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Commentary

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Optimizing complement-activating antibody-based cancer immunotherapy: a feasible strategy?

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Abstract

Passive immunotherapy with monoclonal antibodies (mAb) targeted to specific tumor-associated antigens is amongst the most rapidly expanding approaches to biological therapy of cancer. However, until now a limited number of therapeutic mAb has demonstrated clinical efficacy in selected neoplasia. Results emerging from basic research point to a deeper characterization of specific biological features of neoplastic cells as crucial to optimize the clinical potential of therapeutic mAb, and to identify cancer patients who represent the best candidates to antibody-based immunotherapy. Focus on the tissue distribution and on the functional role of membrane complement-regulatory proteins such as Protectin (CD59), which under physiologic conditions protects tissues from Complement (C)-damage, might help to optimize the efficacy of immunotherapeutic strategies based on C-activating mAb.

Introduction

In view of their potentiality to specifically target tumor cells, antibody-based therapeutic strategies still represent very attractive clinical approaches to cancer treatment. A renewed interest in this field of cancer immunotherapy has derived from the significant clinical results obtained with anti-CD20 and anti-HER2 monoclonal antibodies (mAb) in B cell malignancies and breast cancer, respectively, and from the availability of new molecular techniques such as recombinant DNA technology. Currently, several mAb targeted to different tumor-associated antigens (TAA) are employed in initial clinical studies of passive immunotherapy for solid and hematological malignancies [1].

The tumoricidal activity of therapeutic antibodies depends on different mechanisms of action such as inhibition of downstream signaling events in the target cells. In addition, therapeutic mAb can directly induce cell death by triggering apoptosis or through "indirect" immunologic mechanisms such as antibody-dependent cell-mediated cytotoxicity (ADCC) and/or Complement (C)-mediated cytotoxicity (CDC).

Over the past years, C-activating mAb have been extensively utilized for the treatment of patients with tumors of different histotype, in particular in patients with cutaneous melanoma which represents a "model disease" to design and activate approaches of biological therapy in cancer patients. Among therapeutic mAb that mediate CDC and ADCC of target melanoma cells, anti-GD2 and anti-GD3 mAb have been largely used in the clinical setting, although with rather unsatisfactory results [2-4]. Nevertheless, in light of the promising results obtained in pre-clinical studies, selected engineered C-activating mAb are still utilized in clinical trials. Along this line, results of

a phase I pilot clinical trial of human IgM mAb directed to GM3 ganglioside in 9 patients with metastatic melanoma have been most recently reported [5].

Several *in vitro* and *in vivo* studies, focused on the mechanisms regulating C-activity and tumor-host interactions, have provided insights on distinct biological features of neoplastic cells that may affect the clinical efficacy of passive immunotherapy with antibodies or their derived molecules [6]. Among the different mechanisms of immune escape triggered by neoplastic cells, the expression of high levels of the C-regulatory proteins such as Protectin (CD59) is emerging as an important strategy that limits the potential clinical benefits deriving from antibody-based immunotherapeutic approaches.

Discussion

The long-standing field of cancer immunotherapy clearly needs well-substantiated pre-clinical evidences on the fine modality of action of the different strategies utilized for cancer treatment. In fact, a variety of therapeutic tools, including C-activating mAb have been extensively utilized in the clinic [2-4], in the absence of accompanying studies designed to fully explore their biologic, functional and clinical potential. As a direct consequence of this partially "blind" therapeutic approach, several potentially useful immunotherapeutic agents and approaches have been rapidly dismissed, due to their limited clinical efficacy. Indeed, opposite to chemotherapy, a much broader number of variables must be taken into account to maximize the clinical accomplishment of immunobiologic agents used as therapeutic tools in cancer patients.

As far as the clinical efficacy of passive immunotherapy of cancer patients with therapeutic mAb that mediate the activation of the C cascade, a major limitation is certainly represented by the presence of a functional form of the C-regulatory protein CD59 on the cell membrane of neoplastic cells, as well as in the tumor microenvironment [7,8]. Among solid tumors, the expression and functional role of CD59 has been well investigated in melanoma. CD59 is broadly expressed on normal and neoplastic tissues of melanocytic origin, with few non-CD59 expressing melanomas, has a limited intra- and inter-lesional heterogeneity and, among known C-regulatory proteins, it represents the main restriction factor of C-susceptibility of human melanomas [9,10]. Furthermore, a statistically significant ($r = 0.914$; $p < 0.001$) inverse correlation was identified between absolute levels of CD59 molecules expressed on melanoma cells and their susceptibility to C-mediated cytotoxicity induced by anti-GD3 mAb R24 [11]. Thus, melanomas from distinct patients were highly susceptible to C-mediated cytotoxicity, while neoplastic cells from other individuals were completely resistant to C-cytotoxicity, even in the presence of elevated amounts of C-sensitizing mAb R24 [11]. Conversely, no significant correlation was found between levels of cell membrane GD3 expressed on melanoma cells and their C-susceptibility [11]. Thus, in spite of the efficient and rapid tumor targeting potential of therapeutic mAb, these findings strongly caution that their therapeutic efficacy may be greatly implemented through the treatment of patients bearing melanoma lesions that express weak to intermediate levels of CD59 and, thus, are more susceptible to the cytolytic effect of autologous C activated by therapeutic mAb. This notion is clearly not restricted to human melanomas but rather represents a more general phenomenon; in fact, resistance to rituximab (anti-CD20)-mediated C cytotoxicity is associated with high levels of CD59 expression on neoplastic cells of non-Hodgkin's lymphoma and multiple myeloma patients [12].

A soluble form of CD59 (sCD59) has been identified in body fluids and in the culture supernatants of normal and neoplastic cells [8,13,14]. Concerning melanoma, it was demonstrated that the amounts of sCD59 released from CD59-positive melanoma cells correlate with the levels of CD59 expressed on the cell surface [8]. Noteworthy, sCD59 released from melanoma cells blocks the binding of anti-CD59 mAb to cell surface CD59 neutralizing their functional activity [8]. In light of these evidences, the recent observation that CD59 acts as a triggering co-receptor for Natural Killer (NK) cell-mediated cytotoxicity [15] identifies an additional protective role for CD59 in natural immunity. In fact, high amounts of circulating sCD59 detectable in sera of cancer patients may bind to NK cells affecting CD59-mediated functional activation.

Conclusions

Much remains to be gained to make full use of the potential of immunotherapeutic agents in the clinical setting; nevertheless, we are ever more generating pre-clinical and clinical data that allow us to design prospective trials taking into strict account the characterization of the "biological eligibility" of cancer patients to specific therapeutic options, through the analysis of defined phenotypic characteristics of their malignant lesions. Such a strategy will ultimately lead to the identification and selection of patients who represent the best candidates to specific immunotherapeutic approaches.

Abbreviations

Antibody-dependent cell-mediated cytotoxicity, ADCC

Complement, C

Complement-mediated cytotoxicity, CDC

Monoclonal antibodies, mAb

Natural Killer, NK

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