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Tumor Associated Regulatory Dendritic Cells

Yang Ma¹, Galina V. Shurin¹, Dmitriy W. Gutkin², and Michael R. Shurin^{1,3}

¹Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

²VA Pittsburgh Healthcare System Pittsburgh, PA, USA

³Department of Immunology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Abstract

Immune effector and regulatory cells in the tumor microenvironment are key factors in tumor development and progression as the pathogenesis of cancer vitally depends on the multifaceted interactions between various microenvironmental stimuli provided by tumor-associated immune cells. Immune regulatory cells participate in all stages of cancer development from the induction of genomic instability to the maintenance of intratumoral angiogenesis, proliferation and spreading of malignant cells, and formation of premetastatic niches in distal tissues. Dendritic cells in the tumor microenvironment serve as a double-edged sword and, in addition to initiating potent anti-tumor immune responses, may mediate genomic damage, support neovascularization, block anti-tumor immunity and stimulate cancerous cell growth and spreading. Regulatory dendritic cells in cancer may directly and indirectly maintain antigen-specific and non-specific T cell unresponsiveness by controlling T cell polarization, MDSC and Treg differentiation and activity, and affecting specific microenvironmental conditions in premalignant niches. Understanding the mechanisms involved in regulatory dendritic cell polarization and operation and revealing pharmacological means for harnessing these pathways will provide additional opportunities for modifying the tumor microenvironment and improving the efficacy of different therapeutic approaches to cancer.

Keywords

dendritic cells; cancer; immunosuppression; immune escape; tolerance; immune regulatory cells

Introduction: Dendritic cell dichotomy

Dendritic cells (DCs) are potent antigen presenting cells (APCs) that possess the ability to present antigens to antigen-specific naïve T cells, as well as to maintain both innate and adoptive immune responses. DCs are derived from the bone marrow hematopoietic progenitor cells and circulate in the blood as immature precursors prior to migration into the peripheral tissues. Within the specific tissue microenvironment, DCs differentiate further displaying a potential to pick up and process antigens for their subsequent presentation as

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Correspondence to: Michael R. Shurin, MD, PhD UPMC, Pathology S735 Scaife Hall 3550 Terrace Street Pittsburgh, PA 15261 P: 412-648-9841 F: 412-648-8158 shurinmr@upmc.edu.

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peptide-major histocompatibility complex (MHC) on the surface of DCs. Upon appropriate stimulation, DCs undergo further maturation and migrate to secondary lymphoid tissues where they present antigens to T cells inducing their clonal proliferation and the immune response [1]. However, specific microenvironmental signaling might prevent maturation of DCs or polarize their differentiation resulting in formation of DC subsets with tolerogenic and immunosuppressive potential accountable for antigen-specific unresponsiveness in the lymphoid organs and in the periphery [2].

Thus, DCs represent a heterogeneous hematopoietic lineage with cell subsets in different tissues showing differential morphology, phenotype and function, and often sharing the ability to stimulate T cell proliferation or induce immune tolerance between various DC subsets depending on the environmental conditions. Although it has been suggested that the so-called 'myeloid' versus 'lymphoid' subsets of DCs, or conventional (cDCs) versus plasmacytoid (pDCs) subpopulations perform specific stimulatory or tolerogenic function, respectively, these concepts suffer from numerous exceptions in different experimental systems and clinical situations. Even "classically" inducing immune response by activating CD4⁺ Th1 and Th2 cells and CD8⁺ CTLs, cDC, including tissue-resident DCs, migratory DCs and inflammatory DCs might exhibit immunosuppressive properties under certain circumstances or in immature stage [3–5]. Other DC subsets, such as the pDCs, have also been reported to exhibit potent immunosuppressive and tolerogenic properties by blocking proliferation of naïve and antigen-specific CD4⁺ and CD8⁺ T cells, supporting polarization and activation of Treg lymphocytes or efficiently presenting antigens to CTL and inducing efficient immune responses [6–8].

Another commonly accepted paradigm is that functional properties of DCs are maturation-dependent. However, existing evidence suggests that DCs can exist in a multitude of functional states other than simply immature or mature. Additionally, both phenotypically "immature" and "mature" DCs may be conditioned by the microenvironment to maintain either immune tolerance or immunosuppression [9]. 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.

Dendritic cells in cancer

DCs has been attracting scientific and clinical attention due to their key role in tumor immunity and a potential for being used as biological adjuvants in tumor vaccinations [10]. However, anti-tumor immune responses are often deficient or suboptimal since tumor cells are able to exploit the functional roles of DCs for tumor growth and progression [11]. Suppression and re-polarization of DC function in cancer patients is thought to contribute to the failure of anti-tumor immune responses and consequent disease progression. Subversion of tumor immunity by manipulating the tumor microenvironment and DC subset distribution and function is mediated by various tumor-derived and stromal factors, many of which remain to be identified. Molecular mechanisms of tumor-mediated dysfunction of conventional DC have partly described, although potential signaling pathways responsible for emerging and function of immunosuppressive or tolerogenic DC subsets remain elusive.

Many mechanisms of conventional DC alterations in the tumor microenvironment have been revealed during the last 20 years, and most of them relate to the inhibition of dendropoiesis (DC production), decelerating DC differentiation, induction of functional deficiency of DCs

and acceleration of cell death of semi-mature/mature DCs or DC precursors [12–15]. For instance, in 1991–1995 several groups reported that the antigen-presenting capacity of lymph node cells was impaired during tumorigenesis [16], that tumor was able to regulate DC attraction and homing at the tumor site and inhibit function of DCs and thus, induction of anti-tumor immunity [17, 18] and that DCs were functionally abnormal in patients with cancer [19]. In 1996, Gabrilovich et al. reported that DCs isolated from tumor-bearing mice displayed reduced ability to induce syngeneic tumor-specific CTLs and stimulate allogeneic T cells [20] and Chaux et al. revealed that tumor-associated DCs express low levels of co-stimulatory molecules [21]. Following these initial findings, other groups demonstrated lower generation of human CD34-derived and CD14-derived DCs in patients with cancer, as well as murine bone marrow-derived DCs in tumor-bearing mice and described a significant decrease in the number of circulating DCs in the peripheral blood of cancer patients [22–28].

Elimination of functional cDCs in cancer may be also associated with apoptosis of DCs or acceleration of their turnover. Induction of apoptosis in DCs by tumor-derived factors was first reported by Esche et al. in 1999 [12] and then confirmed by others [29–31]. Tumor-mediated cell death of DC precursors [32] and accelerated early apoptosis of DCs [29, 33] 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 may also support this mechanism of cDC elimination in the tumor environment [34].

Functional deficiency of cDCs in the tumor environment is the best documented type of DC abnormalities observed in cells harvested from cancer patients and cells generated in cultures treated with tumor cell line-derived factors or primary tumor cells. Inhibited ability of DCs to stimulate allogeneic and syngeneic T cell proliferation, 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 were repeatedly described for prostate, breast, renal, liver, lung cancer, head and neck squamous cell carcinoma (HNSCC), melanoma, myeloma, leukemia, glioma, neuroblastoma and other tumor types by our and other teams [32, 33, 35–40] and repeatedly reviewed [15, 41, 42]. It is important to mention here that functionally deficient DCs are usually not immunosuppressive: they are unable to induce activation of antigen-specific or allogeneic T cells, but do not actively suppress proliferation of pre-activated T cells and do not induce functional tolerance or 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 DC subsets in cancer

Tumor-promoted redirection of dendropoiesis and polarization of DC differentiation is commonly associated with the engagement and accumulation of DC subsets that actively block development of anti-tumor immunity, promote appearance of regulatory T cells and myeloid-derived suppressor cells (MDSCs) and support tumor progression by endorsing intratumoral neoangiogenesis and development of metastases. Probably, Enk et al. were the first who in 1997 showed that melanoma-derived factors converted the antigen-presenting function of DCs to tolerance induction against tumor tissue [43].

Although cultured bone marrow-derived immature DCs do not possess immunosuppressive ability, when appropriately conditioned in the tumor microenvironment, *in vivo* and *in vitro*, they may inhibit innate and adaptive immunity by various mechanisms. Immature DCs were found at high levels within tumor-infiltrating leukocytes and increased circulating levels of immature DCs have also been reported in the peripheral blood of patients with lung, breast,

head and neck and esophageal cancer [44]. Certain subsets of immature DCs fail to 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 cells or through the generation of regulatory T cells that prevent immune responses by producing IL-10 and TGF- β [5, 45–48]. These mechanisms usually account for the deletion of autoreactive T cells, but in the tumor environment may be directed towards the inhibition of anti-tumor immunity. In fact, Ghiringhelli et al. have demonstrated 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 [49]. Tumor cells were necessary and sufficient to convert immature DCs into regulatory DCs that secrete TGF- β and stimulate reg cell proliferation. Thus, although it is widely accepted that the ability of DCs to initiate immune responses or induce tolerance is strictly dependent on their maturation state or subsets, increasing evidence suggests that maturation status of DCs should no longer be considered as a distinguishing feature of stimulatory versus regulatory DC phenotype. Several publications describing that mature DCs induce CD4⁺ T cell tolerance [50–52] challenged the model of tolerogenic immature and immunogenic mature differentiation stages in DCs. 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.

Maturation of DCs includes 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 [4, 51]. Recently DCs that express high levels of MHC class II and co-stimulatory molecules but do not secrete IL-1 β , IL-6, TNF- α and IL-12 have been shown to display tolerogenic rather than stimulatory properties and therefore been referred as semi-mature tolerogenic DCs [4]. Furthermore, Akbari et al. showed that 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 [50]. 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

The ability of mature DCs to induce T cell tolerance was explained by a hypothesis that a specialized subset of mature DCs might actively divert T cell responses towards tolerance [53]. DCs treated with IFN- γ and displaying a mature cell phenotype (CD80⁺CD83⁺CD86^{high}HLA-DR^{high}) might exert tolerogenic properties due to an additional expression of indoleamine 2,3-dioxygenase (IDO) [54, 55]. These mature regulatory DCs were effective stimulators of T cell proliferation if IDO was blocked with the specific inhibitor 1-methyl tryptophan (1-MT), suggesting that these cells could also act as competent antigen-presenting cells. These data point towards a functional plasticity of mature DCs, allowing them to adopt either suppressive/tolerogenic or activating/immunogenic phenotypes depending on the signals received [56].

Regulatory properties of plasmacytoid DCs

Plasmacytoid DCs are recognized as the main source of IFN- α after challenge with pathogens [57, 58]. They originate in the bone marrow from DC progenitors common to pDCs and cDCs [59, 60] and can be identified as CD4⁺CD11c[−]lin[−]HLADR⁺ cells expressing CD123/IL-3R α chain. At the steady state, pDCs circulate in the blood and may enter the lymph nodes through the high endothelial venules [61, 62]. While present in tissues at low numbers in the healthy steady state, pDCs accumulate in lymphoid and non-lymphoid tissues under different pathological conditions [63].

Plasmacytoid DCs are considered to be crucial effector cells in innate and adaptive immunity and express distinctive pathogen recognition receptors mainly residing in the endosomes and consisting of TLR-7 and TLR-9. The engagement of TLR-7/9 by viral RNA and DNA leads to powerful type I IFN secretion. In addition to IFN, pDCs produce other cytokines, such as TNF- α , IL-6 and CXCL8 and inflammatory chemokines, such as CXCL9, CXCL10, CCL3, CCL4 and CCL5 [64, 65]. Freshly isolated pDCs can present antigens to T cells to a small extent, but upon activation by viruses, CpG, IL-3 and CD40L, they acquire full DC properties and are capable of presenting antigens to CD4⁺ T cells and cross-prime CD8⁺ T cells [66–69]. Through the release of IFN- α , pDCs can activate NK cells, promote CTL activity and induce differentiation of B lymphocytes into Ig-secreting plasma cells [70].

While the importance of pDCs in innate and adaptive immune responses against pathogens is well established, their role in anti-tumor immunity is not clear. Due to their ability to secrete high levels of type-I IFN and TNF- α , pDCs would appear to have potential to promote anti-tumor immunity: IFN- α has direct antitumor activities by inhibiting tumor cell proliferation and neoangiogenesis and also by promoting immunosurveillance through the activation of B cells, NK cells and macrophages [71]. Theoretically, pDCs have an ability to orchestrate the local immune response to cancer cells by producing IFN, recruiting other immune cells via amplification of the proinflammatory chemokine network and cross-presenting antigens to CD8⁺ T cells [65, 67, 69]. They can also induce apoptosis of tumor cell lines either directly by secreting TRAIL or indirectly via the effect of IFN- α on other cytotoxic cells [72]. However, numerous experimental and clinical evidence shows exactly the opposite: pDCs possess immunosuppressive and tolerogenic property and, thus, promote tumor growth and progression. This apparent discrepancy might be explained, at least in part, by the homing of pDCs into the tumor and the properties of tumor associated pDCs (TApDC).

As has been mentioned above, the number of pDCs in normal peripheral tissues is low. However, circulating pDCs express multiple chemotactic receptors, including CXCR4 and ChemR23 (CMKLR1) [7]. Malignant tumors have been shown to express high levels of CXCR4 ligand, stromal-derived factor-1 (CXCL12), which likely represents the main axis for pDC accumulation in tumors [73–75]. Interaction of stromal cell-derived factor-1 with CXCR4 on pDCs can up-regulate very late antigen-5 for trans-endothelial migration via vascular cell adhesion molecule-1 and can protect pDCs from IL-10-induced apoptosis [73]. Other possible interaction includes CCL20 binding to CCR6 on pDCs that can recruit them to the tumor site [76].

Accumulation of pDCs in tumors has been directly demonstrated in primary carcinomas of different organs (breast, ovary, head and neck, lung, skin, cervix, prostate and liver), as well as cutaneous melanoma and lymphomas [74, 75, 77–81]. They commonly represent a minor fraction (10–15%) of the infiltrating immune cells [7], but at least in some tumors they were found to be the most abundant DC subset [78]. As the well-established methods of isolation and identification of TApDCs are now available, several studies were focused on a functional characterization of these cells. Practically all of the currently existing results point to the same conclusion: TApDCs are defective in IFN- α production and instead secrete immunosuppressive soluble factors responsible for tumor progression. Immunosuppressive and tolerogenic TApDCs were demonstrated in both murine and human prostate carcinoma [57, 80], HNSCC [77] and ovarian carcinoma [75, 78]. It is important to mention that these findings have strong clinical correlations: the results of several studies indicate that prognosis of different types of tumors is inversely related to the number of tumor-infiltrating pDCs [78, 81].

Although the mechanisms of this phenomenon are not known, several possible scenarios can explain its origin. First, it has been proven that TApDCs are disarmed in their ability to produce the required amount of IFN- α to sustain elimination of cancer cells. This functional inhibition of pDCs likely depends on the abundance of ligands to the inhibitory receptors on cancer cells or on cells of the tumor microenvironment [7]. Human pDCs express several receptors that negatively regulate the amplitude of the IFN- α response. One of them, ILT7, recognizes BST2, the protein that is strongly expressed on tumor cell lines and carcinomas [82, 83]. Next, human and mouse pDCs can drive CD4⁺ T cells to the generation of CD4⁺CD25⁺Foxp3⁺ Treg cells, which leads to anergy and immune suppression, favoring the immune escape of tumor cells [84–86]. Recent findings also demonstrate that pDCs infiltrating prostate carcinoma can be polarized to express IDO and other tolerogenic mediators under the control of forkhead box O3 (FOXO3) [80]. Catabolic activity of IDO and arginase in pDCs eventually leads to the inhibition of T cell activation and immunosuppression [87, 88]. Another possible tolerogenic mechanism of TApDCs is the secretion of Granzyme B. It has been shown that under IL-3 and IL-10 exposure, human pDCs release abundant amounts of Granzyme B, which is capable of blocking T cell proliferation [89].

All of these mechanisms underline the active role of the tumor microenvironment in polarizing tolerogenic pDCs. In addition, recent study of Bjorck et al. identified two distinct subsets of pDCs in mice, one of which (CD9⁺ immature pDCs) was found mainly in the bone marrow and spleen and was responsible for IFN- α production, while the other (CD9⁺ mature pDCs) was present in the peripheral tissues and was tolerogenic [8]. These results indicate that even without the negative influence of the tumor microenvironment TApDCs would not be actively producing IFN or other inflammatory cytokines, but instead induce the tolerance. Additional analysis of these pDC subsets in the tumor milieu should provide interesting insights into our understanding of how tumor-derived factors affect immunogenic and constitutively tolerogenic pDC subpopulations.

Regulatory dendritic cells: Initiating mechanisms and factors

The ability of DCs to coordinate the immune response is not an intrinsic quality of the cell but is rather the result of specific microenvironmental signals, including the local cytokine network and the milieu of soluble factors from the neighboring cells. For instance, tumor-derived IL-10, TGF- β and PgE2 can render DCs to acquire regulatory instead of stimulatory capacities. IL-10, which is produced by many cells in the tumor milieu, including T cells, B cells, macrophages, mast cells and cancerous cells, can inhibit maturation of antigen-presenting cells, reduce expression of MHC class I and II molecules and co-stimulatory molecules and attenuate production of inflammatory cytokines [90–92]. CCR-7 dependent migration of DCs to secondary lymphoid tissue is also impaired by the presence of IL-10 [93]. IL-10-treated DCs can be polarized to induce T cell anergy [94]. In fact, tumor-derived IL-10 has been reported to induce tolerance to tumor tissue by changing the phenotypic and functional properties of DCs in the tumor microenvironment [43]. Comparing different factors known to induce regulatory DCs, Boks et al. reported that IL-10-treated human DCs showed most powerful tolerogenic characteristics [95]. Furthermore, in addition to being involved in regDC-induced polarization of Treg cells, IL-10 may participate in Treg cell-mediated polarization of regDCs. Studying the interaction between Treg cells and antigen-presenting cells (APCs), Kryczek et al. demonstrated that Treg cells, but not conventional T lymphocytes, triggered high levels of IL-10 production by APCs, stimulate APC B7-H4 expression, and render APCs immunosuppressive [96]. Initial blockade of B7-H4 reduced the suppressive activity mediated by Treg cell-conditioned APCs. Further, APC-derived, rather than Treg cell-derived, IL-10 was responsible for APC B7-H4 induction, suggesting

that Treg cells convey suppressive activity to APCs by stimulating B7-H4 expression through IL-10 [96].

TGF- β is another soluble factor produced in the tumor microenvironment [97, 98] and associated with the tolerance induction. Similar to IL-10, exposure of DCs to TGF- β inhibits their ability to process antigens, migrate to the draining lymph nodes and stimulate tumor-specific T cells [99]. Murine bone marrow-derived DC that were propagated in IL-10 and TGF- β (so-called “alternatively activated” DCs) expressed low levels of TLR4, MHC class II, CD40, CD80, CD86 and IL-12p70, secreted much higher levels of IL-10 and efficiently expanded functional CD4⁺CD25⁺Foxp3⁺ Treg cells [100]. Regulatory DCs could be also produced from bone marrow precursors in the presence of GM-CSF, IL-10, TGF- β 1, LPS or TNF- α and they retained their T cell regulatory property *in vitro* and *in vivo* even under inflammatory conditions [101]. Interestingly, CCL18 has been reported to differentiate DCs in tolerogenic cells able to prime regulatory T cells [102]. Another minor subpopulation of regDCs has been recently described in murine spleen. These splenic CD19⁺ DCs that did not express the plasmacytoid DC marker acquired potent IDO-dependent T cell suppressive functions [103].

Tumor-derived PgE2 can also induce DC-mediated T cell tolerance. Increased levels of PgE2 were reported for many solid and hematological malignancies, especially in tumors associated with chronic inflammatory responses, such as colon cancer [104], breast cancer [105, 106] and lymphoma [107]. Interestingly, in addition to the ability to directly suppress CD4⁺ T cell proliferation by inhibiting the TCR-associated tyrosine kinase Lck [107] and induce regulatory T cells [108–110], PgE2 has been also shown to affect DC activity by blocking IL-12 expression [111] and inducing expression of regulatory molecules [112] that both result in impaired T cell stimulation.

Human leukocyte antigen G (HLA-G) molecules, which are normally expressed in cytotrophoblasts and play a key role in maintaining immune tolerance at the maternal-fetal interface, was also reported to be expressed on malignant cells and can be regulated by hypoxia [113, 114]. As DCs expressed immunoglobulin-like transcript 4 (ILT4), an inhibitory receptor capable of interacting with HLA-G, DCs may be tolerized by HLA-G through inhibitory receptor interactions. Indeed, the HLA-G-ILT4 interaction leads to development of tolerogenic DCs with the induction of anergic and immunosuppressive T cells [115]. DCs express a number of inhibitory receptors, which are characterized by the presence of cytoplasmic immunoreceptor tyrosine-based inhibitory motifs (ITIMs). Upon receptor engagement, ITIMs are phosphorylated and subsequently activate phosphatases that down-regulate the process of cell activation. Two inhibitory receptors, ILT3 and ILT4, may be connected with the induction of regulatory DCs. Up-regulation of ILT3 and ILT4 was associated with decreased expression of co-stimulatory molecules and induction of T cell anergy by DCs [116].

Regulatory dendritic cells: Initiating signaling pathways

Although the list of tumor-derived and stromal factors involving in the impaired or repolarized DC functions is getting longer, some of them may utilize similar transcription factors and signaling pathways, in particular STAT3, MAP kinase and small Rho GTPases. For instance, treatment of DCs with melanoma-conditioned medium reduced expression of IL-12, MHC class II, and CD40 due to the increased induction of STAT3 [117]. The immunosuppressive effects of tumor-derived factors on DC differentiation were abrogated in cells from STAT3^{-/-} mice and by blocking downstream STAT activation in DC precursors. STAT3 is also involved in the IL-6-mediated regulation of DC activation and maturation [118], the pathway which play an important role in cell interactions in the tumor

microenvironment. In fact, it has been recently reported that phosphorylation of STAT3 in DCs by IL-6-producing tumor cells resulted in acquisition of their tolerogenic phenotype [119]. Interestingly, CD4⁺CD25⁺FoxP3⁺ regulatory T cells from tumor-bearing animals could hamper DC function by activating STAT3 and inducing the Smad signaling pathway [120], which was also associated with down-regulation of activation of the transcription factor NF- κ B, required TGF- β and IL-10 and resulted in strong inhibition of expression of the co-stimulatory molecules CD80, CD86 and CD40, the production of TNF- α , IL-12, and CCL5/RANTES by DCs. Our data revealed that tumor-induced polarization of immunostimulatory cDCs into immunosuppressive regDCs *in vitro* was also accompanied by fast activation of STAT3 in treated cells (Shurin, unpublished data). Interestingly, histone deacetylase inhibition has been also reported to alter DCs to assume a tolerogenic phenotype [121]. Recently, Sun et al. demonstrated that histone deacetylase inhibition acetylates and activates STAT-3, which regulates DCs by promoting the transcription of IDO. These findings demonstrate a novel functional role for posttranslational modification of STAT-3 through acetylation [122].

Other members of the STAT family also play a role in DC differentiation and maturation. For example, the STAT6-mediated signaling is constitutively activated in immature DCs and declines as they differentiate into mature DCs, in contrast to STAT1 signaling, which is most robust in mature DCs and required for the efficient antigen presentation [123]. Down-regulation of STAT6 pathway is accompanied by remarkable induction of suppressors of cytokine signaling 1 (SOCS1), SOCS2 and SOCS3 [124]. Therefore, it is possible that cytokine-induced maturation of DCs is under feedback regulation by SOCS proteins and that the switch from activated STAT6 pathway in immature DCs to predominant utilization of STAT1 signals in mature DCs is mediated in part by STAT1-induced SOCS expression [124]. On the other hand, SOCS1 functions as an antigen-presentation attenuator by controlling the tolerogenic state of DCs and the magnitude of antigen presentation [125]. Since SOCS1 restricts DC ability to break self-tolerance and induce anti-tumor immunity by regulating IL-12 production and signaling, it is likely that tumor-derived and/or stroma-derived factors might induce SOCS1 expression in DCs the tumor milieu. Although not proven experimentally, this pathway may operate in the tumor microenvironment limiting the ability of DC to process and present tumor antigens and secrete IL-12 or attenuate tolerogenic potential of tumor-associated DCs.

Recent data from Wang et al. suggest that tumor-induced p38 mitogen-activated protein kinase (MAPK) and Janus kinase (JNK) activation and extracellular regulated kinase (ERK) inhibition in DCs are involved in dysregulated DC functioning in cancer patients [126, 127]. Additional studies confirmed these findings and revealed that selective ERK activation induced mouse and human DCs to secrete bioactive TGF- β required for suppression of T cell responses and differentiation of antigen-specific Treg cells [128]. Zhao et al. reported a critical role of constitutively activated p38 MAPK in the acquirement of tolerogenic pattern by DCs during melanoma progression that contributes to the suppression of anti-tumor T cell immune responses [129].

Furthermore, based on the previous data demonstrating that key functions of cDCs are regulated by the family of small Rho GTPases (Cdc42, RhoA and Rac1/2) [130], Tourkova et al. determined whether small Rho GTPases might be affected by tumor-derived factors. They found that impaired endocytic activity of cDCs co-cultured with tumor cells was associated with decreased levels of active Cdc42 and Rac1 [131]. Transduction of DCs with the dominant negative Cdc42 and Rac1 genes also lead to reduced phagocytosis and receptor-mediated endocytosis, while transduction of DCs with the constitutively active Cdc42 and Rac1 genes restored endocytic activity of DCs that were inhibited by the tumors [131]. Following these results, we have recently revealed that polarization of cDCs into

immunosuppressive regDCs in tumor-treated cultures can be prevented by toxin B, an inhibitor of small Rho GTPase activity (Zhong et al., submitted). Altogether, these data demonstrate that specific intracellular signal transduction pathways in DCs are responsible for DC differentiation and polarization in the tumor microenvironment that render tolerogenic and immunosuppressive properties. However, it is still unknown whether the involvement of these pathways is tumor-specific or DC subset-specific. Additional studies are required to evaluate the biological significance of multiple signaling activities in regDCs and determine specificity of their activation or suppression in different types of cancer both *in vitro* and *in vivo*.

Regulatory dendritic cells: Inhibitory pathways

Tolerogenic and immunosuppressive properties of regDCs are mediated by either direct effects of regDCs on effector T cells or by the induction or activation of other immune regulatory cells, such as Treg cells and MDSCs. Several soluble regDC-derived factors and membrane-bound or intracellular molecules have been revealed to be responsible for these activities. Production of IL-10 and TGF- β by regDCs has been well established and reviewed [132, 133] and the role of these cytokines in polarization and function of regulatory T cells has been also repeatedly discussed elsewhere. Functionally active expression of COX-2 and iNOS in tumor-associated regDCs has been also documented [134], suggesting additional mechanisms of T cell suppression by regDCs. Furthermore, expression of other enzymes in regDC, including arginase and IDO, is also accounted for their immunosuppressive properties.

The enzyme arginase metabolizes L-arginine to L-ornithine and urea. Besides its fundamental role in the hepatic urea cycle, arginase is also expressed in the immune system of mice and man. Myeloid cell arginase-mediated L-arginine depletion profoundly suppresses T cell immune responses and this has emerged as a fundamental mechanism of inflammation-associated immunosuppression [135]. Influence of L-arginine deficiency on the function of T lymphocytes is mediated by down-regulation of the T cell receptor (TCR) ζ chain, a critical signaling element of the TCR, and an arrest of T cells in the G0–G1 phase of the cell cycle, associated with the absence of up-regulated cyclin D3 and cyclin-dependent kinase 4 (cdk4) [135]. Expression of arginase by MDSC has been proven as a key mechanism of MDSC-induced immunosuppression in cancer [136]. However, evidence of arginase expression in tumor-associated regDCs is limited by a very few papers showing that tumor-infiltrating regDCs can inhibit CD8⁺ T cell function via L-arginine metabolism [88, 134]. Additional results are required to establish the role of this pathway in regDC-mediated immune unresponsiveness in cancer.

Indoleamine-2,3-dioxygenase (IDO) is the rate-limiting enzyme in the tryptophan catabolism, also known as the kynurenine pathway. It degrades the essential amino acid tryptophan thereby leading to an accumulation of its metabolites, the kynurenine [56]. Tryptophan is required for protein synthesis and for the synthesis of serotonin in the nervous system and the gut, as well as for melatonin synthesis in the pineal gland. Lately, IDO, was first reported to be implicated in the inhibition of viruses and intracellular pathogens, whose survival depends on the host tryptophan [137–139]. More recently, IDO has been associated with immune tolerance, as the reduction of tryptophan might prevent T cell proliferation and the elevation of metabolites of the tryptophan catabolism might exert toxic effects on immune cells [140, 141]. Since then, numerous reports revealed the role of IDO activation and subsequent tryptophan depletion in the regulation of immune responses during infections and tumorigenesis [142–144]. Expression of IDO in DCs was documented and implicated to DC-induced immunosuppression [145, 146]. These studies suggest that IDO-expressing regDCs found at the tumor site and in tumor-draining lymph nodes might help

suppress the initiation of immune responses to tumor-derived antigens and perhaps help create systemic tolerance to these antigens [132]. Interestingly, human chorionic gonadotropin (hCG), which serves as an important tumor marker for trophoblastic disease, has been recently shown to up-regulate expression of IDO in DCs [147].

The ability of tumor-derived factors to bias DC differentiation toward providing inhibitory signals to interacting T cells should also be instrumental in tumor immune evasion. For instance, a dominant pathway of immune suppression in ovarian cancer involves tumor-associated and DC-associated B7-H1. The interaction of B7-H1 with PD-1 on tumor-infiltrating T cells is an acceptable theory of immune suppression involving B7-H1 in ovarian cancer [148]. Recent studies suggest that the B7-H1 ligand, programmed death receptor-1 (PD-1), is also expressed on myeloid cells, complicating interpretations of how B7-H1 regulates DC function in the tumor. Krempski et al. have recently found that ovarian cancer-infiltrating DCs progressively expressed increased levels of PD-1 over time in addition to B7-H1 [149]. These PD-1⁺ B7-H1⁺ DCs had a classical DC phenotype, but were immature and immunosuppressive. Accumulation of PD-1⁺ B7-H1⁺ regDCs in the tumor was associated with suppression of T cell activity and decreased infiltrating T cells in advancing tumors [149].

Tumor-infiltrating DCs may be polarize to express programmed death ligand 1 (PD-L1), a known inhibitor of T cell proliferation. The immunohistochemical analysis of 109 non-small cell lung cancer (NSCLC) tissues and demonstrated that immature CD1a⁺ DCs express PDL1 and that PD-L1 might be regarded as a poor prognostic factor [150]. Therefore, different mechanisms of immunosuppression are associated with the functional activity of regulatory DCs in the tumor environment. Understanding of these pathways and revealing of how they can co-interact in regDCs should provide additional insights in developing the effective therapeutic approaches to their blockade.

Conclusions

A growing body of evidence reveals DCs with tolerogenic and immunosuppressive activities within different cell subsets, including immature and mature myeloid cells, conventional DCs and pDCs. This suggests that DCs with “tolerogenic” function may be present in specific environments under specific conditions due to unusual differentional and functional flexibility of DCs. Tumor-induced polarization and differentiation of cDCs and pDCs into immature or mature DCs with the inhibitory and tolerogenic function strongly impair antigen-specific T cell responses. For patients with cancer, the resulting dysfunction or misbalance of the DC system would result in significant deficiency in the induction of anti-tumor immunity, tumor progression and low response to immunotherapy and, probably, other treatment modalities. Given that resident DCs in patients with cancer might be also important for fulfilling the potential of various cancer vaccines, gained knowledge of immunobiology of regulatory DCs in cancer should help find new drugs and agents to selectively block the immunosuppressive pathways and restore the original immunostimulatory function of DCs in the tumor environment.

The term “regulatory” DCs is commonly used interchangeably with “tolerogenic” DCs, creating massive controversy in understanding the nature of DCs with immunosuppressive function, as has been purposely demonstrated in this review. The multiple discrepancies and controversies in phenotypic and functional characterization of the so-called “regulatory” DCs suggest that the use of this term is excessively abused and non-standardized. In fact, conflicting reports further compound the difficulty in understanding the biology of DC subsets with immunosuppressive and/or tolerogenic properties. As has been recently suggested, “One should only assign the term “tolerogenic” to DCs that have been proven to

induce immunological tolerance or, at the very least, encourage the formation of functional Tregs under various experimental and pathophysiological conditions. Similarly, to slow the growing perplexity, the term “regulatory” should be restricted to DC subsets with experimentally established immunosuppressive activity in the tumor microenvironment.” [133].

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