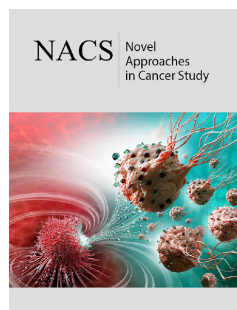



Towards a Holistic Approach in the Immunotherapy of Cancer

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Abstract

The immune response against malignant tumors is performed through multiple immune cell types; each of them has been shown to be effective in its antitumor activity; this has inspired many therapeutic approaches such as adoptive cells transfers or stimulation through antitumoral antibodies or cytokines. The present opinion article is approaching the immune response in cancer from a holistic perspective, exploring the possibility that it may be used in integrated approaches, in cancer immunotherapy.

Keywords: Lymphocyte; Cancer; Integrated; Immunotherapy; Interleukin

Abbreviations: LT-Lymphocyte; NK-Natural Killer Lymphocyte; CD-Cluster of Differentiation; TH-T Helper Lymphocyte; PD-L1-Programmed-Death Receptor Ligand-1

Opinion

The immune response that the organism mounts against malignant tumors involves many types of immune cells, both innate, such as macrophages, neutrophils, eosinophils, or mast cells, or adaptive, such as different types of effectors, helper, T or B Lymphocytes (LTs). These cells infiltrate tumors in response to various danger signals, alterations in cell surface or antigenicity of tumor cells that constitute activation signals for each of them. The existing evidence highlights the potential of these many cell types of being strong antitumoral elements, sometimes completely eradicating tumors. It has been shown that macrophages [1], neutrophils [2], eosinophils [3], mast cells [4] or innate lymphoid cells such as NK [5], NKT [6] or $\gamma\delta$ [7] lymphocytes may have a very strong tumoricidal effect under experimental conditions or in adoptive therapies to patients. Experimental evidence has shown that in addition to the well-known and recognized tumor killers (CD8+ or Th1 LTs), immune subsets that were previously known as protumoral, such as Th2 [8], Th17 [9] or that were considered unimportant, such as B lymphocytes [10] or T follicular LTs [11] may also exert, under certain conditions, very strong antitumor effects, sometimes even stronger than Th1 LTs [12,13]. The result is that many of these immune cells are in use or in trials to be used as therapeutical means for cancer therapy [14]. However, it has been shown that these cells do not act always at their full antitumor potential, due to a complex of factors that are acting on them in tumors. In our recent paper [15], we have reviewed the factors that influence the immune cells to an antitumoral or, conversely, to a protumoral profile; it has been shown that when exposed to factors such as inflammatory or danger signals, specific chemokines, stimulatory or polarizing interleukins or specific antigens, immunocytes are stimulated towards an antitumor profile. In the meantime, following exposure to the immunosuppressive action of the tumor cells and the tumor microenvironment, which contains suppressive cytokines or exosomes, inhibitory molecules such as PD-L1 or CD47 or inappropriate physic-chemical conditions such as lactic acidosis, hypoxia or increased hydrostatic pressure, immunocytes are inhibited or even acquire protumoral properties [16].

Thus, not considering the conditions within tumors that influence immunocytes may lead to unsuccessful immunotherapies or adoptive transfers, due to the inhibition of the immunocytes involved. The factors that influence immune cells are important to be understood as possible causes of therapeutic failures, but also as possible opportunities to influence these cells for an antitumoral use. It has indeed been shown that cells like macrophages or mast cells are versatile cells that may be influenced through action on their TLR receptors to have an antitumoral profile [1,17]; in the meantime, lymphocytes may be directed through monoclonal or bispecific antibodies to the tumor cells to destroy them [18]. In the meantime, approaches that relieve the inhibitions on immunocytes, such as anti-PDL or anti CD47 therapies, have been shown to be extremely effective [19]. These facts, which concern the biology and function of immune cells, must be considered when a single immunocyte therapy, such as CD8+, NK or CAR T cell therapy, is desired. However, if a single immunocyte can be so successful in eradicating tumors (with the mentioned caveats), it seems reasonable to think about the possibility of considering the immune as a whole response, and to use its full power and effectiveness to fight tumors. The present work examines the fascinating possibility of going beyond the use of an immunocyte, an interleukin, a vaccine or an antitumoral antibody, or combinations of few of them, towards a holistic approach in which the entire immune response is used as a weapon in immunotherapy.

There were several recent studies that showed a certain degree of integration in the immune response, with the constitution of immune modules that comprise more than one type of immunocyte [20], which may allow integrated approaches to some of these modules or networks. To our knowledge, there is not yet any study that demonstrates an integrated behaviour of the immune response in tumors. To discuss about manipulating the immune response as a whole, a few facts should be considered. First, to influence the innate side of the tumoral immunity, the TLR receptors of immunocytes must be stimulated by TLR agonist molecules [17]. In addition, using TLR agonists may transform cold tumors into hot, immune-infiltrated tumors [21], by increasing the vascular adhesion and immunocyte influx into tumors, and by stimulating them; this approach may activate more than one innate subset, including dendritic cells. On the other hand, multiple experiments and trials have shown the spectacular effect that CAR-engineered LTs or the use of monoclonal or bispecific antibodies may have, leading to the eradication of even small nests of tumor cells [18]. These therapies, although very effective, also have drawbacks and failures, that may be overcome by the optimization of the approach in its basic mechanism [22] but failures may continue to happen, due to the environment in which these cells work, which is very suppressive [23]. By consequence, relieving the suppression of these cells through anti- PDL-1, anti-TIM-3, anti-CTLA-4, or other mechanism-based therapy proved to greatly extend the effectiveness of the therapies mentioned above. Although very successful, these therapies also have failures, which makes necessary to go deeper into the analysis of the nature of these

inhibitions. Tumors are not sitting duck targets, they are tissues that undergo an aberrant development process which includes, as any tissue regeneration process, an immunosuppressive component [24]. It results that to get to the roots of any immunosuppression in tumors, one must consider the oncogenic process that causes immunosuppression, and, instead (or besides) addressing each of the suppressive mechanisms that were mentioned (which proved otherwise effective), to attack the oncogenic program that causes most of them. It has been shown in experiments that the inhibition of the oncogenic stimulation indeed blocks immunosuppression and changes the composition of the immune infiltrates [25]. Another phenomenon that is present in cancer is the imbalance of the Th subsets, mainly due to a dysfunction of the dendritic cell in cancer [26].

It has been suggested by some recent studies, that in a well-developed Th1-CD8+-NK-IFN γ environment, Th2 and Th17 LTs may be influenced to an antitumoral profile [27]. Polarizing interleukins such as IL-12, IL27 or IL-18 may be used to revert the Th imbalance in the tumor microenvironment, which has been shown to be effective. To summarize, an integrated approach which could involve the whole immune response in tumors would imply (Figure: 1): -stimulation of the main antitumor defense, which is the IFN γ -secreting network (Th1, CD8+, NK,NKT1, $\gamma\delta$ -1 LTs); -modulation of inflammation through TLR agonists ; -inhibition of immunosuppression; a lot of means are used, but the analysis above showed that a reasonable approach is to attack the root of inhibitions which is the oncogenic program; the immunocytes would be freed from many of the conditions which make their activity difficult and ineffective. -optimizing Th balance by stimulating Th1 (using stimulatory or polarizing interleukins -IL-2, IL-12, IL27, IL-18, IL-7, IL-15) while leaving Th2 and Th17 in place, with the expectation that in these conditions they may exert an antitumoral role.

This combined approach would optimize both the innate and adaptive immune response (CD8+, Th and other subsets), by providing to cells their own stimuli, by inhibiting their suppression and by using or stimulating interactions between them, dealing with many of the setbacks of immunotherapies that were mentioned. It also results that a combined, holistic approach to the immune response must address the tumor microenvironment and its tumor cell-centered aberrant development program, with all its branches, which are in permanent interaction with the immune response (Figure 1). However, even such an approach which aims to touch virtually all of the compartments of the antitumor defense, would have to be developed in a personalized manner; measuring and keeping into account the magnitude of each of the factors that are involved: the immunosuppression, (by quantifying PD-L expression or other inhibitory molecules), the tumor antigens, inflammation and the different Th subsets ,which may be done through immune histochemistry, flow cytometry, computerized pathology [28] or by much simpler means such as cytokine profiles [29] ,or by combinations of them, so that peritumoral elements should be approached if their levels are increased. Thus, an optimal response could be obtained by the modulation of the different compartments

of the tumor immunity. The network-based, integrated approaches are a field with great development potential, and they should be kept into account as a complement of the intelligent, mechanism-

based approaches [18,22]. Of course, the proof of the mentioned considerations and approaches should be made in the appropriate experimental conditions.

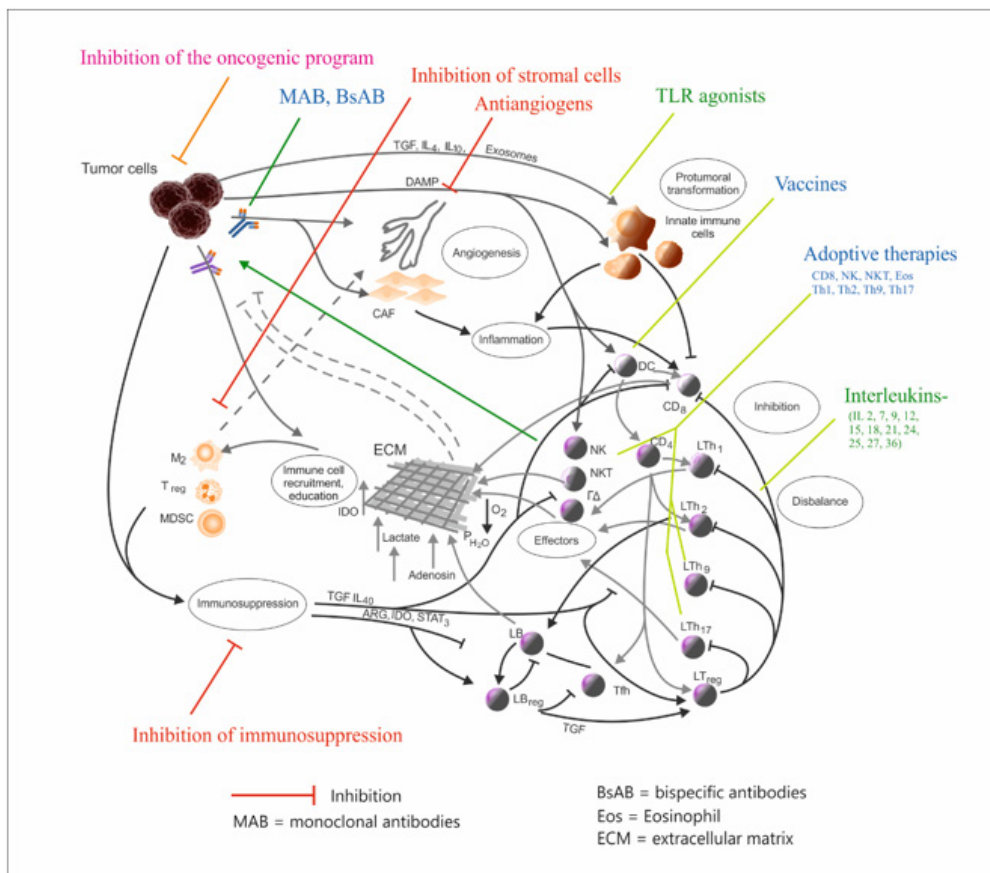


Figure 1: The different immunotherapies that can be used in combined approaches, in the context of the tumor microenvironment interactions [15], modified, with permission]. M2, N2-M2 macrophages, N2 neutrophils; Treg-T Regulatory Lymphocyte; MDSC-Myeloid-Derived Suppressor Cell; Th-T Hepler Lymphocyte; IL-Interleukin; LB- B Lymphocyte; NK, NKT, $\gamma\delta$ - NK, NKT, $\gamma\delta$ lymphocyte; CAF-Carcinoma-Associated Fibroblasts; IDO- Indoleamin-2,3-Deoxygenase; ARG-Arginase; DAMP=Danger-Associated Molecular Pattern; TLR-Toll-Like Receptor; DC-Dendritic Cell; CD-Cluster of Differentiation.

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