OncoImmunology 3, e28964; May 2014; © 2014 Landes Bioscience

Targeting the IL-12/IL-23 axis

An alternative approach to removing tumor induced immune suppression

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Keywords: cancer, immunotherapy, tumor-induced immune suppression, anti-CD40, anti-IL-23

Combination immune checkpoint blockade has demonstrated significant clinical responses in cancers infiltrated by T cells. Many tumors contain high proportions of myeloid cells and these can secrete immunosuppressive cytokines like IL-23. Our data suggest the clinical potential of using anti-CD40 (push) and anti-IL-23 mAbs (pull) to tip the IL-12/23 balance in established tumors and act as an alternative combination cancer immunotherapy.

Cancer immunotherapy has come of age with predictions that immune-based approaches to cancer treatment will increase in use very significantly in the next 10–15 y.[1] Over the past 5 y, the class of immunotherapies that target T cell checkpoint receptors have achieved remarkable success and generated tremendous enthusiasm among oncologists. These include the FDA-approved α-CTLA-4 monoclonal antibody (mAb) and the α-PD-1:PD-1 ligand mAbs.[2] These studies demonstrate that in many cancers, the immune system is not inert, but rather actively suppressed, and that an endogenous anti-tumor response can be reactivated following checkpoint blockade. Although T cell checkpoint blockade has been validated as a means to relieve tumor-induced immune suppression in cancers such as melanoma and non-small cell lung carcinoma (NSCLC)(20–50% response rates),[2] one envisages that multiple suppressive pathways will operate in any given tumor microenvironment. Thus, targeting one pathway may not release full endogenous anti-tumor immunity. Certainly, deeper and more rapid responses were observed in advanced melanoma patients given concurrent α-PD-1 and α-CTLA-4 compared with monotherapy alone.[3] Nevertheless, some cancers (e.g., prostate, pancreatic adenocarcinoma, gastric and esophageal adenocarcinoma did not show objective responses and even in melanoma, there are a large number of patients where checkpoint blockade in combination fails.

Myeloid derived suppressor cells (MDSC) and/or tumor-associated macrophages (TAM) are another major group of immune cells known to suppress anti-tumor immunity.[4] They are prevalent in many human tumors and inhibit T effector function through the production of immunosuppressive cytokines and factors such as IL-10 and TGF-β or indoleamine 2, 3-dioxygenase (IDO) and arginase. Recently, our group and others discovered that IL-23, produced by myeloid cells, is a novel cytokine that promoted tumor growth and development by suppressing T cell and NK cell effector function.[5] Given human tumors are extremely heterogeneous with respect to their proportion of lymphoid and myeloid cells, co-blockade of immunosuppressive pathways mediated by T and myeloid cells may result in a greater release of endogenous anti-tumor immunity. In addition, combination approaches that aim to remove immunosuppression and activate immune cells are currently being examined in clinical trials.[2]

Recently, we demonstrated that the combination of agonistic anti-CD40 mAbs to drive IL-12 production, and anti-IL-23 mAbs to counter the tumor promoting effects of IL-23, had greater anti-tumor activity than either agent alone.[6] This increased anti-tumor efficacy was observed in several experimental and spontaneous lung metastases models as well as in models of de novo carcinogenesis. The combination effects were dependent on host IL-12, perforin, IFNγ, NK and/or T cells and independent of host B cells, IL-17A, and IFNαβ sensitivity. Thus, we have demonstrated that a combination of agonistic CD40 antibody to activate Th1 immune response and anti-IL-23 mAbs to neutralize myeloid immunosuppression of T and/or NK cells is an alternate approach for cancer immunotherapy (**Fig. 1**). Although the mechanism of action of agonistic anti-CD40 mAbs was thought to be through licensing of antigen presenting cells to activate effector T cells; in recent years, studies have demonstrated that a T-cell independent response is also activated.[7] Using a genetic mouse model of pancreatic ductal adenocarcinoma, agonistic CD40 mAb

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Submitted: 04/17/2014; Accepted: 04/22/2014; Published Online: 05/23/2014 Citation: Smyth MJ, Teng MWL. Targeting the IL-12/IL-23 axis: An alternative approach to removing tumor induced immune suppression. OncoImmunology 2014; 3:e28964; http://dx.doi.org/10.4161/onci.28964

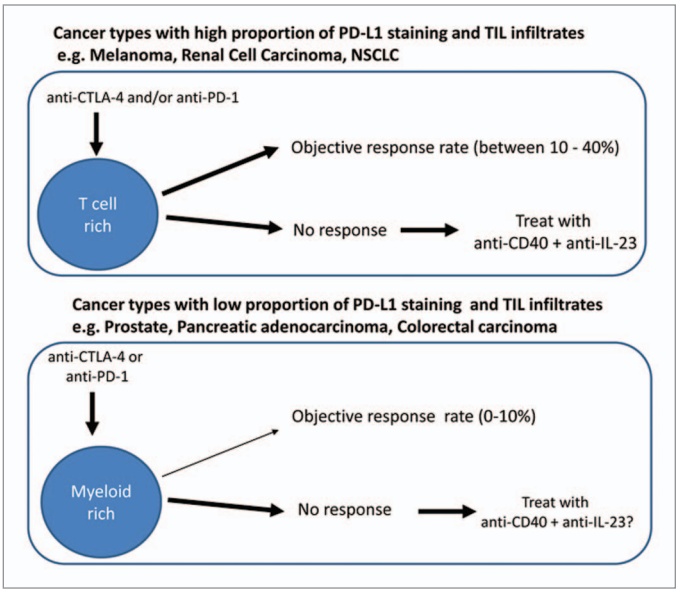

Figure 1. An alternative strategy for alleviating tumor induced immunosuppression by targeting the IL-12/IL-23 axis of inflammation. Cancer patients have heterogeneous infiltrates of T and/or myeloid cells and varying levels of IL-23 in their tumors. Targeting the IL-12/23 axis using anti-CD40 and anti-IL-23 may be an alternative approach to treat cancer patients whose tumors are T cell rich but do not respond to combination checkpoint blockade. Similarly, in cancer types that are myeloid rich, anti-CD40 and anti-IL-23 therapy may induce better anti-tumor response than checkpoint receptor blockade.

induced tumor regression in the absence of T cells. This was mediated by activating CD40-expressing macrophages to become tumoricidal or by converting M2 tumor promoting macrophages into M1 phenotype.[7] Indeed many cancer subtypes are enriched in myeloid infiltrates including pancreatic adenocarcinoma, colorectal carcinoma, breast and prostate cancer. In addition, significant upregulation of IL-23p19 mRNA expression has also been detected in human cancers that are myeloid rich, including colorectal carcinoma, lung and breast cancer[8] with one report suggesting that circulating IL-23 was increased in breast cancer patients and negatively correlated with survival.[9] Although we showed that the combination effects in our study were dependent on host NK and/or T cells in the tumor models we used, we envisage this combination may also be effective in patients whose cancer display rich myeloid infiltrates and upregulated IL-23 (**Fig. 1**). In this setting, neutralization of IL-23 in the tumor microenvironment may allow the agonistic activity of anti-CD40 to be fully maximized. Other cancer types that may benefit from this combination are sarcomas, a disease not well explored immunologically and immunotherapeutically, yet surveillance studies from our group and others suggests that they are highly immunogenic and a good target for immunotherapy. In a de novo mouse model of soft tissue sarcoma, combination anti-CD40/IL-23 therapy of established tumors significantly suppressed tumor growth.[6]

The source of IL-23 and how it mediates its suppression are key questions that remain to be addressed. Interestingly, in the experimental lung metastases tumor models used in our study,[6] we observed that intracellular IL-23 production was specifically restricted to MHC-II^{hi}CD11c^{+}CD11b^{+} cells. We are currently characterizing the phenotype of these cells and determining if they are also present in subcutaneous tumor models where neutralization of IL-23 was therapeutic. Given that IL-12 and IL-23 share a common receptor subunit, IL-12Rβ1, it was assumed that expression of the IL-12 and IL-23 specific receptors would be expressed on cells where IL-12Rβ1 was present; neutralization of IL-23 therefore allowed the activation of a Th1 signaling pathway. However, a recent paper has demonstrated a dichotomous pattern of expression for IL-12 and IL-23 receptors in both mouse and human,[10] suggesting that immune cells involved in anti-tumor responses may be quite distinct from those that are tumor promoting.

Overall, our data suggest the clinical potential of using anti-CD40 (push) and anti-IL-23 mAbs (pull) to tip the IL-12/23 balance in established tumors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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