Immunosuppressive Cells

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Tumor-associated macrophages (TAMs) produce various chemokines and angiogenic factors that promote tumor development, along with other immunosuppressive cells. TAMs generated from monocytes develop into functional, fully activated macrophages, and TAMs obtain various immunosuppressive functions to maintain the tumor microenvironment. The main population of TAMs comprises CD163+ M2 macrophages, and CD163+ TAMs release soluble (s)CD163 and several proinflammatory chemokines as a result of TAM activation to induce an immunosuppressive tumor microenvironment. Since direct blockade of PD1/PD-L1 signaling between tumor cells and tumor-infiltrating T cells is mandatory to induce an anti-immune response by anti-PD1 Abs. Understanding the crosstalk between TAMs and immunosuppressive cells is important for optimizing PD1 Ab-based immunotherapy.

tumor-associated macrophages (TAMs) Immunosuppressive microenvironment tumor-associated neutrophils (TANs) PD1/PD-L1 signaling regulatory T cells (Tregs) myeloid derived suppressor cells (MDSCs)

1. Definition

Tumor-associated macrophages (TAMs) have been detected in most skin cancers. TAMs produce various chemokines and angiogenic factors that promote tumor development, along with other immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs) and tumor-associated neutrophils. TAMs generated from monocytes develop into functional, fully activated macrophages, and TAMs obtain various immunosuppressive functions to maintain the tumor microenvironment. Since TAMs express PD1 to maintain the immunosuppressive M2 phenotype by PD1/PD-L1 signaling from tumor cells, and the blockade of PD1/PD-L1 signaling by anti-PD1 antibodies (Abs) activate and re-polarize TAMs into immunoreactive M1 phenotypes, TAMs represent a potential target for anti-PD1 Abs.

2. Introduction

Tumor-associated macrophages (TAMs) have been detected in most skin cancers [1]. TAMs produce various chemokines that attract other immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs) and tumor-associated neutrophils (TANs) to maintain an immunosuppressive tumor microenvironment [1]. TAMs also produce matrix metalloproteinases (MMPs), which play critical roles in the tissue remodeling associated with protein cleavage to modify the immune microenvironment, angiogenesis, tissue repair,

local invasion, and metastasis [1][2]. In addition, TAMs express immune checkpoint modulators (e.g., programmed death ligand 1 [PD-L1], B7-H3, B7-H4) [3] that directly suppress activated T cells. Moreover, TAMs also express PD1, which is necessary for maintaining M2 phenotypes in TAMs via PD-L1/PD1 signaling from tumor cells [4]. Taken together, TAMs are a heterogeneous population of macrophages that play a central role in the induction of immune tolerance in the tumor microenvironment [1].

Not only TAMs, but also other immunosuppressive cells such as MDSCs, Tregs and TANs, should be taken into account when evaluating the immunosuppressive microenvironment of skin cancers [5][6][7]. Similar to TAMs, both MDSCs and TANs directly or indirectly suppress anti-tumor immune response [6][7], whereas Tregs directly suppress tumor-specific cytotoxic T cells in the tumor microenvironment [5]. Notably, environmental risk factors for skin cancer (e.g., sun exposure, chemical exposure) have been widely reported [8]. These risk factors modulate the profiles of tumor-infiltrating leukocytes (TILs), at least in part, through aryl hydrocarbon receptor (AhR)-dependent signal pathways [9]. Chronic exposure to AhR ligands at skin lesions is known to induce chronic inflammation, including macrophages, neutrophils and T cells [10]. Skin cancer is thus one of the optimal models to discuss the development of immunosuppressive microenvironments in cancers.

Since PD-L1/PD1 signaling is necessary for maintaining TAMs as immunosuppressive macrophages in PD-L1-expressing cancers such as melanoma, non-small cell lung cancer, colorectal cancer and Hodgkin's lymphoma [4][11][12], anti-PD1 antibodies (Abs) such as nivolumab and pembrolizumab could activate and re-polarize TAMs into anti-tumor macrophages. In another report, Wang et al. reported that $PD1^+$ TAMs suppress $CD8^+$ T-cell function in gastric cancer [11]. More recently, Li et al. reported that exosomal HMGB1 could trigger the generation of $PD1^+$ TAMs in esophageal carcinoma [12]. Notably, anti-PD1 Abs are useful and clinically permitted to be used for these cancer species. Taken together, anti-PD1 Abs could not only abrogate the immune suppression and re-activate $CD8^+$ cytotoxic T cells [5], but also activate TAMs to induce an anti-tumor immune response by blocking of PD-L1/PD1 signaling pathway. Not only TAMs, but also MDSCs and Tregs help maintain an immunosuppressive microenvironment through PD-L1/PD1 signaling [3]. MDSCs can induce Tregs [13], and Tregs regulate the immunosuppressive function of MDSCs through PD-L1 [3].

3. Significance of Immunosuppressive Cells in Developing Skin Cancers

3.1. Significance of TAMs in Developing Skin Cancers

3.1.1. Chemokines from TAMs Determine Profiles of Tumor-Infiltrating Lymphocytes (TILs) in the Tumor Microenvironment

Since TAMs are stimulated by stromal factors, and produce characteristic chemokines in each tumor site in melanoma and non-melanoma skin cancers [1], understanding the correlations between chemokines derived from TAMs and stromal factors in each cancer species is important. The extracellular matrix protein periostin (POSTN) is expressed in the region surrounding melanoma cell nests in metastatic melanoma lesions [14], and could be a

stimulator for TAMs in melanoma [1]. Notably, CD163$^+$ M2 macrophages increase the production of chemokine C-C motif (CCL)17 and CCL22, both of which are known to recruit regulatory T cells (Tregs), by POSTN stimulation in vitro [15], and chemokine production is suppressed by type I interferons (IFNs) [16][17], suggesting that TAMs could also be used as a target of immunotherapy. Indeed, Georgoudaki et al. reported that TAMs derived from mouse B16 melanoma expressed macrophage receptor with collagenous structure (MARCO), and intravenous administration of anti-MARCO antibodies (Abs) reprogrammed the TAMs population to a proinflammatory phenotype and increased tumor immunogenicity [18]. In another report, IFN-β decreases the production of CCL22 from TAMs in B16F10 melanoma, leading to suppression of tumor growth by the modulation of TIL profiles in vivo [17]. Based on these pre-clinical findings of TAM-targeting therapies, a clinical study has already been undertaken [19]. Taken together, these reports suggest the significance of chemokines from TAMs that can be influenced by stromal factors to induce melanoma-specific profiles of TILs in melanoma.

Non-melanoma skin cancers such as extramammary Paget's disease (EMPD), cutaneous squamous cell carcinoma (cSCC) and Merkel cell carcinoma (MCC) also possess heterogeneous CD163$^+$ TAMs that could secrete an array of cytokines and chemokines in lesional skin to regulate the tumor microenvironment [1][20][21][22]. For example, serum sCD163 is increased in patients with EMPD compared to healthy donors [23], suggesting that CD163$^+$ TAMs are constitutively activated in the lesional skin of EMPD. Indeed, soluble receptor activator of nuclear factor kappa-B ligand (RANKL) released by Paget's cells activates TAMs and increases the production of CCL5, CCL17 and chemokine CXC motif (CXCL)10 from RANK$^+$CD163$^+$ M2 polarized TAMs [20]. These data suggested that sCD163 could represent a biomarker for the progression of EMPD. On the other hand, as Petterson et al. reported [21], CD163$^+$ TAMs in cSCC heterogeneously polarized from M1 to M2, suggesting heterogeneous activation states of TAMs. CD163$^+$ TAMs contribute to the tumor microenvironment in MCC to promote tumor development by inducing lymphangiogenesis and immunosuppressive cells such as Tregs [22][24]. These reports suggested that CD163$^+$ TAMs could represent a therapeutic target for the treatment of these non-melanoma skin cancers.

3.1.2. Angiogenic Factors from TAMs

TAMs produce angiogenic factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor, and matrix metalloproteinases (MMPs) to induce neovascularization [1][25][26][27]. Recent reports have suggested that melanoma-derived factors could differentiate M2 macrophages that produce angiogenic factor such as VEGF and MMP9 [25][27]. Among these, Tian et al. reported that expression of tripartite motif (TRIM)59 on TAMs attenuates the tumor-promoting effect of TAMs by inhibiting MMP9 expression on melanoma cells [25]. They conclude that TRIM59 in TAMs could be a potential regulator of tumor metastasis, and thus provide a target for immunotherapy [25]. Notably, MMP9 facilitates MMP9-dependent cleavage of PD-L1 surface expression, leading to anti-PD1 Ab resistance [27]. Taken together, the decreased expression of MMP9 achieved by targeting TAMs would suppress anti-PD1 Ab resistance by inhibiting PD-L1 downregulation.

Overall, TAMs produce a series of chemokines and angiogenetic factors under the stimulation of cancer-specific stromal factors to maintain an immunosuppressive tumor microenvironment in each cancer species.

3.2. Myeloid-Derived Suppressor Cells (MDSCs)

3.2.1. Significance of MDSCs in Developing Skin Cancers

MDSCs are one of the key types of immunosuppressive cells with heterogeneous cell populations that can be found in tumor-bearing mice and in patients with cancer (Table 1) [6]. In humans, MDSCs are defined by a combination of several surface markers (e.g., $CD11b^{+}CD14^{-}HLA\text{-}DR^{-}$ for monocytic (Mo-)MDSCs, or $CD11b^{+}CD14^{-}CD33^{+}CD15^{+}CD66b^{+}$ for granulocytic (G)MDSCs) [28][29]. Since these markers are also expressed on other immune cells, such as neutrophils (e.g., CD15, CD66b), evaluation of direct immunosuppressive function is mandatory for the definition of MDSCs [28].

Table 1. Positive and negative markers for TAMs and MDSCs.

	Subtypes	Positive	Negative
TAMs	M1	CD68, CD86, CD169, HLA-DR, CCR7	
	M2	CD163, CD204, CD206, PD-L1, ARG1	
MDSCs	MoMDSC	CD11b, PGE2, IL-10, TGFb, iNOS, ARG1	HLA-DR, CD14
	G-MDSC	CD15, CD33, CD66b, ROS, G-CSF, ARG1	HLA-DR, CD14

The immunosuppressive functions of MDSCs are mediated by several secreted factors, including prostaglandin E2 (PGE2), IL-10, transforming growth factor (TGF)-β, nitric oxide (NO) and arginase 1 (Arg1) for Mo-MDSCs [28][30], and reactive oxygen species (ROS), granulocyte-colony stimulating factor (G-CSF) and Arg1 for G-MDSCs [28]. Since Mo-MDSCs are generated from monocytes, and further differentiate to TAMs, Mo-MDSCs and TAMs in human tumors share several cell surface markers [28][30][31]. On the other hand, although several reports have suggested that G-MDSCs are generated from the neutrophil linage, the differentiation of G-MDSCs remains under discussion [28][32]. Notably, both Mo-MDSCs and G-MDSCs correlate with poor prognosis IN cancer patients [32][33]. Targeting MDSCs for the treatment of cancer patients is thus considered to resemble targeting TAMs.

3.2.2. MDSCs and ICIs

Recent reports have suggested the significance of MDSCs in patients with advanced cancer treated using immune checkpoint inhibitors (ICIs) [29]. Increased microRNAs in the plasma of melanoma patients are associated with the generation of MDSCs mediated by melanoma extracellular vesicles, and are even associated with resistance to treatment with ICIs in melanoma patients [29], suggesting that MDSC-related miRs could offer a biomarker of poor prognosis in melanoma patients treated with ICIs. Moreover, among the miRs, a recent report also suggested that miR-150-5p mediates angiogenesis function through the secretion of vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP)9 [30]. In another study, hypoxia induced miR-210 to modulate MDSC function by increasing Arg activity and NO production, without affecting ROS, IL6, or IL10 production or expression of PD-

L1 [34]. Notably, as we described above, since MDSCs (like TAMs) secrete MMP9 [35] to facilitate MMP9-dependent cleavage of PD-L1 surface expression anti-PD1 Ab resistance [36], hypoxia hinders the anti-tumor effects of anti-PD1 Abs. Since hypoxia-inducible factor (HIF)-1a is one of the key regulators for the differentiation and accumulation of MDSCs in hypoxic tumor regions [37][38], targeting HIF-1a might improve anti-tumor immune responses in patients with anti-PD1 Abs.

3.2.3. Cross-Talk between MDSCs and Other Immunosuppressive Cells

Not only direct immune suppression, MDSCs induce other immunosuppressive cells, such as regulatory T cells (Tregs) and TAMs to maintain the immunosuppressive tumor microenvironment [32]. For example, Hwang et al. reported that $Gr1^+CD115^+$ MDSCs can induce de novo generation of Tregs from adoptively transferred antigen-specific $CD25^-CD4^+$ T cells in the presence of IL-10 and interferon (IFN)-γ in vivo [13]. In another report, MDSCs expanded tumor-specific Tregs via Arg-dependent and TGF-b-independent pathways [39]. On the other hand, Tregs regulated the immunosuppressive function of MDSCs through B7 homologs (B7-H1, B7-H3, B7-H4) in a mouse ret tumor model in vivo [3]. In addition to Tregs, TAMs could also affect MDSC recruitment at the tumor site [40][41][42]. Since several types of MDSCs express CXCR2 [41][42], intratumor production of CXCL5 and CXCL8 is important to migration of MDSCs in the tumor microenvironment [40]. Since one of the main sources of CXCL5 in advanced melanoma is TAMs [35], and CXCL5 could be a predictive biomarker for the efficacy of anti-PD1 Abs in advanced melanoma patients [43], the CXCR2/CXCL5 axis should play a significant role in recruiting MDSCs to the tumor site, and blockade of CXCR2 enhanced anti-tumor immune responses in a melanoma model [44]. Notably, TAMs also produce CCL17 and CCL22 to promote migration of $CCR4^+$ Tregs to the tumor site [29]. Since TAMs are a heterogeneous population of cells, and could re-polarize from immunosuppressive M2 phenotypes to classically activated phenotypes by immunotherapy such as type 1 IFN [45] and anti-PD1 Abs [4], these reagents could inhibit migration of $CCR2^+$ MDSCs and $CCR4^+$ Tregs to the tumor site to induce anti-tumor immune responses in the tumor-bearing host.

In summary, another type of immature macrophage, the MDSC, maintains an immunosuppressive microenvironment by suppressing tumor-specific T cells directly or indirectly. Notably, MDSCs expressed PD-L1, and thus could also represent a target for immunotherapy using anti-PD1 Abs.

3.3. Regulatory T Cells: Tregs

3.3.1. Significance of Tregs in Developing Skin Cancers

As described above, Tregs maintain an immunosuppressive tumor microenvironment in skin cancers together with other immunosuppressive cells. Previous report has suggested that a large number of effector (e)Tregs ($CD45RA^-Foxp3^{high}CD25^{high}$) infiltrate tumor sites to induce tolerance by various pathways and thus suppress the function of tumor-specific T cells, contributing to poor prognosis in cancer patients [5]. Notably, eTregs highly express various immune checkpoints, including CTLA4 and PD1, to suppress activated cytotoxic T cells, suggesting that eTregs could represent an optimal target for ICIs such as ipilimumab and nivolumab [5][43][46]. Indeed, Romano et al. reported that ipilimumab depletes $CTLA4^+$ Tregs through antigen-dependent cell-mediated

cytotoxicity (ADCC) in melanoma patients [46]. In addition, eTregs express inducible T-cell costimulator (ICOS), which promotes the proliferation of activated eTregs by ICOS ligand expressed by plasmacytoid dendritic cells (DCs) [47].

3.3.2. Tregs and ICIs: Anti-PD1 Abs and Anti-CTLA4 Abs

As we described above, eTregs express various immune checkpoints and suppress the cytotoxic function and proliferation of conventional effector T cells to maintain an immunosuppressive tumor microenvironment [5][43]. Indeed, $CD45RA^{-}Foxp3^{high}CD25^{high}$ eTregs express CTLA4 as well as PD1, ICOS, GITR, OX-40 and LAG3 [43]. CTLA4 expressing Tregs bind to CD80/86 on DCs to inhibit maturation of DCs [48]. Moreover, eTregs produce inhibitory cytokines (TGF-b, IL-10, IL-35) to promote B lymphocyte-induced maturation protein (BLIMP1)-dependent exhaustion of $CD8^{+}$ TILs in the tumor microenvironments of B16 melanoma and the BrafPten melanoma model [49]. In addition to being a therapeutic target, $PD1^{+}$ Tregs are also a useful diagnostic target for anti-PD1 Ab monotherapy [50][51][52]. For example, decreased circulating $PD1^{+}$ Tregs could offer a predictive marker for favorable clinical outcomes from anti-PD1 Abs in advanced melanoma [50]. Moreover, in another report, nivolumab monotherapy in an adjuvant setting decreased circulating $PD1^{+}$ Tregs in stage III melanoma patients [51].

Although nivolumab plus ipilimumab combined therapy is one of the first-line therapies for unresectable melanoma, and is a most effective protocol for BRAF wild-type melanoma, the frequency of serious adverse events is higher than that with anti-PD1 Ab monotherapy [53]. As mentioned above, since ipilimumab depletes $CTLA4^{+}$ Tregs through ADCC, as one of the mechanisms for inducing anti-tumor immune response in melanoma patients that leads to induction of high therapeutic efficacy when administered with nivolumab [46][53], investigations for other drugs that selectively deplete eTregs are ongoing.

For these reasons, several recent studies have targeted eTregs to establish novel anti-PD1 Ab-based immunotherapies [6][52][54]. Among those, Doi et al. reported a phase 1 study of mogamulizumab, an anti-CCR4 Ab, in combination with nivolumab for the treatment of solid tumors [54]. They concluded that mogamulizumab decreased the population of eTregs ($CD4^{+}CD45RA^{-}Foxp3^{high}$) during treatment, with an acceptable safety profile in combination with nivolumab [49]. More recently, Schoonderwoerd et al. reported that Abs for endothelin, a coreceptor for TGF-β ligands, significantly decreased the number of intratumoral Tregs, leading to enhanced anti-tumor immune response with anti-PD1 Ab therapy [52]. Hu-Lieskovan et al. reported that dabrafenib monotherapy increased TAMs and Tregs in melanoma, which decreased with the addition of trametinib, suggesting that dabrafenib plus trametinib combination therapy could decrease immunosuppressive Tregs, and enhance the anti-tumor effects of anti-PD1 Abs in melanoma patients [6].

Taken together, Tregs suppress tumor-specific T cells, leading to induction of tolerance in the tumor microenvironment in skin cancers. Since Tregs express both PD1 and CTLA4, Tregs could represent an optimal target for nivolumab plus ipilimumab combination therapy.

3.4. TANs in Developing Skin Cancers

Neutrophils are polymorphonuclear cells that are classically known to play roles in acute immune responses (e.g., host defense, immune modulation, tissue injury) as one of the innate immune cells [7]. Since oncologists started focusing on cancer inflammation as one of the main facilitators for development of the tumor microenvironment, TANs have recently been taken into accounts as immunosuppressive cells, even in skin cancer [55][56][57]. Indeed, TANs could drive tumor progression through various pathways. For example, TANs not only eliminate the pathogen by phagocytosis, but also lead to DNA base damage and mutation, and subsequent initiation of tumor development [58]. In addition, TANs produce various tumor-driving cytokines such as TGF-β into the tumor microenvironment to maintain macrophages as an M2-polarized phenotype [59], leading to promotion of tumor progression. TANs also produce inducible nitric oxide synthase (iNOS) to directly suppress $CD8^+$ effecter T cells at the tumor site [60]. Such reports suggest the significance of inhibiting TAN recruitment at tumor sites.

Among the inducers of TANs, IL-17 could play a significant role in developing skin cancers. Indeed, several reports have suggested the significance of IL-17 in the development of skin cancers such as cutaneous squamous cell carcinoma (cSCC) [61][62] and extramammary Paget's disease (EMPD) [23]. For example, Wu et al. reported that IL-17 signaling in keratinocytes drives IL-17-dependent sustained activation of the TRAF4-ERK5 axis, leading to keratinocyte proliferation and tumor formation in cSCC [61]. Gasparoto et al. reported a significant correlation between IL-17 and development of mouse cSCC [62]. More recently, a possible correlation of CCL20/IL-23/IL-17 axis in the development of EMPD has been reported [23]. These reports suggest the significance of IL-17 in the carcinogenesis of skin cancers, and IL-17 might be partially caused by the induction of TANs at the tumor site.

In aggregate, TANs are induced by IL-17-related cancer inflammatory factors. TANs produce iNOS to directly suppress the proliferation of effector T cells at a tumor site to promote cancer development.

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