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Role of dendritic cells in the regulation of antitumor immunity

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Abbreviations: DC, dendritic cell; HMGB1, high mobility group box 1; ICAM1, intercellular adhesion molecule 1; LFA1, lymphocyte function-associated antigen 1; NRP1, neuropilin 1; PD1, programmed death 1; PD-L1, PD1 ligand 1; TIM3, T-cell immunoglobulin mucin 3

The majority of rodent and human tumors express antigens that can be recognized by T lymphocytes and are infiltrated by immune cells. Although tumor infiltration by T lymphocytes has been associated with a favorable prognosis, the role of dendritic cells (DCs), which may present tumor-associated antigens in an immunogenic or tolerogenic context, remains elusive. Here, we discuss recent observations suggesting that the function of DCs in the tumor microenvironment may impact the spontaneous resistance of neoplasms to chemotherapy as well as treatment outcome.

Introduction

Accumulating evidence indicated that spontaneous antitumor immune responses exert a strong impact on the clinical outcome of malignant diseases, confirming the concept of cancer immunosurveillance. Moreover, the infiltration of tumors by immune cells in response to radio- or chemotherapy has been associated with a favorable prognosis, suggesting that these conventional therapeutic regimens may not only affect tumor growth in a cell-intrinsic manner, but also activate anticancer immunity, at least in some settings.[1]

Large clinical studies have revealed the prognostic impact of tumor infiltration by T lymphocytes for colorectal cancer,[2,3] ovarian carcinoma,[4,5] and metastatic melanoma[6] patients. In addition, a few studies have linked immune system-related genes to the response to chemotherapy.[7,8] In patients as well as in murine models, there is ample evidence for a critical role of T_H1 and cytotoxic responses in tumor rejection,[9,10] although innate immunity, in particular as mediated by natural killer (NK) cells, is also clearly involved in this process.[11,12]

Collectively, these observations highlight a critical role for T lymphocytes in antitumor immune responses. An important issue in this context is the contribution of DCs to T-cell priming, which presumably occurs in tumor-draining lymph nodes, as well as to the functional differentiation of intratumoral T lymphocytes.

Here, we review a few recent reports illustrating how DCs may affect anticancer immunity and the efficacy of chemotherapy. Some observations suggest indeed that intratumoral DCs may dysregulate tumor-specific immune responses.

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HMGB1, a Prototypic Tumor-Derived Immunostimulatory Factor

To identify the Toll-like receptors (TLRs) that might control the immune response to dying tumor cells, Apetoh et al. inoculated oxaliplatin-treated EG7 cells into the footpads of either wild-type or TLR-deficient hosts and monitored interferon (IFN)γ production upon re-stimulation in vitro with the model antigen ovalbumin (OVA).[13] IFNγ was produced by lymph node cells in WT mice as well as in animals individually lacking several TLRs but not in *Tlr4*$^{-/-}$ mice. Moreover, DC depletion abrogated the priming of T lymphocytes against dying tumor cells and high mobility group box 1 (HMGB1) was shown to constitute the principal damage-associated molecule to activate TLR4. These data identified one TLR ligand as a critical factor in death-derived immunoadjuvant effect of chemotherapy. HMGB1 is a non-histone chromatin-binding nuclear protein that interacts with TLR4, advanced glycosylation end product receptor (AGER) and probably other receptors, hence modulating inflammatory responses. These results illustrate the contribution of the immune system to the efficacy of chemotherapy, although this depends on the nature of the cytotoxic agent, tumor type,[14] the host immunocompetence. In addition, this work highlights the critical role of TLR4$^+$ dendritic cells as sensors and efficient cross-presenters of tumor-associated antigens (TAAs) derived from dying cancer cells (**Fig. 1**).

This said, it has recently been demonstrated that DCs may inhibit pattern recognition receptor (PRR)-mediated innate immune responses in the tumor microenvironment. In particular, Chiba et al. elegantly identified the receptor T-cell immunoglobulin mucin 3 (TIM3) as a key factor that prevents the immunological response of DCs to nucleic acids.[15] The authors first noticed

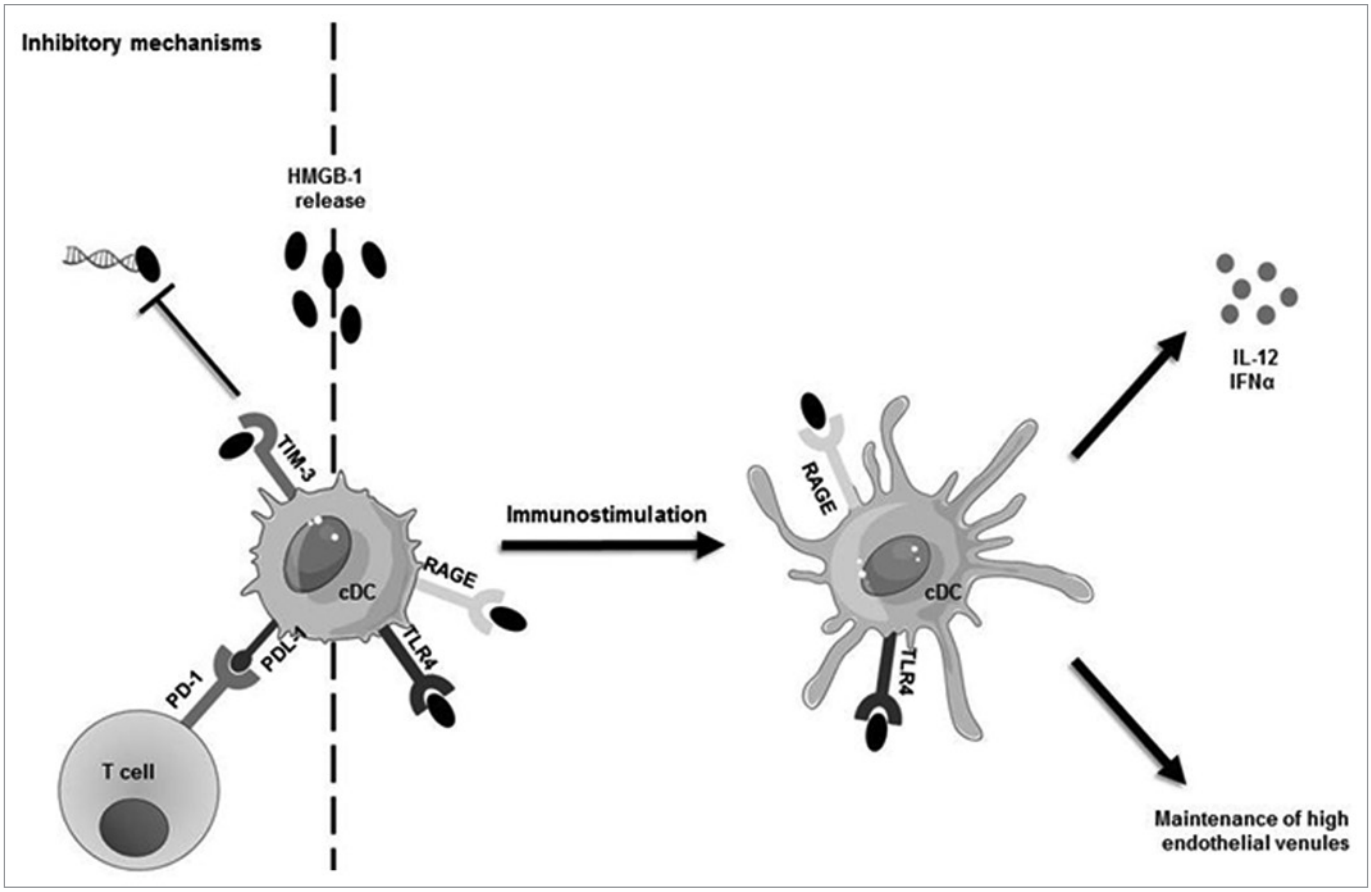

Figure 1. Functional defects of conventional dendritic cells in the tumor microenvironment. The release of high mobility group box 1 (HMGB1) by dying tumor cells may trigger dendritic cell (DC) activation, leading to the presentation of tumor-associated antigen to T cells, the secretion of interferon α (IFNα) and intereleukin-12 (IL-12) as well as to the formation of high endothelial venules. This immunogenic pathway may be prevented by the activation of T-cell immunoglobulin mucin 3 (TIM) or by the interaction between programmed death 1 (PD1) ligand 1 (PD-L1) with its cognate receptor on T cells.

that CD11c^{high} conventional DCs expressed much higher levels of TIM3 when they infiltrate subcutaneous Lewis lung tumors or MC38 colorectal adenocarcinomas than when they are found in autologous normal lymphoid organs. They identified vascular endothelial growth factor (VEGF), interleukin (IL)-10 and arginase I as soluble factors that upregulate TIM3 expression on DCs. Moreover, TIM3 was shown to interfere with the response of DCs to immunostimulatory nucleic acids, as TIM3 prevented the nucleic acid-triggered production of Type I IFN and IL-12 by DCs (**Fig. 1**). TIM3 and nucleic acids compete for binding HMGB1,[13] resulting in the inhibition of the HMGB1-dependent transfer of nucleic acids to endosomes. Based on results from previous studies,[16,17] Chiba et al. propose that HMGB1 may promote the access of nucleic acids to endosomal vesicles, thereby inducing innate responses. Of note, a similar mechanism may occur in cancer patients, as high expression levels of TIM3 have been detected on tumor-associated DCs isolated from patients bearing advanced non-small cell lung carcinoma (NSCLC), gastric adenocarcinoma or neuroendocrine tumors.[15]

In the same study, TIM3 appeared to be expressed on T cells at late time points,[15] and it had previously been demonstrated that inhibiting TIM3- and programmed death 1 (PD1)-transduced signals reverse the exhaustion of tumor-specific CD8$^+$ T cells isolated from melanoma patients in vitro. Most of these cells express indeed TIM3 and PD1 and are dysfunctional in terms of cytokine production.[18] In a model of murine colon carcinoma (based on CT26 cells), the combined administration of anti-TIM3 and anti-PD1 ligand 1 (PD-L1) antibodies resulted in delayed tumor growth, with 50% of the mice exhibiting complete tumor regression and long-term survival.[19] Thus, TIM3 may impair the function of several types of immune cells in the tumor microenvironment and may constitute a promising target to enhance spontaneous tumor-specific immune responses.

Maturation of DCs

One of the hallmarks of DCs is their progressive acquisition of specialized functions. Immature DCs efficiently take up and process antigens (usually in peripheral tissues), whereas mature DCs become fully competent to prime naïve T cells (mainly in lymphoid organs). The maturation of DCs is induced by microbial components (so-called pathogen-associated molecular patterns, PAMPs) or pro-inflammatory factors, eventually resulting in the elicitation of immune responses against non-self, microbial

antigens. Of note, immature DCs can induce a state of unresponsiveness in T lymphocytes (anergy) via poorly defined mechanisms, hence preventing or dampening antitumor T-cell responses in vivo. In addition, immature DCs appear to interact preferentially with regulatory T cells, as compared with naïve helper T cells, hence mediating to a "default immunosuppression." Indeed, $CD4^+CD25^+$ cells preferentially interact with immature DCs as compared with their $CD4^+CD25^-$ counterparts, correlating with a comparatively higher expression of the adhesive molecule neuropilin 1 (NRP1).[20] Thus, immature DCs may directly or indirectly dampen helper T-cell functions.

Several reports suggest that tumor-infiltrating DCs are functionally impaired. Early evidence in support of this notion was provided in 2002 by Vicari and colleagues, who observed that DCs infiltrating transplantable tumors and hepatocarcinomas developing in X/myc transgenic mice essentially displayed an immature phenotype.[21] Moreover, these immature DCs were refractory to lipopolysaccharide (LPS) plus IFNγ plus anti-CD40 antibody stimulation, but could be re-activated by CpG oligonucleotides (a TLR9 agonist) coupled to anti-IL-10 receptor (IL-10R) antibodies. This combination induced the secretion of IL-12 by a large proportion of DCs infiltrating CCL21-expressing C26–6CK colon carcinoma and exerted therapeutic antitumor effects in vivo. More recently, Engelhardt et al. have shown that DCs found at the margins of mouse breast tumors are engaged in non-productive interactions with T cells. These authors tracked the cells presenting a specific TAA in the tumor microenvironment, using a model of spontaneous breast cancer in which the fluorescent protein mCherry was co-expressed with the initiating oncogene and the selected TAA.[22] In this model, $CD11c^+$ DCs captured and presented tumor-derived proteins to T cells and initiated stable interactions with infiltrating tumor-specific T cells. These conjugates, however, were not productive as T cells were unable to lyse TAA-expressing target cells. Thus, tumor-associated DCs appear to be incompetent to sustain cytotoxic T lymphocyte (CTL) activity. The administration of IL-2, CpG or imiquimod (a TLR7 agonist) in vitro partially restored the capacity of tumor-infiltrating DCs to stimulate CTLs.

Accumulating evidence indicates that the stage of maturation of tumor-infiltrating DCs may be of prognostic value. Immunohistochemistry- and immunofluorescence microscopy-based analyses of DCs infiltrating 20 lung cancer specimens from randomly selected patients indicated that the presence of $PD\text{-}L1^+$ lung carcinoma cells as well as the presence of immature DCs correlates with poor patient prognosis.[23] The authors suggest that the expression of PD-L1 by DCs may prevent their maturation and contribute to tumor immune escape. Ovarian cancer is an immunologically active tumor and studies have demonstrated the importance of the immune system in this setting, even though a robust immunosuppressive microenvironment generally prevent antitumor immune response from being efficient. Of note, the predominant leukocytes that infiltrate human ovarian carcinomas appear to be DCs. $CD11c^+$ cells derived from the murine ID8 ovarian cancer model reportedly exhibit an immature, immunosuppressive phenotype as well as an altered secretory profile (i.e., they spontaneously release high levels of IL-6 and IL-10 but no IL-12p40).[24] Ovarian cancer-infiltrating DCs appear to become $PD1^+B7\text{-}H1^+$ with time (**Fig. 1**), and the blockade of PD1 in tumor-bearing mice has been shown to reduce tumor burden while enhancing intratumoral T-cell immunity.

Conversely, modulating the PD1/PD-L1 axis did not improve T-cell responses in a murine model of cancer prostate, in spite of the expression of both molecules. Bak et al. developed a transgenic model of prostate adenocarcinoma expressing a MHC Class I-restricted epitope recognized by the 2C clonotypic T-cell receptor (TCR).[25] In these mice, the adoptive transfer of $CD8^+$ 2C cells followed by infection with a SIY-expressing influenza virus results in the differentiation of transferred lymphocytes into effector cells that rapidly become tolerize upon tumor infiltration. Such tolerized 2C T cells have been shown to reside in the prostate tumor tissue and to expressed PD1, similar to what occur in patients. The same authors had previously shown that the intraprostatic injection of bone marrow-derived DCs delays the induction of tolerance and, if bone marrow-derived DCs are pulsed with SIY before administration, leads to the reactivation of unresponsive T cells.[26,27] This model was suitable to test the role of various co-stimulatory molecules in the DC function. Thus, CD70 turned out to be required for the delay in T-cell tolerance mediated by bone marrow-derived DCs,[25] in line with the established role of CD70 in the maintenance of T-cell survival and proliferation in the periphery,[28] as well as to prevent tolerance.[29] By contrast, CD80 and CD86 appeared to be required for the reactivation of previously tolerized T cells, as assessed by a cytotoxic assay in vivo. Of note, the critical contribution of CD70 to the efficacy of antitumor immunotherapy has been recently confirmed in clinical settings.[30,31]

The maturation of DCs has been correlated with their migration from the periphery to lymphoid organs, where they instruct adaptive responses. The magnitude and quality of the maturation response reportedly depends on the number of $CCR7^+$ DCs that carry antigens to lymph nodes.[32] A recent report highlighted the role of the NOD-like receptor NLRP10 in the migration of DC to lymph nodes. In particular, the loss of NLRP10 in DCs has been shown to impair their ability to exit inflamed tissues and to result in profound defects in helper T-cell activation upon immunization in the presence of various adjuvants.[33] Of note, defects in DC migration may be linked to the resistance of tumors to immune responses. Indeed, as recently demonstrated by Villablanca et al. human and mouse tumors produce cholesterol metabolites that dampen the expression of CCR7 receptor on maturing DCs as they activate the liver X receptor α (LXR). In this setting, preventing LXR activation in vivo promoted tumor rejection.[34]

Interestingly, mature DCs may not only function as antigen-presenting-cells, but also participate in the maintenance of high endothelial venules (HEVs) in lymphoid organs[35,36] and in tumors (**Fig. 1**). A retrospective study on 74 NSCLC patients revealed a correlation between the density of mature DCs (which homed to intratumoral lymphoid structures) and favorable clinical outcomes. $CD4^+$ T cells co-localized with DCs within these tertiary lymphoid structures.[37] In addition, the analysis of 225 primary melanoma samples showed that the density of tumor-associated HEVs correlate with increased tumor infiltration by

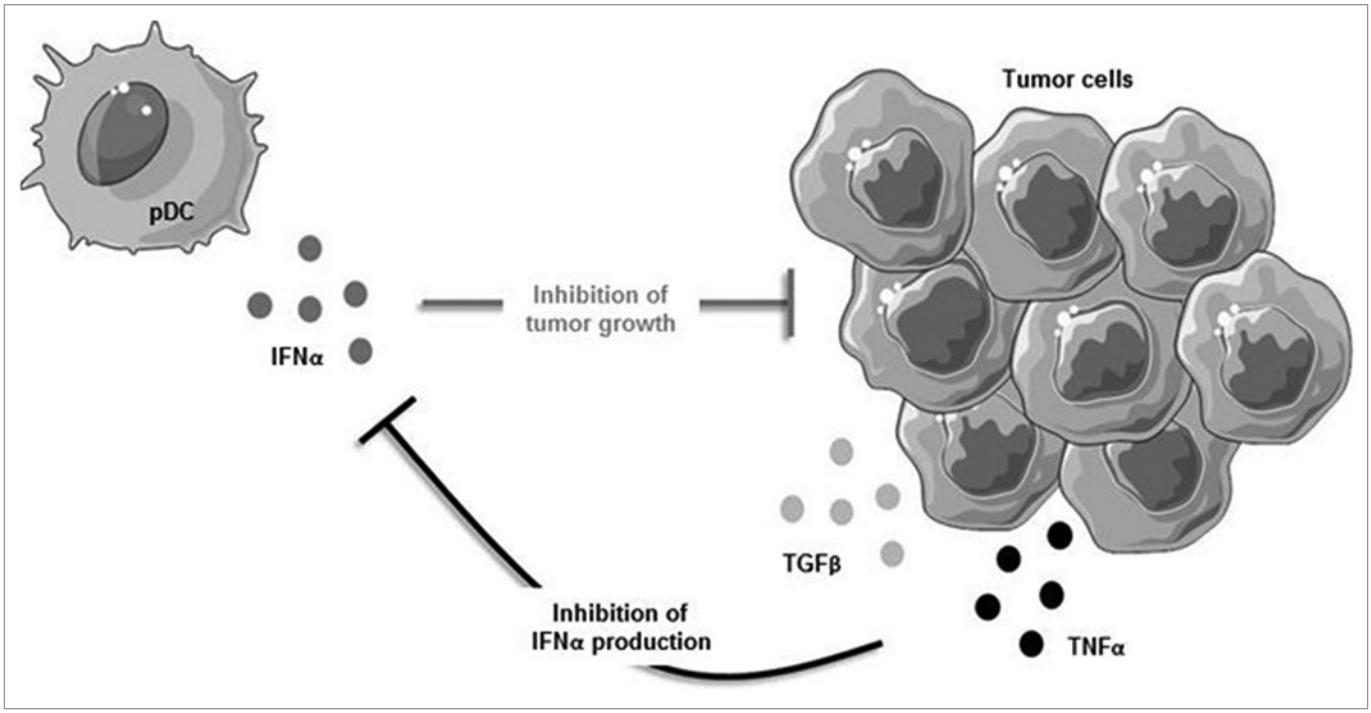

Figure 2. Tumor-infiltrating plasmacytoid dendritic cells (pDC) correlate with poor prognosis. The secretion of tumor necrosis factor α (TNFα) and transforming growth factor β (TGFβ) in the tumor microenvironment may inhibit the production of interferon α (IFNα) by plasmacytoid dendritic cells, negatively affecting anticancer immunity.

lymphocytes as well as with the amount of mature DCs within primary lesions.[38]

Plasmacytoid DCs

In addition to their maturation status, the precise nature of tumor-infiltrating DCs also influences tumor-specific immune responses. Thus, the presence of plasmacytoid DCs (pDCs) in the ovarian cancer epithelium was associated with an early relapse.[39] This report confirmed initial results on 33 ovarian cancer patients showing that pDCs infiltrating primary lesions, but not ascitic tumors, was an independent negative prognostic factor.[40] The deleterious prognostic effect of tumor-associated pDCs in ovarian cancer could be related to an altered IFNα production caused by tumor-derived soluble factors such as tumor necrosis factor α (TNFα) and transforming growth factor β (TGFβ) (**Fig. 2**). Along similar lines, several studies have correlated high levels of tumor-infiltrating pDCs with poor prognosis in breast carcinoma,[41] multiple myeloma[42] and melanoma[43] patients.

Functional Changes in DCs

The analysis of ovarian cancer progression revealed unexpected changes in DCs that turned out to accelerate tumor expansion. To recapitulate in rodents the immune infiltrates of human tumors, Scarlett et al. generated a p53-dependent, inducible metastatic ovarian carcinoma in C57Bl/6 mice.[44] These authors used the ablation of *p53* and the constitutive activation of *K-Ras* (two oncogenes that are dysregulated in a majority of cancer patients) to induce palpable abdominal tumors exhibiting 100% penetrance and short latencies. In this model, a homogenous population of DCs resembling the cells that infiltrate human ovarian carcinomas was found in neoplastic lesions as well as in tumor-draining lymph nodes. Interestingly, the tumors developing in *p53*/*K-Ras* double transgenic mice remained under control for about 28 d, became palpable after approximately 35 d and then grew very aggressively. This growth coincided with a change in their inflammatory infiltrate: DCs isolated from advanced tumors expressed high levels of tolerogenic PD-L1 and displayed immunosuppressive arginase I activity. Consequently, tumor-specific T cells became progressively less responsive and neoplastic cells escaped the immune control. Of note, the depletion of DCs accelerated tumor progression when performed 7 d after tumor induction, whereas it retarded tumor growth in 100% of mice if performed at the beginning of the immunoescape phase. These data highlight a critical role for tumor-associated DCs during the equilibrium phase and indicate that tumor-derived mediators including prostaglandin E_2 (PGE_2) and TGF-β may convert immunocompetent DCs into immunosuppressive APCs. These findings are in line with previous results demonstrating that the DCs that infiltrate ovarian cancers growing in C57Bl/6 mice acquire the expression of both PD-L1 and PD1.[24]

Concluding Remarks

Collectively, these observations demonstrate that tumor-infiltrating DCs may constitute an important aspect of the dysregulation of antitumor immunity and critically contribute to immune

evasion. The identification of the mechanisms whereby malignant cells subvert DC function may help to define interventions that reinforce spontaneous antitumor immune responses by interfering with the immunosuppressive tumor microenvironment and may provide clues to select the best cell population for DC-based anticancer immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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