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ROLE OF B7-H1 AND B7-H4 MOLECULES IN DOWN-REGULATING EFFECTOR PHASE OF T-CELL IMMUNITY: NOVEL CANCER ESCAPING MECHANISMS

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1. ABSTRACT

The majority of human and rodent cancers display various antigens which could elicit cellular and humoral immune responses. Such immunity, however, often fails to prevent progressive growth of cancers. It has long been speculated that tumor antigens may not be presented in appropriate fashion, which subsequently fails to elicit a strong immune response. Recent studies, however, indicate that immunization by formulated tumor antigens or even transfer of pre-activated T lymphocytes also have limited impact on cancer growth despite the fact that these methods could often enhance immune responses in cancer patients. These findings imply that even afferent arm of immunity are strengthen, it is not necessarily being translated to tumor regression. It is possible that the development of evasion mechanisms in tumor microenvironment play a critical role in the resistance of therapeutic immune responses. Recent studies provide compelling evidence that human and rodent cancers develop evasion mechanisms by aberrantly expressing normal proteins, which are required for normal tissue homeostasis, to either build a microenvironment locally or reach other organs systemically. In this review, we will focus our discussion on two recently described molecules, B7-H1 and B7-H4, in the context of their roles in the evasion of tumor immunity and possible approaches for therapeutic manipulation.

2. TUMOR EVASION: WHY IT IS IMPORTANT?

High proportion, if not all, of human and rodent cancers are found to express arrays of tumor antigens, which are capable of eliciting specific antibodies and T cells. Therefore, these antigens are considered to be immunogenic for their hosts. Although it is rare, human cancers could regress spontaneously without specific treatment and it is widely believed that the regression is mediated by the immune system (1). These observations lead to hypothesis in which, in most of cancer patients, tumor antigens are not appropriately presented to immune system in their best stimulatory format. This in turn leads to partial activation or tolerance (2). As a result of these efforts, cancer vaccines, which are based on tumor antigen formulated with various immune stimulatory content such as adjuvant, viral vector, dendritic cells et al. could often enhance T cell responses against cancer antigens in experimental animals and in advanced cancer patients (3, 4). However, cancers in the majority of these patients progress continuously (5, 6). Furthermore, adoptive transfer of large number of pre-activated T cells to bypass the priming process in vivo has limited impact in the regression of cancers (7). Therefore, existence of active immune responses to cancer antigens in patients does not always correlate with elimination of cancer cells in vivo. These clinical observations thus are consistent with the findings that cancer cells often develop evasion mechanisms in their microenvironment, which protect cancer cells from destruction by immune responses.

Overwhelming evidences indicate that tumors employ various mechanisms, which are required for normal cell growth, differentiation and metabolism, to evade destruction by active immune responses. For example, a portion of colorectal cancers lost MHC class I molecules to prevent recognition of tumor cells by activated T cells (8). Glioma and head and neck cancer secrete cytokines including TGF-beta or PGE2 (9, 10), which have potent suppressive activity for effector T cells (11). Ovarian cancers produce a large number of VEGF growth factor (12, 13) and CCL7 chemokine (14), which regulates dendritic cell differentiation and attracts regulatory T cells, respectively, so as to modulate T cell responses in effector phase. As a result, tumor cells can be avoid of attack by T cells or induce functional deficiency of T cells such as ignorant, anergic or deleted (15, 16). It should be emphasized that although these factors can evade active T cell immunity, their role in the progression of human cancers are not well established. It is likely that cancer progression is decided by multiple factors and a comprehensive analysis will be required in the future.

3. B7-H1 IN THE EVASION OF TUMOR IMMUNITY

B7-H1 is one of the B7 family molecules belonging to immunoglobulin (Ig) superfamily. Like other B7 family molecules, B7-H1 has one Ig V, one Ig C in its extracellular domain with a transmembrane and an intracellular domain. While its message RNAs are found to be widely distributed in virtually every tissues, cell surface B7-H1 is only found in macrophage-origin cells such as Kupffer cells in liver and dust cells in lung by immunohistochemistry analysis using a human B7-H1 specific monoclonal antibody (mAb). In contrast, B7-H1 is abundant on the surface of a variety of human cancers and its expression could be readily induced by IFN-gamma (17). Consistent to this finding, mouse and human cancer cell lines, which are negative for B7-H1, could be induced by IFN-gamma to express high level. Further, normal cells of epithelial, endothelial and hematopoietic origin, although they are B7-H1 negative, could be induced to upregulate B7-H1 in vitro by IFN-gamma or other cytokines (13, 18). For example, B7-H1 is only found on the surface of a small fraction of myeloid dendritic cells. Its expression, however, could be upregulated by IFN-gamma, IL-10 and VEGF (13). This data suggests that B7-H1 is a normal host component serving in response to environmental changes.

Program death one (PD-1), an Ig superfamily molecule, is found to interact with B7-H1 (19). PD-1 is not detectable in resting cells but is found on the surface of activated T cells, B cells and myeloid cells (20). PD-1 knockout mice spontaneously develop systemic autoimmune symptoms with lupus-like diseases in C57BL/6 strain and dialated cardiomyopathy in BALB/c mice (21, 22). These observations support a role for PD-1 in negative regulation of immune responses. Several studies suggest that at least some of immunological functions of B7-H1 are mediated by PD-1 (23), while others may be mediated by an additional receptor (17, 23, 24).

Constitutive and inducible expression of B7-H1 by human cancers has a profound effect in the inhibition of immune response. At least three mechanisms have been proposed. Dong et al. report that tumor-associated B7-H1 promotes apoptosis of tumor antigen-specific human T cells in vitro (16). This finding is consistent with the observation in B7-H1 knockout mice that apoptosis of antigen-specific CD8+ T cells is dramatically decreased in peripheral organs such as liver. As a consequence, B7-H1 deficient mice were prone to experimentally induced hepatitis (25). In addition, B7-H1 on Kupffer cells in the liver suppresses the proliferation of effector-phase T cells and leads to aggravation of adenovirus-induced liver infection (26). Whether or not B7-H1 effects on apoptosis is mediated by PD-1, is not yet clear. However, at least in one report, the effect of B7-H1 in apoptosis is independent on PD-1 (17). Dong et al. reported that autoantibodies to B7-H1 could be detected in patients with rheumatoid arthritis and these antibodies increased apoptosis of T cells in vitro (27). Because activated T cells express a high level of B7-H1, this finding supports a direct role of B7-H1 as a signaling molecule transmitting apoptotic signals to T cells. Taken together, over-expression of B7-H1 may play an important role in promoting apoptosis of effector T cells in cancers and other diseases.

B7-H1 on cancer cells may also reduce cytotoxicity of T cells. Iwai et al showed that B7-H1 on mouse P815 mastocytoma cells decreased the killing activity of CTL in 4 hour Cr release assay (28) by using the allo-reactive cytotoxic T cell clone 2C and polyclonal T cells acquired by the immunization with P815 mastosytoma

into a syngeneic mouse. Similarly, Blank et al. showed that B7-H1 transfected B16-F10 melanoma expressing H-2K^b binding peptide SIYRYYGL acquired resistance in vitro for cytotoxic lysis by 2C T cell receptor transgenic T cells (29). In a recent study, Hirano et al. showed that by using the P1A-specific CTL clone that recognized the P1A antigen on P815, expression of B7-H1 on P815 cells reduced the killing activity of the CTL. This effect, however, was not observed in a 4 hour incubation with T cells, but required a long incubation time (12 hours). Interestingly, by mixing B7-H1- and B7-H1+ P815 cells with pre-activated P1A CTL clone in vitro, only B7-H1- P815 cells were selectively lysed. Similar results were also found in vivo by co-injection of a mix of B7-H1- or B7-H1+ P815 cells with P1A-CTL. Furthermore, after incubation with B7-H1+ tumor for 12 hours cytolytic activity of P1A-CTL did not decreased, because those cells could very well kill the targets in the following 4 hour CTL assay (30). This finding suggests that the resistance of tumor cells conferred by B7-H1 is not due to modulation of cytolytic function of P1A-CTL, but might be due to a shield to prevent contact with immune cells. Blocking B7-H1 or PD-1 by specific mAb, could largely eliminate B7-H1 mediated resistance. These findings provide direct evidence that B7-H1 inhibits the efficacy of cytolysis of effector CTL in tumor sites.

Another mechanism for the evasion of tumor immunity by B7-H1 is through inhibition of dendritic cell function and aberrant induction of cytokines. It was shown that B7-H1 could stimulate IL-10 production from T cells in vitro (31) and that IL-10 levels in sera is associated with immunosuppressive status and virus load in HIV patients (32). Dendritic cells from ascites of ovarian cancer patients had significantly inhibited stimulatory function for allogeneic and autologous T cells and blockade of B7-H1 by specific mAb increased production of IL-2 and IFN-gamma and increased cytolytic function against cancers (13). Interestingly, the effect of B7-H1 in this setting is not mediated through PD-1 because the mAb used in these experiments does not block B7-H1 interaction with PD-1 (13). Taken together, aberrant expression of B7-H1 by antigen-presenting cells may modulate the tumor microenvironment and profoundly affect tumor immunity.

In summary, B7-H1 expressing tumor cells could evade cancer immunity by inducing apoptosis of T cells, by rendering resistance to effector T cells, by inhibiting DC function and/or inducing aberrant cytokine production. These mechanisms could operate either individually or cooperatively dependent on the location and tissue origin of cancers. Therefore, current results support that intervention of B7-H1 may be beneficial for enhancement of tumor immunity. This issue will be discussed below in this review.

4. B7-H4 IN THE NEGATIVE REGULATION OF TUMOR IMMUNITY

B7-H4, also called B7S1 and B7x, is a recently identified B7 family molecule (33-35). Injection of mAb to mouse B7-H4 promoted CTL responses to nominal and allogeneic antigens in mouse models (33) and ameliorated experimental allergic encephalitis (34), supporting a role for this molecule in the suppression of T cell immunity. The mechanisms for B7-H4 mediated immune inhibition are not yet clear. By in vitro analysis, B7-H4 has potent activity in arresting cell cycle progression of T cells after exposure to antigen signal, leading to decreased proliferation and cytokine secretion (33). This observation largely explains dominant effect of B7-H4 in the inhibition of T cell responses to costimulation.

Despite the fact that B7-H4 mRNA could be detected broadly in normal human tissues, immunohistochemistral analysis does not reveal positive staining in any tissues and organs from healthy individuals (36). In contrast, cell surface expression of B7-H4 is found in a variety of human cancers including 31% of Lung cancer (5/16) and 85% of ovarian cancer (22/26). Interestingly, B7-H4 is not detectable at all in 17 samples of melanoma, which is different from nearly 100% expression of B7-H1, suggesting there is certain tissue-specific control in B7-H4 gene expression taking place. Therefore, it is likely that expression of B7-H4 by cancer cells may contribute to escape of cancers from immune attack.

5. IMPLICATIONS IN IMMUNOTHERAPY

Several recent studies directly link tumor evasion with B7-H1 mediated immune suppression. In a large immunohistochemistral analysis of B7-H1 expression in renal cell carcinoma (RCC), 130 out of 196 patient samples were found to express B7-H1 in more than 10% RCC cells. The expression of B7-H1 is statistically significantly associated with poor survival of patients in follow-up for 3 years. Interestingly, expression of B7-H1 on RCC, on infiltrating T cells or both is all significantly associated with poor prognosis (37). In a small study, expression of B7-H1 on lung small cell carcinoma appears to be associated with less infiltration of T cells in the lesion. However, there was no association between B7-H1 expression and survival of these patients (38). Because this is a relatively small study, the results may not be conclusive. In addition, all these studies are conducted in retrospective fashion and other factors thus may bias the conclusion. In mouse tumor models, the relationship between B7-H1 expression and cancer progression are established in several studies. In an early study, inoculation of P815 tumor cells expressing transfected B7-H1 into syngeneic naïve mice induced progressive tumor growth. However, the growth kinetics of this tumor is not different from mock-transfected or wild type P815 tumors (17). In contrast, using a more immunogenic version of the P815 line, which regresses spontaneously in syngeneic naïve mice after inoculation, transfected B7-H1 was shown to enhance tumor growth (28).

Blockade of inhibitory B7 family molecules by mAb may be an excellent addition in the context of active immunotherapy. For example, it has been shown that administration of B7-H1 blocking mAb enhanced therapeutic effects of anti-CD137 agonistic mAb (30),

which could augment tumor specific CTL activity (39). In addition, anti-B7-H1 mAb also increased therapeutic effects of pre-activated T cells in the treatment of established metastasis in a mouse head and neck cancer model (40). In effector phase, suppressive effect of B7-H1 appears to be very potent because co-expression of B7-H1 on P815 tumor could abolish the effect of B7-1 costimulation (17), which could lead to complete regression of these tumors (41). Blocking B7-H1 by designing genetic and pharmaceutical methods such as interference RNA or small molecules will also be promising approaches for broad application in cancer treatment.

6. CONCLUSION

Escape mechanisms developed in the cancer microenvironment may contribute to resistance of tumor cells to immune destruction and to progression of human cancers. Two newly described B7 family molecules, B7-H1 and B7-H4, are expressed either constitutively or inducibly on human cancer and employ various ways to prevent the attack by activated T cells. Elucidation of cellular and molecular mechanisms underlying these escape mechanisms will shed the light on designing new strategies to protect T cells in effector phase as a means to improve the efficacy of immunotherapies.

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