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Review

Dendritic Cells in the Cancer Microenvironment

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Abstract

The complexity of the tumor immunoenvironment is underscored by the emergence and discovery of different subsets of immune effectors and regulatory cells. Tumor-induced polarization of immune cell differentiation and function makes this unique environment even more intricate and variable. Dendritic cells (DCs) represent a special group of cells that display different phenotype and activity at the tumor site and exhibit differential pro-tumorigenic and anti-tumorigenic functions. DCs play a key role in inducing and maintaining the antitumor immunity, but in the tumor environment their antigen-presenting function may be lost or inefficient. DCs might be also polarized into immunosuppressive/tolerogenic regulatory DCs, which limit activity of effector T cells and support tumor growth and progression. Although various factors and signaling pathways have been described to be responsible for abnormal functioning of DCs in cancer, there are still no feasible therapeutic modalities available for preventing or reversing DC malfunction in tumor-bearing hosts. Thus, better understanding of DC immunobiology in cancer is pivotal for designing novel or improved therapeutic approaches that will allow proper functioning of DCs in patients with cancer.

Key words: dendritic cells, regulatory dendritic cells, immunosuppression, tumor microenvironment, tumor escape.

Functional subsets of dendritic cells

Dendritic cells (DCs) are known as the most potent professional antigen presenting cells (APCs), which can uptake, process and present different types of antigens, including tumor antigens (1), to antigen-specific naïve T cells. DCs also play an important role in maintaining innate and adoptive immune responses by interacting with a variety of lymphoid and myeloid cells in normal and various pathophysiological conditions. DCs originate from the bone marrow hematopoietic progenitor cells, although can be propagated from monocytes under certain conditions. Usually DCs in immature or semi-mature state can be found in different non-lymphoid tissues and organs, but upon activation DCs migrate to lymphoid tissues to interact with T cells and induce immune responses (2). Immature DCs express low levels of MHC and co-stimulatory molecules and unable to efficiently activate T cells, although their endocytic potential is high (3-5). Activation of DCs with different maturation stimuli is associated with developmental up-regulation of expression of distinct intracellular and surface molecules required for trafficking to secondary lymphoid tissues and providing Signals 1-3 to T cells. However, activation and maturation of DCs depends on the local microenvironment and can be blocked or polarized by specific factors or their combinations resulting in formation of DC subsets with tolerogenic and immunosuppressive activities (6).

DCs represent a heterogeneous hematopoietic lineage with subsets of cells demonstrating differential morphology, phenotype and function in different tissues under different conditions (Ma et al. 2012). However, even in multiple environmental milieus, the various DC subsets often share the ability to stimulate T cell proliferation or induce their unresponsiveness (3-5). Interestingly, in spite of a common believe that the so-called 'myeloid' or conventional (cDCs) provide specific stimulatory functions, while 'lymphoid' or plasmacytoid (pDCs) subpopulations exhibit tolerogenic properties, these concepts have been challenged by growing number of exceptions reported in different experimental systems and clinical conditions. It was shown that cDC, including tissue-resident DCs, migratory DCs and inflammatory DCs might exhibit immunosuppressive properties under certain circumstances or in immature stage (3-5). Furthermore, pDCs, for instance, have not only been reported to exhibit potent immunosuppressive and tolerogenic properties by blocking proliferation of naïve and antigen-specific CD4+ and CD8+ T cells and supporting polarization and activation of Treg lymphocytes, but have also been shown to efficiently present antigens to CTLs inducing efficient immune responses (7-9).

Another commonly accepted paradigm is that functional activity of DCs is basically maturation-dependent. However, existing evidence suggests that DCs can exist in a multitude of functional states other than simply immature or mature. Moreover, both phenotypically "immature" and "mature" DCs may be conditioned by the microenvironment to maintain either immune tolerance or immunosuppression (10). Thus, DCs are a specialized group of antigen-presenting cells with high functional plasticity that express immunostimulating or immunosuppressive potential, or both, depending on the consequence and combination of microenvironmental stimuli affecting DC differentiation, maturation, activation and polarization. A wide spectrum of cells and factors in the tumor microenvironment represent an excellent example of differential stimuli that affect all aspects of DC biology and thus control functionality and longevity of all DC subsets (11).

Tumor Infiltrating Dendritic Cells

The immune system is able to detect and eliminate emerging malignant cells to prevent their uncontrolled proliferation according to the cancer immunosurveillance and immunoediting paradigm (12). DCs play the major role in cancer immunesurveillance as the antigen-presenting cells (APC) initiating the antitumor immune responses. In fact, the infiltration of DCs into primary tumor lesions has been associated with significantly prolonged patient survival and a reduced incident of metastatic disease in patients with oral, head and neck tumors, nasopharyngeal tumors, lung, bladder, esophageal, and gastric carcinomas (13). Furthermore, regression of primary cutaneous melanomas was associated with Langerhans cell (LC) infiltration (14,15). These early findings were confirmed by the growing body of data for different types of solid tumors. For instance, immunohistochemical (IHC) analysis of DCs in the tumor glandular epithelium and surrounding tumor interstitial tissue demonstrated that the proportion of invasion of the S100- and HLA-DR-positive DCs was negatively correlated with the clinical stage and lymph node metastasis (16). The authors concluded that functioning of tumor-infiltrating DCs (TIDCs) may be associated with the delay of tumor progression and lymph node metastasis. Similarly, based on S-100 staining, intratumoral DC infiltrates were low (<10 DCs per high-power field, HPF) in 20% of oral squamous cell carcinoma (OSCC) specimens, intermediate (10-20 DCs per HPF) in 42% of OSCC specimens and high (>20 DCs per HPF) in 37% of OSCC specimens (17). A low number of S-100+ TIDCs was more predictive of poor survival than lymph node involvement or late T stage. Thus, the number of DCs infiltrating the tumor is a highly significant prognostic parameter in patients with OSCC, as the levels of S-100+ DCs in the tumor independently predicted overall survival, disease free survival and time to disease recurrence in patients with OSCC.

Therefore, in the majority of solid tumors, more TIDCs are present in well-differentiated and less-invasive tumors which proved that TIDC density inversely correlates with tumor pathologic grade and stage and positively correlates with favorable prognostic features (Shurin and Lotze 2009). This conclusion is well aligned with the concept of the important role of DCs in antitumor immune surveillance, as functional TIDC migrating to the regional lymph nodes are capable of presenting tumor antigens to naïve tumor-specific T cells. It is generally believed that tumor-specific T lymphocytes activated in the lymph nodes by DCs specialized in cross-presentation, then reach the tumor through inflammation-induced ligand/receptor pairs. However, as has been recently reported that naïve T lymphocytes are able to infiltrate tumors in some conditions and to undergo activation at the tumor site. For example, targeting of lymphotoxin-α to mouse melanoma elicited the formation of a lymphoid-like tissue with the presence of clonally expanded T cells, suggesting that priming occurred in the tumor, as it was

not detected in the lymph nodes (18). Interestingly, recent evidence suggests that naïve T lymphocytes can also reach common tumors: The recruitment of naïve T cells occurred in various murine tumor types in the absence of any intentional inflammation and resulted in their proliferation and differentiation into cytotoxic effectors (19). Thus, the data demonstrating that immune responses can develop independently of secondary lymphoid organs in tertiary lymphoid structures associated with the tumor mass suggest an important function of TIDC and explain the clinical significance of high levels of tumor infiltration by DCs.

The retrospective study of the IHC presence and the correlation of tertiary lymphoid structures with clinical outcome in non-small-cell lung cancer (NSCLC) revealed that tertiary lymphoid structures were detected in some tumors but not in nontumoral lungs (20). The authors called these structures tumor-induced bronchus-associated lymphoid tissue (Ti-BALT): as in lymph nodes, Ti-BALTs were composed of mature DC/T cell clusters adjacent to B cell follicles and had features of an ongoing immune response. Univariate analysis showed that the density of mature DCs was highly associated with a favorable clinical outcome (overall, disease-specific, and disease-free survival), suggesting that Ti-BALT may participate in anti-tumor immunity. The density of tumor-infiltrating lymphocytes, in particular, CD4+ and T-bet+ Th1 T cells, was profoundly decreased in tumors weakly infiltrated by mature DCs. The density of mature DCs was found to be a better predictor of clinical outcome than the other parameters tested. Thus, the number of tumor-infiltrating mature DCs may identify patients with early-stage NSCLC who have a high risk of relapse (20).

Additional data confirmed that the maturation state of DCs represents a potential clinical prognostic significance. For instance, IHC analysis of the density of DCs expressing CD1a and the maturation marker DC-LAMP in cutaneous malignant melanoma demonstrated that CD1a+ DCs were detected both infiltrating melanoma cell nests and in the surrounding stroma, while DC-LAMP+ mature DCs were generally confined to the peritumoral areas, associated with lymphocytic infiltrates (21). The degree of infiltration by CD1a+ and DC-LAMP+ DCs showed strong inverse correlation with the thickness of melanomas and high peritumoral density of mature DCs was associated with significantly longer survival, while density of CD1a+ cells had a prognostic impact (21). These results suggest that the presence of CD1a+ DCs primarily depends on the thickness of melanomas, without direct relationship with the patients' survival. On the other hand, the density of mature DCs, especially in association with that of activated T cells, proved of prognostic importance, suggesting that these parameters could be considered as signs of a functional immune response associated with better outcome of the disease.

Therefore, there is ample evidence that the presence of tumor-infiltrating DCs is associated with a favorable prognosis in patients. These observations suggest that one of limiting steps to immune resistance and immunotherapy could be the capacity of TIDC to survive in the tumor microenvironment.

Tumor-induced Apoptosis of Dendritic Cells

Association between the low levels of TIDCs and cancer aggressiveness has been repeatedly reported for different types of tumors. In fact, early IHC analysis of DCs, including epidermal LCs, in tumor specimens commonly described low numbers of DCs at the tumor site. For instance, Gatter et al. (1984) demonstrated that in benign skin lesions LCs were increased, whereas in malignant tumors they were not only markedly depleted or absent but also grossly stunted and deformed in outline (22). Similar data were reported by Facchetti et al. (1984), who observed that epidermal LCs were rare in the central part of the tumor biopsies which showed a primary malignant melanoma in its vertical growth (23). LCs were often seen depleted above "deeply invasive" melanomas and they declined in number as melanoma progresses (24). These results were later confirmed by Toriyama et al. (1993), who reported a substantial reduction in LCs in the epidermis over melanoma (25). These data lead to the hypothesis that tumor-induced apoptosis of DCs or acceleration of their turnover may be related to the elimination of functional DCs in the tumor microenvironment (26), which was tested by Esche et al. (27). Using both the in-vitro and ex-vivo models, they reported for the first time that tumor-derived factors could induce apoptosis in murine and human DCs (27). The same group characterized primary mechanisms of this new phenomenon and the approaches to DC protection (28-32). This work was confirmed by others (33-35). Tumor-mediated cell death of DC precursors (36) and accelerated early apoptosis of DCs in cancer (33,37) were also described.

The presence of a significantly higher proportion of apoptotic blood DCs in patients with early stage breast cancer compared to healthy volunteers also supports this mechanism of DC elimination in the tumor environment (38). In addition, the apoptotic rate of TIDCs in endometrioid adenocarcinoma has

been reported to be significantly higher than that in normal endometrium (39). Lower generation of human CD34-derived and CD14-derived DCs in cancer patients and also murine bone marrow-derived DCs in tumor-bearing mice, as well as a significant decrease in the number of circulating DCs in the peripheral blood of cancer patients have been repetitively reported (40-49).

Several different tumor-derived factors, including gangliosides, neuropeptides, NO and other molecules may decrease longevity of DCs (50). For instance, MUC2 mucins purified from the conditioned medium of a colorectal cancer cell line were reported to increase the number of apoptotic cells in human monocyte-derived DC cultures, which was partially mediated by the ligation of the MUC2 mucins with Siglec-3 on DCs (51).

Tumor-derived gangliosides are well known as inhibitors of DC function and inducers of DC apoptosis. At concentrations close to those detected in the sera from melanoma patients, GM3 and GD3 gangliosides decreased the viable cell yield in DC cultures and induced significant DC apoptosis (34). Both GM3 and GD3 gangliosides enhance human epidermal Langerhans cell spontaneous apoptosis (52). Apoptosis induced by GM3 and GD3 gangliosides was not blocked by inhibitors of de novo ceramide biosynthesis, whereas the acid sphingomyelinase inhibitor desipramine only prevented apoptosis induced by GM3. DC apoptosis was triggered via caspase activation, and it was ROS dependent with GD3 ganglioside, suggesting that GM3 and GD3 induced apoptosis through different mechanisms (53).

Interestingly, high mobility groupbox-1 (HMGB1) is a multifunctional cytokine secreted by cancer cells, which accelerates cell growth, invasion and angiogenesis in cancer, and induces apoptosis in macrophages and DCs. HMGB1-treated DCs showed clear signs of apoptosis and increased levels of phosphorylated JNK (54). Intraperitoneal administration of HMGB1 decreased CD205+ splenic DCs in mice. To confirm the HMGB1-induced inhibitory effect on DCs, the authors examined 16 cases of human colon cancer invaded into the subserosal layer The 8 nodal metastasis-positive cases showed higher nodal HMGB1 concentrations in lymph node tissues and lower CD205+ nodal DC numbers than those in the 8 metastasis-negative cases. Primary tumor tissues of metastasis-positive cases showed higher tumor HMGB1 levels and lower CD205+ intratumoral DC numbers than those in metastasis-negative cases. These findings suggest that HMGB1 produced by colon cancer cells suppressed nodal DCs (54).

Thus, since programmed cell death in DCs plays essential roles in the regulation of the duration and magnitude of immune responses (55), elimination of DCs from the tumor environment contributes significantly to inefficient induction of anti-tumor immunity and tumor escape from immune recognition.

Dysfunctional Dendritic Cells in Cancer

Tumors that progress do so via their ability to escape the anti-tumor immune response through several mechanisms, including developing ways to impair functional differentiation and activation of DCs.

In a tumor-free environment, hematopoietic precursors give rise to progenitors which differentiate into immature DCs. Following antigen/"danger signal" encounter, immature DCs undergo maturation and become specialized in antigen presentation. However, in the tumor microenvironment, differentiation of DCs is often hampered resulting in the recruitment and accumulation of functionally deficient and frequently immature DCs. For instance, analysis of tumor-infiltrating DCs in murine melanoma specimens revealed the presence of both myeloid and plasmacytoid DC populations (56). Most of these DCs appeared immature, but about a third expressed a mature phenotype. TIDCs did not present tumor-derived antigen, as they were unable to induce the proliferation of tumor-specific CD4+ and CD8+ T cells. Some presentation of tumor-derived antigen could be demonstrated in the tumor-draining lymph node using in vivo proliferation assays. However, while proliferation of CD8+ T cells was reproducibly demonstrated, no proliferation of CD4+ T cells was observed (56,57).. These results clearly showed that DCs in tumors have limited antigen-presenting function and that inefficient antigen presentation extends to the tumor-draining lymph node affecting the generation of anti-tumor immune responses.

Tumor-induced functional deficiency of DCs has been first reported more than two decades ago and stimulated proliferative studies seeking explanation of abnormal anti-tumor immunity in cancer patients. Abnormal antigen-presenting capacity of lymph node cells during tumorigenesis and inhibited function of DCs isolated from tumor-bearing animals and patients with cancer have been initially described by several groups (58-62). Chaux et al. revealed that tumor-associated DCs express low levels of co-stimulatory molecules (63). Additional studies revealed more abnormalities in tumor-associated or tumor-treated DCs, including low production of IL-12, suppressed endocytic activity, inhibited antigen-processing machinery, abnormal motility, etc. (11,64-68). These and other results suggest that tu-

mor-mediated blockage of DC functionality represents a unique mechanism of tumor escape, in addition to the tumor-mediated suppression of DC generation (dendropoiesis) and survival. However, in spite of available information, many clinical protocols utilizing DC-based vaccines do not consider the fact that DCs administered in patients with cancer might quickly lose their activity in the cancer environment.

Thus, many studies showed that DC abnormalities observed in cancer patients or in tumor-treated DCs in vitro are due to malfunction of immaturity of DCs. Low or blocked ability of tumor-associated DCs to simulate allogeneic and syngeneic T cell proliferation because of decreased uptake, processing and presentation of antigens, lowered expression of co-stimulatory signal, inefficient motility and migration towards specific chemokines, suppressed endocytic potential and decreased production of IL-12 has been described for prostate, liver, breast, renal, lung cancer, head and neck squamous cell carcinoma (HNSCC), melanoma, myeloma, leukemia, glioma, neuroblastoma and other tumor types by our and other groups (36,37,47,69-73). These data have also been repeatedly reviewed (68,74-76). It is conceptually important that functionally deficient DCs are usually not immunosuppressive: they are unable to neither induce activation of antigen-specific or allogeneic T cells, nor suppress proliferation of pre-activated T cells; they neither induce functional tolerance, nor Treg cell differentiation. However, in specific tumor microenvironment conditions, the loss of function in DCs may, at least in part, be associated with DC polarization and acquisition of tolerogenic and/or immunosuppressive activities.

Regulatory Dendritic Cell Subsets in Cancer

In 1997, Enk et al. showed that melanoma-derived factors converted the antigen-presenting function of DCs to tolerance induction against tumor tissue (77). In malignant disease, redirection of dendropoiesis and polarization of DC differentiation by tumor- or stroma-derived factors usually relate to the engagement and accumulation of DC subsets, which actively block anti-tumor immunity, promote appearance of regulatory T cells and myeloid-derived suppressor cells and support tumor progression by endorsing intratumoral neoangiogenesis and development of metastases (78). Tolerogenic properties of DCs are commonly attributed to their immature status or specific conditions that they experience in the tumor microenvironment. High-levels of immature DCs were found among tumor-infiltrating leukocytes, but in the peripheral blood of patients with head and neck, esophageal, lung and breast cancer, increasing of circulating levels of immature DCs have also been reported (79). Certain subsets of immature DCs cannot provide an appropriate co-stimulatory and cytokine signals to T cells and might induce tolerance through abortive proliferation or anergy of antigen-specific CD4+ and CD8+ T lymphocytes or through the generation of regulatory T cells that prevent immune responses by producing IL-10 and TGF-β (4,80-83). Although these mechanisms are usually recognized as the reason for the deletion of autoreactive T cells (6), in the cancer environment, they might account for the direction towards the inhibition of anti-tumor immunity (84). For instance, Ghiringhelli et al. have described that during tumor progression, a subset of immature myeloid DCs is recruited to draining lymph nodes and selectively promotes the proliferation of Treg cells in a TGF-β-dependent manner (85). This shows that tumor cells can convert 'classical' immature DCs into regulatory DCs secreting TGF-β and stimulating Treg cell proliferation. Importantly, cultured bone marrow-derived immature DCs cannot possess immunosuppressive ability, but when appropriately condition offered in the tumor microenvironment, they might inhibit innate and adaptive immunity by various mechanisms. Thus maturation status of DCs should not be considered as a general distinguishing feature of stimulatory versus regulatory DC phenotype (86).

Maturation of DCs is accompanied by up-regulation of MHC class II and co-stimulatory molecules as well as secretion of proinflammatory cytokines. Mature immunogenic DCs produce large amounts of IL- 12, TNF-α, IL-1 and IL-6 (3,87). However, mature DCs might also induce T cell tolerance (87-89) challenging the model of tolerogenic immature and immunogenic mature differentiation stages in DCs lifespan. A hypothesis that a specialized subset of mature DCs might actively divert T cell responses towards tolerance might explain T cell tolerance induced by mature DCs, but should include the role of local environmental conditions that direct or re-direct functional polarization of DCs. DCs treated with IFN-γ and displaying a mature cell phenotype might exert tolerogenic properties due to an additional expression of indoleamine 2, 3- dioxygenase (IDO) (90,91). These mature regulatory DCs could also act as competent antigen-presenting cells since they were effective stimulators of T cell proliferation if IDO was blocked with the specific inhibitor 1-methyl tryptophan (1-MT). These data point towards a functional plasticity of mature DCs, allowing them to adopt either suppressive/tolerogenic or activat-

ing/immunogenic phenotypes depending on the signals received (92).

Recently DCs that express high levels of MHC class II and co-stimulatory molecules but do not secrete cytokines have been reported to display high tolerogenic rather than stimulatory properties; therefore they have been referred as semi-mature tolerogenic DCs (3). Moreover, IL-10-producing DCs with a mature phenotype could initiate CD4+ T cell unresponsiveness after exposure to an antigen and induce Treg cells that also produce high amounts of IL-10 (88). Thus, the IL-10/IL-12 production profile of DCs along with the low grade phenotypic maturation might distinguish between semi-mature DCs with the regulatory properties and fully mature stimulatory DC subpopulations. Furthermore, it seems that regDCs can exist as immature, semi-mature and fully mature DC subpopulations that use different mechanisms for induction of immune tolerance and immune suppression (84). Interestingly, our data demonstrate that phenotipically semi-mature/mature DCs that can actively stimulate proliferation of T cells, could be converted into immunosuppressive regulatory DCs in the tumor environment both in vitro and in vivo (Zhang et al., submitted). Thus it became clear that the specific microenvironment, including the tumor milieu, controls functional polarization of DC differentiation and activity, as well as their ability to interact with other immune cells. This conclusion is correct for conventional DCs and might not fully apply to plasmacytoid DCs due to limited information. In any way, tolerogenic and immunosuppressive properties of plasmacytoid DCs were also established and reviewed elsewhere (93,94).

Several different molecules and signaling pathways may be involved in tolerogenic and immunosuppressive properties of tumor-associated regDCs, including production of IL-10 and TGF-β, expression of IDO, iNOS and arginase, or expression of inhibitory B7-related molecules. For instance, within the ovarian cancer microenvironment, there are several mechanisms that suppress the actions of antitumor immune effectors and a dominant pathway of immune suppression involves tumor-associated and DC-associated B7-H1. The interaction of B7-H1 with programmed death receptor-1 (PD-1) on tumor-infiltrating T cells is a widely cited theory of immune suppression involving B7-H1 in ovarian cancer. Recent studies suggest that the B7-H1 ligand, PD-1, is also expressed on myeloid cells, complicating interpretations of how B7-H1 regulates DC function in the tumor. Krempski et al. found that ovarian cancer-infiltrating DCs progressively expressed increased levels of PD-1 over time in addition to B7-H1 (95). These dual-positive PD-1+B7-H1+ DCs have a classical DC phenotype, but are immature, suppressive and respond poorly to danger signals. Accumulation of PD-1+B7-H1+ DCs in the tumor was associated with suppression of T cell activity and decreased infiltrating T cells in advancing tumors. T cell suppressor function of these DCs appeared to be mediated by T cell-associated PD-1 (95).

Other members of the B7 family of molecules may be also involved in regDC functioning in cancer. CD277, a member of the butyrophilin subfamily 3 (BTN3), shares significant sequence similarities with inhibitory B7-H4 and other members of the B7 superfamily. CD277 is consistently expressed in stromal, as well as tumor cells in the microenvironment of human advanced ovarian carcinoma specimens, both of primary and metastatic origin (96). It has been recently reported that DCs express significantly higher levels of surface CD277 compared to other tumor-infiltrating leukocytes, and engagement of CD277 on the surface of TCR-stimulated T cells inhibits their otherwise robust expansion and production of Th1 cytokines by preventing the up-regulation of cFLIP (96). These results point to a role for CD277 up-regulation by microenvironmental signals in the acquisition of a regulatory phenotype by tumor-associated DCs as regular players in the orchestration of immunosuppressive networks in ovarian cancer patients.

Thus, the network of tolerogenic immunosuppressive DCs controlled by the tumor environment plays an important role in supporting tumor progression and limiting the success of different therapeutic modalities in patients with cancer. Regulatory DCs should be characterized further to be considered as a novel and important target for preventing CTL tolerance and enhancing immune responses to cancer by modulating their immunosuppressive activity found in the tumor microenvironment.

Conclusions

Although tumor antigens have been discovered several decades ago in human melanomas, cancer immunotherapy is still at a developing stage. Several limiting pathways have been identified that hamper the capacity of existing tumor-specific T lymphocytes to control tumor growth. The correlation between specific subsets of leukocytes infiltrating the tumor mass and favorable or poor prognosis of tumors suggests that antigen expression and immunosuppressive mechanisms may not be the only limiting factors. Furthermore, the coordination of the events required to guide different subpopulations of immune cells to the tumor bed and direct their activation, differentiation, polarization and homing is clearly more complex

than expected and include the control of tumor vasculature, the expression of correct sets of adhesion molecules and chemokines and management of multiple inhibitory mechanisms. Different subsets of DCs have been shown to play an important role in both induction of antitumor immunity and support of tumor growth and progression, suggesting the developmental and microenvironment-dependent plasticity of these cells. Although immunogenic and tolerogenic properties of DCs are relatively well characterized and DC-based vaccines are widely tested in pre-clinical and clinical trials, an interesting question is whether immunological or pharmacological therapy might alter the proportion of conventional immunogenic versus regulatory DCs in the tumor environment and thus boost tumor-specific responses in cancer patients. Similarly, whether administration of DC vaccines might affect interaction, longevity and homing of different subsets of DCs in the tumor environment is still a matter of speculation. In addition, some non-immunological mechanisms associated with radiation or chemotherapy may indeed result in decreased tumor progression and favor re-polarization of the tumor immunoenvironment, attraction of immune effectors to tumor bed and interaction of immune cells at the tumor site. An in depth analysis of tumor biology and the analysis of the DC repertoire at different time points in the tumor and the draining lymph node, and their correlation with immune responses may help clarify these issues and lead to novel approaches required for increasing the efficacy of cancer immunotherapy.

Competing Interests

The authors have declared that no competing interest exists.

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