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Tumor-derived factors affecting immune cells

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ABSTRACT

Tumor progression is accompanied by the production of a wide array of immunosuppressive factors by tumor and non-tumor cells forming the tumor microenvironment. These factors belonging to cytokines, growth factors, metabolites, glycan-binding proteins and glycoproteins are responsible for the establishment of immunosuppressive networks leading towards tumor promotion, invasion and metastasis. In pre-clinical tumor models, the inactivation of some of these suppressive networks reprograms the phenotypic and functional features of tumor-infiltrating immune cells, ultimately favoring effective anti-tumor immune responses. We will discuss factors and mechanisms identified in both mouse and human tumors, and the possibility to associate drugs inhibiting these mechanisms with new immunotherapy strategies already entered in the clinical practice.

1. Introduction

The deep analysis of the tumor microenvironment has revealed in recent years several immunosuppressive networks dampening the anti-tumor immune responses both in mouse and human tumors. Some of these immunosuppressive networks are promoted by soluble factors produced and released by the tumor cells themselves or non-tumor cells within the tumor microenvironment [1]. Overall, the establishment of the immunosuppressive networks contributes to tumor growth, invasion and metastasis [2], both directly through the inhibition of immune cells crucially involved in the eradication of tumors, *i.e.* T cells and antigen presenting cells (APCs), and indirectly through the reprogramming of myeloid cells creating a hospitable and protective niche for metastasizing tumor cells [3]. Moreover, they also endow tumor cells with the ability to resist chemotherapy and immunotherapy [3] [4]. Soluble factors can dampen or shape distinct subsets of immune cells infiltrating the tumor microenvironment among which APCs, such as dendritic cells (DCs) and monocytes/macrophages, and T cells. Various immunosuppressive mechanisms have been identified so far, we will mainly discuss those induced by factors released by both mouse and human tumors with the ultimate goal to provide a rationale to combine drugs and immunotherapeutic drugs/strategies already on the market or close to enter the clinical arena in order to improve the anti-tumor immune response.

2. Tumor microenvironmental factors influencing DC function

DCs play a key role in the induction of the antitumor immune response, as demonstrated by the ability of DC-based vaccines to induce objective clinical responses in cancer patients [5]. Recent reviews focusing on the mechanisms leading to DC dysfunction in solid tumors have been published [6,7], here we focus on the role of soluble factors present in the tumor microenvironment directly impacting on DC number and function. The factors/molecules that we will discuss are summarized in Table 1.

Abbreviations: APC, antigen presenting cells; CRD, carbohydrate recognition domain; DCs, dendritic cells; GDF-15, growth differentiation factor-15; IL, interleukin; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon-γ; LXR, liver X receptors; M-CSF, macrophage-colony stimulating factor; mAbs, monoclonal antibodies; NO, nitric oxide; NOS, nitric oxide synthase; RNS, reactive nitrogen species; ROS, reactive oxygen species; SULT2B1b, sulfotransferase 2B1b; TCR, T cell receptor; TGF-β, transforming growth factor-β; TILs, tumor infiltrating lymphocytes; Th, T helper; TNF-α, tumor necrosis factor-α; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor; XBP1, x-box-binding protein 1.

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Table 1
Soluble factors affecting DC function.

Molecule	Expressed by	Function	Reference
Cytokines and growth Factors			
VEGF	Tumor cells, endothelial cells	Inhibition of DC differentiation and maturation	[8]
IL-6	Tumor cells, immune cells	Inhibition of DC differentiation and maturation	[11]
M-CSF	Tumor cells, immune cells	Inhibition of DC differentiation and maturation	[11]
IL-10	Tumor cells, immune cells	Inhibition of mono-DC differentiation and of antigen presenting capabilities of DCs. Increase of PD-L1 expression	[19,20,7]
TGF-β	Tumor cells, immune cells	Down-regulation of DC costimulatory and presenting molecules. Inhibition of TNF-α and IL-12 production. Increase of PD-L1 expression	[29,30,32,33]
TSLP	Tumor cells, cancer associated fibroblasts	Induction of naïve $CD4^+$ T cells towards inflammatory Th2 cells	[36,37]
Oncometabolites			
Lactic acid accumulation	Tumor cells	Inhibition of mono-DC differentiation and of antigen presenting capabilities of DCs. Inhibition of IL-12 production.	[47,46]
Triglycerides accumulation	DC accumulation	Reduction of DC antigen processing capabilities. XBP1 is involved in lipid-laden DC generation	[48,50]
Oxysterols	Tumors, immune cells	Inhibition of CCR7-dependent DC migration.	[61]
Adenosine accumulation	Hypoxic tumor cells	Induction of aberrant DC differentiation	[74]

2.1. Cytokines and growth factors

In 1996 Gabrilovich and colleagues extensively investigated the role played by the Vascular Endothelial Growth Factor (**VEGF**) produced by human and mouse tumors on DCs [8]. They demonstrated that VEGF was able to impair the differentiation and maturation of DCs from hematopoietic precursors both in vitro and in vivo [8]. The inhibition of VEGF was reported to recover DC differentiation and maturation. Of note, studies investigating DC numbers in the blood of cancer patients inversely correlated with VEGF serum levels [9], thus suggesting the possibility that neutralizing VEGF by the well-known monoclonal antibody (mAb) bevacizumab could target at the same time both neoangiogenesis and DC recovery in cancer patients [10].

Interleukin (IL)-6 (**IL-6**) and the Macrophage-Colony Stimulating Factor (**M-CSF**), both produced by human renal carcinoma cells were reported to induce effects similar to those observed with VEGF. These factors were shown to inhibit the differentiation of $CD14^+CD1a^-$ precursors into DCs and to block the acquisition of APC function of the $CD14^-CD1a^+$-derived DCs [11]. Blocking these two cytokines with specific mAbs restored DC differentiation and APC function in vitro. Interestingly, it was also reported that IL-4 and IL-13 were able to reverse the inhibitory effects of tumor-conditioned media or IL-6 plus M-CSF on the phenotypic and functional differentiation of $CD34^+$ cells into DCs. In particular, IL-4 was found to act through the blockade of M-CSF and IL-6 receptor-transducing chain (gp130) expression [12].

In ovarian cancer patients increased plasma levels of **IL-8** and IL-6 correlated with the production of both cytokines by cultured ovarian cancer cell lines [13], and specific blockade of IL-6 and IL-8 production restored the T cell stimulatory activity of human DCs.

IL-10 is the prototype of the anti-inflammatory cytokines and it is produced by innate and adaptive immune cells, including T cells, natural killer cells, as well as APCs [14] [15]. In cancer immunology IL-10 has been long considered an immunosuppressive cytokine: however, its role remains controversial (see also below) [16]. Several human and mouse tumors have been reported to release IL-10 [17]. In agreement with these data increased levels of IL-10 in the sera of patients affected by liver cancer were found to correlate with circulating DC subsets with an immature phenotype [18]. IL-10 may affect DCs at distinct differentiation/maturation steps. The addition of IL-10 to human monocytes differentiating into DCs induced the development of macrophages with lower levels of MHC-II and the acquisition of markers typically expressed by macrophages, such as the nonspecific esterase and high levels of CD14, CD16 and CD68 [19,20]. When IL-10 was added to already differentiated DC, IL-10 induced only a slight reduction of MHC class II and CD1a expression, with no acquisition of the macrophage markers CD14, CD16 and CD68. Nevertheless, IL-10-treated DCs, while acquiring high endocytic activity, were poor stimulators in mixed lymphocyte reaction and of tetanus toxin-specific T-cell lines [20]. Of note, a microarray analysis of monocyte-derived DCs treated with a combination of LPS and IL-10 showed a reduced expression of several LPS-inducible pro-inflammatory molecules and among genes uniquely modulated by the combined treatment PI3Kγ was down-regulated while SOCS3 was up-regulated [21]. Tumor-derived IL-10 was also shown to inhibit CD40 expression, to suppress CD40-dependent IL-12 production, to decrease chemokine receptor expression, to blocks antigen presentation and to induce up-regulation of B7-H1/PD-L1 expression on DCs [7]. Accordingly, Steinbrink [22], and colleagues investigated the effect of IL-10-treated human DCs on the function of melanoma-associated antigen-specific $CD8^+$ T cells and showed induction of antigen-specific anergy when tyrosinase-specific cytotoxic $CD8^+$ T cells were co-cultured with IL-10-treated tyrosinase-pulsed DCs [22].

Interestingly, treatment of melanoma cells with the MEK inhibitor U0126 or RNA interference for BRAF $V600^E$ mutation was reported to decrease the production of IL-10, VEGF and IL-6 [23]. In addition, DCs treated with LPS and concomitantly exposed to supernatants of BRAF $V600^E$ silenced melanoma cells produced high levels of the inflammatory cytokines IL-12 and tumor necrosis factor-α (TNF-α), as compared to mock-treated melanoma cells. These effects were comparable to those observed with STAT3 silencing [23]. The above-reported immunosuppressive effects exerted by melanoma cells harboring the BRAF $V600^E$ mutation could be alleviated by the treatment with BRAF inhibitors. BRAF inhibitor-based treatments abrogated immunosuppression present in the tumor microenvironment of melanoma patients by increasing T-cell infiltration and function, improving NK cell activity as well as DC function [24]. These studies provide the rationale for the combination of target therapies and immune checkpoint blockers in melanoma patients. Indeed, both the blockade of the continuous BRAF $V600^E$ signaling and of the release of immunosuppressive cytokines, induced by selective BRAF inhibitors, would synergize with the invigoration of anti-tumor

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