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Cell Differentiation Agent Formulations to Win the War on Cancer

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ABSTRACT

Solution of cancer was obviously an important national interest for President Nixon to declare 'War on Cancer" in 1971. Health professionals failed the challenge to put cancer away during the 5 years of intensive presidential support and in the following 46 years of exclusive medical support allocated to cancer. Cancer stem cells (CSCs) stood in the way to deny the success of cytotoxic agents, the choice of cancer establishments in the past, to put cancer away. Cancer arises due to wound not healing properly. Consequently, the process of wound healing is the most appropriate modality of cancer therapy. Cytotoxic agents creating wounds are apparently contra-indication on cancer therapy. Cytotoxic agents are, however, the most effective agents to eliminate the most outstanding feature of cancer, namely the perpetual replication of cancer cells (CCs). A critical mechanism of wound healing is the induction of terminal differentiation of progenitor stem cells (PSCs) which are the precursors of CSCs.

Wound healing metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs) are required to direct the terminal differentiation of PSCs to heal the wound. Cell differentiation agent (CDA) formulations are preparations of wound healing metabolites most fit to take out PSCs and CSCs by directing these cells to undergo terminal differentiation, which are protected by drug resistance and anti-apoptosis mechanisms, thus unresponsive to cytotoxic agents. CDAs alone or in combination with cytotoxic agents become perfect drugs to take out both CCs and CSCs, and to restore the functionality of chemo-surveillance necessary to win the war on cancer.

Keywords

Cancer stem cells, Chemo-surveillance, Cell differentiation agents, Progenitor stem cells, Wound healing.

Introduction

President Nixon declared "War on Cancer" in 1971, obviously based on his belief that winning the war on cancer was a monumental national interest [1]. Health professionals, however, failed to meet the challenge to solve cancer during the five years of intensive presidential support. A presidential project carries a five years limit to conclude. War on Cancer was the only presidential project that failed to achieve the goal. Among the three presidential projects, nuclear physicists achieved the goal of Manhattan project, and rocket engineers achieved the goal of Apollo project within 5 years limit. Health professionals failed the relatively easy presidential project among the three, using 50 years. President Nixon was right to recognize solution of cancer as a monumental national interest to commit national resources to solve the problem. Cancer establishments were unfortunately trapped in the unwinnable modality of cytotoxic agents. A shift of strategies is necessary to win the war on cancer. We have proposed that cancer arose as a consequence of wound not healing properly [2]. The concept of cancer as a non-healing wound was introduced by Virchow in 19th century [3], and was again brought up by Harold and Dvorak in 1986 [4]. We provided the important details including abnormal methylation enzymes to block differentiation, DIs and DHIs as wound healing metabolites which are also the basis of chemo-surveillance as a natural mechanism to ensure perfection of wound healing, and to avoid the evolution of CSCs from PSCs.

Acute wounds are always healed naturally without having to put up any effort. Winning the War on Cancer must have to put up some efforts, efforts such as CDA formulations that include wound healing metabolites and anti-cachexia agents.

Commentaries and Discussions

Synopsis

Perpetual cell replication is the hallmark of cancer. There are multiple issues involved to make CCs to replicate perpetually: membrane hyperpermeability caused by tumor necrosis factor (TNF) [5]; breakdown of chemo-surveillance due to TNF [6]; abnormal methylation enzymes (MEs) to block terminal differentiation [7-9]; evolution of CSCs from PSCs by silencing of TET-1 enzyme [10]; and activation of oncogenes and/or inactivation of suppressor genes. A perfect cancer drug must be able to take out both CCs and CSCs, and to restore the functionality of chemo-surveillance [11].

CSCs Evolves from PSCs as a Consequence of Wound Not Healing Properly Due to Breakdown of Chemo-surveillance

Myelodysplastic syndrome (MDS) is a classic disease to illustrate the evolution of cancer due to wound not healing properly. Chronic wounds caused by injuries, toxic chemicals including carcinogens, or infections trigger immunological responses to produce inflammatorycytokines. TNF among such cytokines produced is most closely related to the development of cancer [12]. TNF is also named cachectin after its effect to cause cachexia symptom [13,14]. A characteristic manifestation of cachexia is the excessive urinary excretion of low molecular weight metabolites which include essential components of chemo-surveillance to ensure perfection of wound healing. Chemo-surveillance was a natural defense mechanism brought up by Ming C. Liau to ensure wound healing as the primary objective, and to avoid cancer and to cure cancer as the secondary consequence [6,15,16]. The proposal of chemo-surveillance was based on the observation that healthy people were able to maintain a steady level of wound healing metabolites active as DIs and DHIs, whereas cancer patients tended to show deficiency of such metabolites due to display of cachexia symptom. Without sufficient wound healing metabolites, PSCs cannot be efficiently induced to undergo terminal differentiation, thus allowing PSCs to evolve into CSCs, and then to progress to faster growing CCs. Wound healing requires the proliferation and the terminal differentiation of PSCs. Proliferation of PSCs always runs a risk for PSCs to evolve into CSCs. It takes a single hit to silence TET-1 enzyme to convert PSCs into CSCs, which is a task easily accomplished by PSCs equipped with abnormally active MEs like CCs [7]. Cells with abnormal MEs cannot undergo terminal differentiation. Wound healing metabolites are required to destabilize abnormal MEs for the terminal differentiation of PSCs to take place in order to heal the wound. Collapse of chemo-surveillance is very critical to the development of cancer. MDS is a disease at the stage of CSCs which can progress to acute myeloid leukemia by activation of oncogenes and/or inactivation of suppressor genes.

CSCs Stood in the Way to Deny the Success of Cytotoxic Agents to Put Cancer Away

Perpetual cell replication is the most outstanding feature of cancer. Naturally, cytotoxic agents were the choice of cancer establishments to combat cancer in the past. Cytotoxic agents are, however, inappropriate for the therapy of cancer which arises as a consequence of wound not healing properly as above described. They create more wounds to aggravate the already bad situation. Their inability to eradicate CSCs due to the protection of these cells with drug resistance and anti-apoptosis mechanisms [10], and their contribution to further damage the functionality of chemo-surveillance lay the ground for inevitable recurrence and fatality. So even the few lucky patients to achieve complete remission are eventually succumbed to recurrence [15,16]. Perhaps only the early stage cancer patients whose functionality of chemo-surveillance is not fatally damaged in the process can manage to recover the function to subdue the surviving CSCs to stay alive [17,18]. Implementation of drugs capable of eradication of CSCs is essential to prevent killing of cancer patients by cytotoxic agents [19]. CDA formulations are ideal drugs to come to the rescue of cytotoxic agents to take out CSCs [20-22]. Apparently, cytotoxic agents are the best to take out CCs. A supplement with CDA formulations to eradicate CSCs and to restore the functionality of chemo-surveillance can be a perfect combination to win the war on cancer.

CDA-2 as A Perfect Cancer Drug

CDA-2 was a cancer drug developed by Ming C. Liau [23]. It is a preparation of wound healing metabolites purified from urine. The active components are mostly DIs and DHIs. Arachidonic acid is the major DI [22,24], and pregnenolone and uroerythrin are the major DHIs [22,25].

Phenylacetylglutamine is a major chemical component which is effective as an anti-cachexia chemical to stop excessive urinary excretion of low molecular weight metabolites [6]. So CDA-2 has all necessary ingredients to resolve issues important to the development of cancer including the issues of gene abnormalities. By pushing CCs out of cell cycle to undergo terminal differentiation, CDA-2 can also put to rest gene abnormalities. Afterall, oncogenes and suppressor genes are cell cycle regulatory genes. They have important roles to play when cells are in cell cycle replicating. But if replicating cells exit cell cycle to undergo terminal differentiation, they have no roles to play. Therefore, induction of terminal differentiation is an easy solution of gene abnormalities which are otherwise very difficult to solve. Cytotoxic agents can also accomplish the goal of solving gene abnormalities and the blockade of differentiation. But cytotoxic agents cannot save patients' lives [19].

CDA-2 has been approved by the Chinese FDA for the therapy of cancer in 2004 [26] and for the therapy of MDS in 2017 [27]. Apparently, CDA-2 is a drug of choice for the therapy of MDS as it has slightly better therapeutical efficacy based on cytological evaluation and a markedly better therapeutical efficacy based on hematological evaluation in comparison to Vidaza and Decitabine, the two drugs approved by US FDA for the therapy of MDS. Better yet, CDA-2 is totally devoid of serious adverse effects, whereas Vidaza and Decitabine are proven carcinogens [28,29] and quite toxic to DNA [30-32]. MDS is a disease attributable entirely to CSCs [33]. Therefore, CDA-2 is a clinically proven drug to show effectiveness against CSCs.

Cancer therapies mediated through DIs and DHIs yield excellent results. All-trans retinoic acid, a DI, is the standard care of acute promyelocytic leukemia. Imatinib mesylate, a DHI, is the standard care of chronic myeloid leukemia. Phenylbutyrate, a moderately active DHI, is quite effective against untreatable malignant brain tumors [34,35]. Untreatable cancers are usually enriched with CSCs [10]. Cancer therapies mediated through DIs and DHIs are indeed quite remarkable. The only disadvantage is the inability to cause solid tumor to shrink. Therapeutic endpoint must be set differently from that for the evaluation of cytotoxic agents. Disappearance of cancer markers or circulating CCs and CSCs may be a valid endpoint for the evaluation of CDA formulations on cancer therapy. We have discovered many excellent DIs and DHIs not normally functioning as natural wound healing metabolites [36,37], which can be used to make effective CDA formulations.

Conclusion

Cancer is a disease contributed by multiple factors. Consequently, it takes multiple agents to achieve effective therapy. Cytotoxic agents were the choice of cancer establishments for the obvious reason they were the best to solve the problem of perpetual cell replication, the most outstanding feature of cancer. But CSCs stood in the way to deny the success of cytotoxic agents to win the war on cancer. CDA formulations are best suited to eradicate CSCs and to restore the functionality of chemo-surveillance. CDA formulations alone or in combination with cytotoxic agents may be the most promising drugs to win the war on cancer.

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