

Importance of the Frequency at Using Immunomodulatory Therapies with Evidence Based and Standardized Plant Biomodulators

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ABSTRACT

Many years ago, a great deal of research was carried out to improve the suppressed activity of innate immune system in cancer patients using various immunomodulators originated from microorganisms or plants. However, more than 30 years ago these investigations were stopped since their repeated applications often led to a tolerance which could not be explained at the level of science at that time and in spite of a great amount of data, the curative role of innate system was poorly understood. Today, growing evidence suggests that the adaptive cytotoxic T cells have rather prophylactic effects working more proficiently in the early phases of tumor development, whereas the innate cellular system acts more curatively in parallel with disease progression. It's now also known, that tumor-induced dysregulation of the innate immune system leads to a decreased function of type-1 effector cells and a predominance of type-2 cells, promoting the development of tumors. In this review article a number of results originating from old publications are discussed and presented again in order to interpret them according to our current knowledges which appear to be helpful for more correct application of standardized and evidence based immunomodulators (SEIM) from plant or microbes. Conclusions: 1.) Since the chemistry is not able to produce appropriate structures of Pathogen Associated Molecular Pattern (PAMP) molecules, we need PAMP containing SEIM from plants and microbes which can activate the type-1 phagocytic cells by binding their Pattern Recognition / Toll Like Receptors (RCC/TLR) on their cell membrane. 2.) PAMP molecules have a direct effect only on RCC/TLR molecules of phagocytes and only thereafter with a minimum time delay of 24 hours are the regulatory cascade mechanisms activated which can increase the function of the for the curative tumor defense important MHC-I unrestricted effectors (such as NK, $\gamma\delta$ T and type-1 NKT cells). 3.) A permanent activation of phagocytic cells can result in a decrease in MHC-I unrestricted immune function, which may explain the tolerance observed often during continuous SEIM treatments. 4.) Since short-term activations of type-1 phagocytic cells causes more antitumor benefit, on the base of kinetic investigations a necessity to insert of 72h therapy-free intervals during SEIM therapy must be taken into consideration.

Keywords

Immunomodulation, Innate immune system, Phagocytic activity, NK-cells.

Introduction

Since a very long time improving the immune system in cancer therapy became a fashionable slogan. Countless so-called immune boosters have flooded the market, most of which have little clue as to which part of immune system they are supposed to be supporting. Parallely, the tumor research has focused on the high

specific cytotoxic T cells which are able, as a highest developed member of the adaptive system, to recognize and remove tumor cells if tumor antigens are presented by MHC-I antigens. However, with the progression of tumor (very often at the time of its first diagnosis) tumor cells lose their MHC-I antigens and thereafter parallel to their hypo-responsiveness to T lymphocytes, there is a growing sensitivity to the MHC-I unrestricted effectors which belong to innate immune system. Therefore, we can rightly assume that adoptive T cells are much important in prophylaxis than in healing since during tumor progression, effector cells of the innate

immune system take over the curative role.

Polarization of the Innate Immune System

It is very important to note that, in contrast to the adaptive system, the innate immune cells usually have a primed activity (so called priming) which can determine their function. It is also known, that this priming exhibits a polarity. Namely, as shown in figure 1, the innate immune system is committed in two directions.

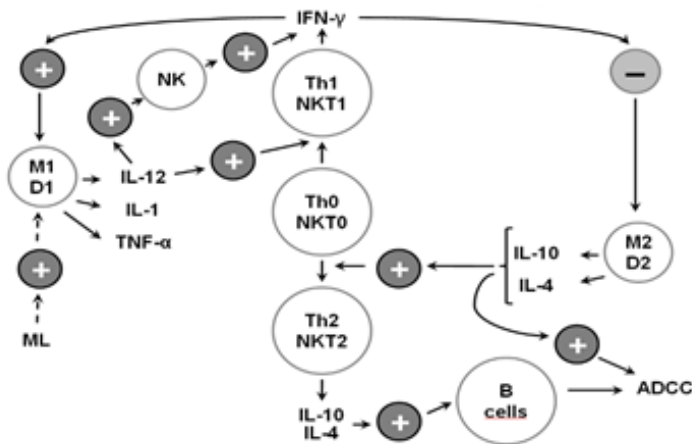


Figure 1: The innate immune system is committed in two directions: M1 and D1 are type-1 macrophages and dendritic cells, which take part in the regulation of antitumor killer cells. M2 and D2 are type-2 macrophages and dendritic cells, which facilitate the generation of Th2 cells and inhibit the type-1 system. Moderately modified Illustration from JS. Murray [Immunol Today 1998; 19: 157-63].

Type-1 macrophages (M1) and monocyte-derived type-1 dendritic cells (D1) generate proinflammatory cytokines (shortly and at the picogram/ml level), and facilitate the production of IL-12, activate cytotoxic effectors such as NK, gamma-delta T and type-1 NKT1 cells – all of which are potent inhibitors of tumor growth in an MHC unrestricted manner. However, these type-1 innate immune cells are down-regulated in tumor disease. Available information suggests that there is a tumor-induced dominance of type-2 macrophages (M2) and from the plasmacytoid precursor derived type-2 dendritic (D2) cells, which generate IL-4 and IL-10. These facilitate the generation of Th2 cells and inhibit the type-1 system. It has also been shown that these M2 and D2 cells affect chronic inflammation, promote cell proliferation by producing Growth Factors (GFs), and stimulate angiogenesis. Parallel with the down regulation of type-1 cells, it was also found that tumor patients can have up to 40% type-2 peripheral monocytes in contrast to healthy persons who have only 10% [1,2].

Standardized and Evidence Based Immunomodulators Must Activate the Type-1 Effector Cells Using PAP-PRR Interactions but PAMP Molecules are Existing Only in the Nature (Microbes and Plant)

It is now well known that Pathogenic Associated Molecular Pattern (PAMP) molecules on microbes, are facilitating one of the most effective ways to trigger natural immune defenses against both tumor and virus-infected cells. The Pattern Recognition Receptors

(PRR) on phagocytic cells, to which Toll-like Receptors (TLR) also belong, are responsible for the activation of type-1 innate mechanisms by the binding to appropriate PAMP molecules which are conserved structures only expressed by microbes and not by the host. The chemical composition of PAMP molecules consists of sugar, proteins, lipids, nucleic acid or combination of these types of substances. These chemical combinations in PAMP molecules show always a heterogeneity but their structures appear to be more important than their chemical composition. Therefore, their chemical definition and production were hindered and because of these problems the research of biomodulators was held back since a long time.

A lot of RCC (TLR) agonist are known in the field of cancer immunotherapy but only two of them - Bacillus Calmette-Guérin (BCG) and Lipopolysaccharide (LPS) originated monophosphoryl lipid A (MPLA) – have been approved by the FDA for cancer treatment. We know today that PAMP – TLR interaction can explain their clinical benefit resulting in a stimulatory effect on type-1 natural immune mechanisms. Since PAMP molecules are existing only in the nature, innumerable attempts were carried out to use bacteria as immunomodulators. Since spontaneous remissions have been observed after bacterial infections, the use of PAMP molecules from bacteria was a great dream in cancer therapy. However, even the most effective pathogenic bacteria can cause undesirable side effects. If we try to diminish their toxicity, we can damage the structure of their PAMP molecules. Fortunately, growing attention has been focusing on the plant-derived PAMP-like molecules, which - in contrast to bacteria – have considerably fewer side effects. At the moment, in spite of their standardization and scientific evidences the research of plant preparations is hindered because of their difficulties concerning the exact chemical definition. Since with chemically produced and therefore approved PAMP immunomodulators, such as Isoprinosine (synthetic purine derivate) was not successful in anti-tumor therapy, several standardized and evidence-based plant immunomodulators (with PAMP properties) are becoming increasingly popular in form of healthy supplements. Since plant PAMP-like molecules with their appropriate structures fitting to PRR/TLR have no side effects and case reports suggest their clinical benefit, probably it represents one of the most promising future immunomodulatory therapy. The first evidence-based plant immunomodulator was a mistletoe lectin [3-6] with clinical benefit [7] but the clinical research of its isolated form was stopped 30 years ago in spite of the results of a double-blind cross over study in that mistletoe lectin (ML) was found to activate significantly both the phagocytic activity (after 5h) and NK activity (after 24h) in peripheral blood of healthy volunteers indicating its important beneficial effect on type-1 innate immune mechanisms [4]. Unfortunately, 30 years ago the curative effects of the innate MHC-I unrestricted immune mechanisms were poorly understood and its tumor-induced dysregulation was believed as an epiphenomenon. Therefore, only to lectin content standardized mistletoe plant extracts are available as described previously [5].

to be dependent on the degree of phagocyte activation. PAMP molecules have a direct effect only on phagocytic cells and after their binding to PRR molecules is a regulatory cascade will activate the MHC-unrestricted killer cells causing an enhanced tumor- defense.

What is the Optimal Frequency of an Immunomodulator?

The biomodulator-induced cascade responses may explain the exhaustion phenomenon during a continuous immunomodulatory therapy. As shown in figure 2, during the activation of phagocytic cell after six hours a decrease in NK activity was observed but 24 hours later there is an increase in NK function and as shown in figure 3, the degree of augmentation of these two effectors correlate with each other [23]. In another study [25], the effect of frequency of a biomodulator on NK-increases was investigated. Figure 4 represents that daily application of optimal lectin (ML) dose induce an exhaustion phenomenon in NK activity after two days. Using suboptimal doses, this NK-relapse occurs only after three days [25]. If we try to understand these exhaustive results, we must take into account the already mentioned cellular cascades and polarity of innate immunity and introductions of 72-hour therapy—free intervals seem obvious. Further clinical trials are necessary but today it is not easy to get an approval for investigation of plant preparations. However, always more case reports are now available [26-33], which support the clinical benefit of evidence-based, plant immunomodulators with these therapy-free intervals.

NK activity of mononuclear cells in peripheral blood of 9 tumor patients was determined by measuring their effect on DNS-synthesis of proliferating target (K562) cells 24 hours after daily injections of optimal (A= 1 ng/kg) or suboptimal (B= 0.6 ng/kg) doses of mistletoe lectin given in extracts [24]. Using optimal doses 24 hours after the second injection and in case of suboptimal doses 24 hours after the third injection diminished the NK increase pointing to the importance of therapy-free interval to avoid a tolerance.

It is obviously, that evidence based and standardized plant immunomodulators alone cannot bring a break-through in cancer therapy but their combination with appropriate oncological treatments, which for example are able to enhance the tumor sensitivity to MHC-I unrestricted effectors by activation of stress—related molecules on tumor cells [34,35] can result in astonishing clinical results [33]. The discovery of the polarization and cascades of the curative natural immune system will open a great number of possibilities to manipulate and improve the effects of oncological treatments. It was now published that a patient with inoperable pancreas adenocarcinoma (39x46 mm) and multiplex liver (10 - 30 mm) metastases (having 27 kg decrease in body weight and intensive pains) after a treatment with rice bran arabinosylian concentrate (given with 72 h therapy-free intervals) together with gemcitabine had a nearly complete remission and three years survival [33].

Conclusions

The great development of clinical tumor immunology highlights more and more that during the progression of the tumor disease, the MHC-I unrestricted effector cells of innate system increasingly take over the curative role from the adaptive system. Therefore, the activation of type-1 innate immune cells by PAMP-PRR interaction belongs to one of most promising directions of tumor immunological research. Since the chemistry is not able to produce appropriate structures of effective PAMP molecules, besides microbes the plant origin appears always to be more exciting. The plants are full with “PAMP-candidates”. Many years ago, a lot of research with plant PAMP molecules were stopped because of an oft-observed tolerance and poor understanding of curative role of innate system. The currently described and discussed results from old research points to a possible renaissance of plant—derived immunomodulators. The cascade mechanisms in the polarized innate immune system may now explain the oft observed tolerance during a continuous immunomodulatory treatment since a permanent activation of type-1 cells can induce a predominance of type—2 cells. Since the neuroendocrine system plays also an important role in the regulation of the balance between type-1 and type-2 innate immune cells, new perspectives are opened to improve the tumor-induced dysregulation, if we learn to manipulate it. For example, preliminary results suggest that insulin can diminish the type-1 functions [36]. The benefit of therapy-free intervals with biomodulators can support old clinical experiences with chronic inflammation that short-term activation of phagocytic cells brings more antitumor benefit than a permanent one.

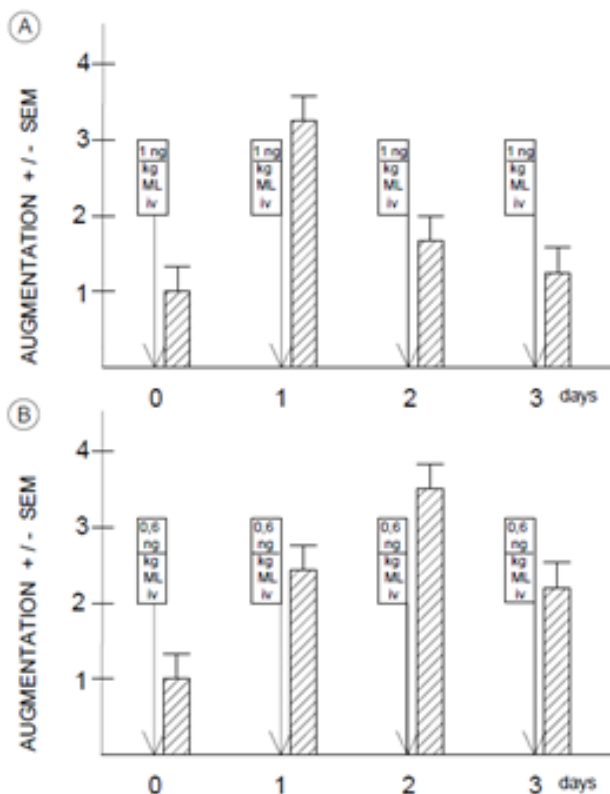


Figure 4: Relative increases in NK-activity during daily application of biomodulator (ml) given in optimal (A) or in suboptimal (B) doses.

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