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Hot Topic

Targeting immune checkpoints: New opportunity for mesothelioma treatment?

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ABSTRACT

Malignant pleural mesothelioma is an aggressive cancer linked to asbestos exposure in most patients. Due to the long latency between exposure and presentation, incidence is expected to further increase in the next decade, despite the ban on asbestos import which occurred at the end of last century in industrialized countries. Platinum-based palliative chemotherapy is the only treatment with proven benefit on outcome, resulting in selected patients in a median overall survival of about 1 year. Therefore, there is room for therapeutic improvement using a new strategy to prolong survival. Dealing with cancer cell induced immunosuppression is a promising approach. Reactivating immune responses that are silenced by immune checkpoints recently gained a lot of interest. Checkpoint blockade has already shown promising preclinical and clinical results in several cancer types and is currently also being investigated in mesothelioma. Here, we discuss the expression patterns and mechanisms of action of CTLA-4 and PD-1 as the two most studied and of TIM-3 and LAG-3 as two interesting upcoming immune checkpoints. Furthermore, we review the clinical results of molecules blocking these immune checkpoints and point out their future opportunities with a special focus on mesothelioma.

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive and nearly always fatal cancer, causally linked to previous, mostly professional, exposure to asbestos [1]. The highest incidence rates, around 30 cases per million inhabitants, are reported for Australia, Belgium and the UK [2,3]. The incidence of MPM is still expected to increase over the next decades due to the long latency between exposure to asbestos and diagnosis and because asbestos is still being used in developing countries [4]. The prognosis of MPM patients remains poor with a median overall survival time in untreated patients of about 10 months and a 5 year survival rate of less than 5% [4,5]. Palliative platinum–antifolate chemotherapy is the only treatment with proven improvement of outcome in MPM, resulting in a median survival of about 1 year. There is therefore a need for new therapeutic strategies. The discovery of immune checkpoint receptors such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and more recently programmed death-1 (PD-1) introduced a new, exciting era in cancer immunotherapy [6]. Immune checkpoints are responsible for controlling and inactivating the immune system in order to avoid autoimmunity and prevent collateral tissue damage [7]. The new paradigm consists of reactivating silenced immune responses by neutralizing molecules that induce T-cell exhaustion and immune tolerance. Immune checkpoint blocking antibodies have already shown promising results in several cancer types [8–13]. Recently antibodies blocking immune checkpoints are being investigated in mesothelioma patients. In this review, we discuss the expression pattern and mechanisms of action of CTLA-4 and PD-1 as the two most studied checkpoint receptors and of T-cell immunoglobulin mucin-3 (TIM-3) and lymphocyte activation gene-3 (LAG-3) as two interesting upcoming immune checkpoints. Furthermore, we review the clinical results of therapeutic molecules blocking these immune checkpoints with primary focus on CTLA-4 and PD-1 since FDA approved antibodies are available for both of them. Future opportunities of immune inhibitory molecules will be pointed out, with a special focus on MPM.

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CTLA-4 and PD-1: High priority targets

CTLA-4: The first clinically targeted immune checkpoint receptor

CTLA-4 is an immune inhibitory receptor that is mainly found on T-cells and to a lower extent on activated B-cells, monocytes, dendritic cells and granulocytes [14–17]. Its primary role is to regulate T-cell activation upon antigenic stimulation of the T-cell receptor (TCR). T-cell activation can be explained by the two-signal model. The first signal is provided when an antigen, presented by an antigen presenting cell (APC) in combination with a major histocompatibility complex (MHC) molecule, interacts with the T-cell receptor (TCR) and a CD4 or CD8 co-receptor. Secondly, interactions between co-stimulatory molecules on the T-cell and APC will then result in priming and differentiation of naïve T-cells or reactivation of effector T-cells to exert their function [18].

CTLA-4 is a transmembrane protein that is retained in intracellular vesicles [19]. The intracellular and surface expression are induced by T-cell activation, after which the vesicles travel to the cell surface where CTLA-4 expression is then upregulated [20]. Wang et al. [21] described that interferon (IFN)γ induces CTLA-4 expression in human T-cells in the presence of APC, suggesting that the effect of IFNγ might be exerted via monocyte activation resulting in T-cell stimulation and hence the expression of CTLA-4.

CTLA-4 exerts its modulatory function by competing with the CD28 molecule for the B7 ligands CD80 and CD86, expressed on APC [22] (Fig. 1). Engagement of CTLA-4 by CD80 and CD86 limits and decreases T-cell activation. Under physiological conditions the immune inhibitory effect of CTLA-4 is involved in provoking an effective immune response without causing excessive damage to the normal surrounding tissue. However, tumor cells can stimulate abnormal expression of CTLA-4 by secreting transforming growth factor-β (TGF-β), an immunosuppressive cytokine that induces CTLA-4 overexpression, resulting in T-cell exhaustion [23–25]. T-cell exhaustion is a state of T-cell dysfunction which represents a mechanism of immunosuppression [26]. Exhausted T-cells fail to proliferate and are no longer able to exert their effector functions. Among the different suppressive mechanisms and pathways by which CTLA-4 modulates T-cell activation are: (i) expression of CTLA-4 on the surface of T-cells outcompetes the CD28 co-stimulation by higher overall affinity for both CD80 and CD86 [27]; (ii) through activation of protein phosphatases SHP2 and PP2A, CTLA-4 transduces co-inhibitory signals in the T-cell kinase signaling pathway by inhibiting Akt phosphorylation [28,29]; (iii) CTLA-4 is constitutively expressed on regulatory T-cells (Tregs) that are activated upon CTLA-4 ligation to CD28, resulting in secretion of the immunosuppressive cytokine TGF-β [23,30].

Due to its immunosuppressive effects, CTLA-4 is an interesting target for enhancing the anti tumor activity of T-cells. Allison and colleagues were the first to discover that CTLA-4 is vital for maintaining host immune tolerance to established tumors. Melanoma and colon cancer mouse models showed consistent and durable anti tumor responses following systemic treatment with CTLA-4 monoclonal blocking antibodies [12,13]. Promising preclinical findings were the impetus to test CTLA-4 immunotherapy in patients leading to FDA approval of the human IgG1 monoclonal antibody 'ipilimumab' (Yervoy®, BMS) for late-stage melanoma in 2011. In addition to ipilimumab, another human anti CTLA-4 antibody, called 'tremelimumab', is under clinical investigation. While ipilimumab is an IgG1 isotype antibody, tremelimumab is an IgG2 antibody. This difference in isotype class might explain the variation in clinical effectiveness of both antibodies. Antibodies with an IgG1 isotype have been described to better induce antibody dependent cell-mediated cytotoxicity (ADCC) and fixing complement compared to IgG2 [31]. ADCC is mediated via binding to activating $F_c\gamma$ receptors expressed on immune cells, natural killer (NK) cells among them. Laurent et al. [32] described that activated T-cells are not killed by ADCC probably due to transient CTLA-4 expression upon activation and that blocking CTLA-4 even puts off the brake on effector T cells. On the other hand, ADCC does result in depletion of Tregs through activating $F_c\gamma$ receptors as described by Selby et al. [33]. So at least for ipilimumab, ADCC is part of the working mechanism of the antibody to induce strong anti tumor immune responses. Cancer patients treated with anti CTLA-4 therapy initially showed disease progression followed by disease regression that can be delayed up to 6 months after treatment initiation [34–36]. These kinetics are an interesting feature described for immunotherapies. While early clinical effects are mostly observed using cytotoxic agents, immunotherapeutic agents often demonstrate delayed clinical effects [37]. This difference in response pattern can be explained by the dynamics of the immune system: due to T-cell expansion and infiltration the tumor lesion initially increases in size [12]. According to the Response Evaluation Criteria in Solid Tumors (RECIST), this is considered as disease progression and treatment should be stopped. However, response to immunotherapy may occur after progressive disease and therefore immune related response criteria (irRC) were developed. For the irRC, radiographic measurements, such as helical computer tomography, are used to assess the tumor burden and the size of new lesions. If there is an increase in tumor burden of at least 25% compared to baseline after 2 consecutive measurements (at least 4 weeks apart) it is defined as progressive disease and treatment cessation is recommended [37]. Immunotherapeutic treatments are associated with immune-related adverse events. Diarrhea, fever and rash have been reported for anti CTLA-4 treatment but most of them are reversible after corticosteroid treatment. However, 10–15% of patients show severe adverse events, such as colitis, that can be long lasting, difficult to treat and even lethal [38].

PD-1: Cancer breakthrough target of the year 2013

In the nineties, the discovery of another T-lymphocyte-associated immune checkpoint receptor, PD-1, and its ligands PD-L1 and PD-L2 triggered a major breakthrough in oncology research. The PD-1 protein has a structure similar to CTLA-4 but it has a distinct biological function and ligand specificity. It is hypothesized that CTLA-4 is responsible for modulating central T-cell activation in the lymph nodes, while PD-1 in contrast is responsible for controlling peripheral T-cell activation at the tumor site [39]. Like CTLA-4, PD-1 is a transmembrane protein, mainly expressed on activated T-cells, B-cells and macrophages [40]. In analogy with CTLA-4, PD-1 also binds to inhibitory molecules of the B7 family, more specifically to PD-L1 (also known as B7-H1) and PD-L2 (also known as B7-DC) thereby preventing autoimmunity and avoiding tissue damage. As for CTLA-4, PD-1 its homeostatic immune function is regulated by a feedback loop via IFNγ [36]. T-cell activation not only induces the expression of PD-1 but it also results in secretion of several cytokines, IFNγ among them, which in turn causes an upregulation of PD-L1 and/or PD-L2 that can interact with PD-1. In this way, immune response are attenuated and the extent of immune mediated tissue damage is controlled.

PD-L1, is constitutively expressed on various hematopoietic cells (T cells among them), some parenchymal cells and tumor cells of many tumor types such as melanoma, lung cancer, breast and ovarian cancer, pancreatic and esophagus adenocarcinoma, renal cell carcinoma and bladder cancers as well as in hematopoietic malignancies [41–44]. In addition to binding PD-1, PD-L1 can also

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