236.

131. Hua H, Zhang H, Kong Q, et al. Mechanisms for estrogen receptor expression in human cancer. Exp Hematol Oncol. 2018; 7: 24.

132. Adena E Rosenblatt, Maria Ines Garcia, Leah Lyons, et al. Inhibition of the Rho GTPase Rac1 decreases estrogen receptor levels and is a novel therapeutic strategy in breast cancer. Endocr Relat Cancer. 2011; 18: 207-219.

133. Lorenza Magno, Tom D Bunney, Emma Mead, et al. TREM2/PLCγ2 signalling in immune cells: function, structural insight and potential therapeutic modulation. Molecular Neurodegeneration. 2021; 16: 22.

134. Kurisu K, Zheng Z, Kim JY, et al. Triggering receptor expressed on myeloid cells-2 expression in the brain is required for maximal phagocytic activity and improved neurological outcomes following experimental stroke. J Cereb Blood Flow Metab. 2019; 39: 1906-1918.

135. Juliane Obst, Hazel L Hall-Roberts, Emma Mead, et al. PLCγ2 regulates TREM2 signalling and integrin-mediated adhesion and migration of human iPSC-derived macrophages. Scientific reports. 2021; 11: 19842.

136. Naoya Kawakita, Hiroaki Toba, Akira Tangoku, et al. Bronchioalveolar stem cells derived from mouse-induced pluripotent stem cells promote airway epithelium regeneration. Stem Cell Res Ther. 2020; 11: 430.

137. Lincey Alexida, Pranav Patel, Palos Heights, et al. Interactive Case Report: Diffuse Large B-Cell Lymphoma. Citation Consultant. 2017; 57: 506-507.

138. Medikonda Suresh Kumar, Ashalata Gannepalli, Konda Amarnath, et al. Diffuse Large B-Cell Lymphoma of Maxilla0-A Case Report of Late Relapse. J Clin Diagn Res. 2016; 10: ZD12-ZD14.

139. Ramandeep Singh Narang, Adesh Singh Manchanda, Harshveer Kaur. Evaluation of a case of diffuse large B-cell lymphoma. J Oral Maxillofac Pathol. 2019; 23: 7-11.

140. Manas Pustake, Grant Medical College, Tushar Ashokrao Vidhale. Psoriatic Arthritis With Dactylitis: A Case Report and Concise Review of Treatment Options. Cureus. 2021; 13: e16966.

141. Samantha C Shapiro, Jemima Albayda, Ana-Maria Orbai. Case Report: A Psoriatic Arthritis Patient with Dactylitis and Enthesitis. The Rheumatologist. 2018.