Cancer Immunol Immunother (2016) 65:821–833
DOI 10.1007/s00262-016-1820-y

FOCUSSED RESEARCH REVIEW

# Tumor-derived factors modulating dendritic cell function

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Received: 3 November 2015 / Accepted: 26 February 2016 / Published online: 16 March 2016


**Abstract** Dendritic cells (DC) play unique and diverse roles in the tumor occurrence, development, progression and response to therapy. First of all, DC can actively uptake tumor-associated antigens, process them and present antigenic peptides to T cells inducing and maintaining tumor-specific T cell responses. DC interaction with different immune effector cells may also support innate antitumor immunity, as well as humoral responses also known to inhibit tumor development in certain cases. On the other hand, DC are recruited to the tumor site by specific tumor-derived and stroma-derived factors, which may also impair DC maturation, differentiation and function, thus resulting in the deficient formation of antitumor immune response or development of DC-mediated tolerance and immune suppression. Identification of DC-stimulating and DC-suppressing/polarizing factors in the tumor environment and the mechanism of DC modulation are important for designing effective DC-based vaccines and for recovery of immunodeficient resident DC responsible for maintenance of clinically relevant antitumor immunity in patients with cancer. DC-targeting tumor-derived factors and their effects on resident and administered DC in the tumor milieu are described and discussed in this review.

**Keywords** Immunosuppression · Dendritic cells · Tolerance · Tumor immunoenvironment · Regulatory dendritic cells · Cytokines

**Abbreviations**

| | |
|---|---|
| ACVR1 | Activin receptor 1 |
| BMPR | Bone morphogenetic protein receptor |
| COX | Cyclooxygenases |
| CSF-1 | Colony-stimulating factor 1 |
| CSIF | Cytokine synthesis inhibitory factor |
| CTL | Cytotoxic T cell(s) |
| DAMP | Damage-associated molecular pattern |
| DC | Dendritic cell(s) |
| DR6 | Death receptor 6 |
| ER | Endoplasmic reticulum |
| FABP4 | Fatty acid-binding protein |
| GDF-15 | Growth differentiation factor-15 |
| HCG | Human chorionic gonadotropin |
| HMGB1 | Chromatin-binding protein high-mobility group box 1 |
| HSP | Heat-shock protein(s) |
| IDO | Indoleamine-2, 3-dioxygenase |
| IL-10 | Interleukin-10 |
| LPL | Lipoprotein lipase |
| M-CSF | Macrophage colony-stimulating factor |
| MIC-1 | Macrophage inhibitory cytokine-1 |
| MMP | Matrix metalloproteinase |
| MUC1 | Mucin 1 |
| NMDAR | *N*-methyl-d-aspartate receptor |
| PD-L1 | Programmed death ligand 1 |

This paper is a Focussed Research Review based on a presentation given at the *Fourth International Conference on Cancer Immunotherapy and Immunomonitoring* (CITIM 2015), held in Ljubljana, Slovenia, 27th–30th April 2015. It is part of a series of Focussed Research Reviews and meeting report in *Cancer Immunology, Immunotherapy*.

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|---|---|
| PSA | Prostate-specific antigen |
| RAGE | Receptor for advanced glycation end product |
| regDC | Regulatory dendritic cell(s) |
| ROS | Reactive oxygen species |
| SDF-1 | Stromal cell-derived factor-1 |
| STAT3 | Signal transducers and activators of transcription 3 |
| TGF-β | Transforming growth factor beta |
| TGFBR | TGF-β receptor |
| TIM-3 | T cell immunoglobulin domain and mucin domain-3 |
| TLR | Toll-like receptor |
| Treg | Regulatory T cell(s) |
| TREM1 | Triggering receptor expressed on myeloid cell-1 |
| UPR | Unfolded protein response |
| VEGF | Vascular endothelial growth factor |
| XBP1 | X-box-binding protein 1 |

## Introduction

The development and progression of a tumor is a complex process that includes multidirectorial interactions between malignant and non-malignant cells occurring systemically in lymphoid and non-lymphoid tissues and in the local tumor milieu. Active and passive communications between different cell types direct formation of the tumor microenvironment and may result in either elimination of cancerous cells or their growth and spreading. Immune effector cells are able to recognize tumor cells, initiate the antitumor immune reactions and erase tumors, while immune regulatory cells support tumor escape from immune attack by different mechanisms and pathways. Tumor- and tumor stroma-derived factors include both "danger signals" activating immune responses and various molecules suppressing and polarizing immune cells, thus leading to tumor survival and progression. Although many of these factors are identified and characterized, there are no effective tools to control their levels or expression in the tumor environment in order to shift their balance from the protumorigenic to proimmunogenic outcome in a clinical setting.

Dendritic cells (DC) are well-characterized antigen-presenting cells known to play a key role in initiating and maintaining the antitumor immunity, bridging innate and adaptive immune responses, and sustaining immune tolerance. The proven role of DC in the tumor immunosurveillance supported designing and testing of DC-based vaccines for different types of cancer, which, however, demonstrated different levels of efficacy and feasibility [1]. Further analyses of DC functioning and longevity in the tumor environment revealed that DC may be inhibited or functionally polarized and thus unable to support the development of antitumor immunity [2]. Furthermore, new data demonstrated that DC polarized in the tumor milieu were immunosuppressive and tolerogenic, and supported tumor growth and spreading [3]. It is well established now that there are several phenotypic functional subsets of tumor-associated DC: fully functional immunostimulatory DC, abnormal functionally deficient DC, dying DC and polarized immunosuppressive regulatory DC (regDC) [4, 5]. Thus, identification of tumor-derived factors targeting DC, understanding the mechanisms of DC modulation in cancer and revealing the means of changing the balance between DC-altering molecules in the tumor environment will not only improve the efficacy of DC vaccine and allow development of novel DC-based and DC-targeting therapies, but also provide novel perspectives for revealing complex cellular interactions during cancer development and therapy [6].

## Tumor-derived DC-activating factors

DC are proven to play a central role in the initiation and regulation of antitumor immunity—proactive anticancer immunosurveillance mechanism—which suggests that in many instances, DC uptake malignant cells or their bodies and respond to local stimulation leading to DC maturation, emigration from the tumor mass and homing in the regional lymph nodes to present tumor antigens to antigen-specific T cells. Immunogenic signals released by dying tumor cells are able to prompt antigen uptake, antigen processing and antigen presentation by DC. Cancerous cells may undergo cell death due to hypoxia, nutrient deprivation and innate immune responses resulting in the release of host-derived damage-associated molecular pattern (DAMP), sometimes termed alarmins or danger signals, as an indicator of dying, stressed or dead cells. Such type of apoptotic and necroptotic cell death is characterized by the induction of endoplasmic reticulum stress and autophagy, exposure of calreticulin on the cell surface, the secretion of adenosine triphophosphate and the release of the chromatin-binding protein high-mobility group box 1 (HMGB1) [7]. DAMP-associated proteins include endogenous molecules, such as HMGB1, heat-shock proteins (HSP), histones, the S100 family of proteins and serum amyloid A, whereas nonprotein DAMP includes heparin sulfate, uric acid, ATP, DNA (genomic and mitochondrial DNA) and RNA [8].

*HMGB1* is one of the HMGB family members consisting of three domains—HMGB A box, HMG B box and the C-terminal acidic tail [9]. HMGB1 functions to protect cells from injury in normal conditions, but may serve as DAMP in inflammation, cancer, sepsis, trauma and autoimmunity. HMGB1 receptors include toll-like receptors (TLR) TLR-2, TLR-4 and TLR-9, receptor for advanced

glycation end product (RAGE), CD24, α-synuclein filaments, proteoglycans, the T cell immunoglobulin domain and mucin domain-3 (TIM-3), *N*-methyl-d-aspartate receptor (NMDAR) and the triggering receptor expressed on myeloid cell-1 (TREM1) [9, 10]. HMGB1, via its *B* box domain, has been reported to induce phenotypic maturation of DC demonstrated by increased expression of CD83, CD54, CD80, CD40, CD58 and MHC class II molecules and decreased CD206 expression [11, 12]. The *B* box also caused increased secretion of the proinflammatory cytokines IL-12, IL-6, IL-1α, IL-8, TNF-α and RANTES. Saenz et al. [13] showed that peptide Hp91, whose sequence corresponds to an area within the B box domain of HMGB1, activates DC and acts as an adjuvant in vivo. Hp91-induced DC activation is mediated by a MyD88- and TLR4-dependent pathway involving p38 MAPK and NF-κB. Thus, HMGB1 released by dying cells may be a signal of tissue or cellular injury that, when sensed by DC, induces or enhances an immune reaction. Interestingly, new results revealed that HMGB1 secretion during cervical carcinogenesis could support the achievement of a tolerogenic activity by plasmacytoid DC [14].

There is rising evidence that *S100 proteins*, which are structurally similar to calmodulin, may also act as DAMP and might play a role similar to HMGB1 in regulating tissue injury and inflammation operating via the same receptors [15]. This is a family of 24 related calcium-binding proteins that display differential tissue and cell-type expression profiles in vertebrates. The functions of intracellular S100 proteins have been extensively studied, and most members participate in the regulation of a diverse set of intracellular processes such as cell cycle progression, cell proliferation, differentiation and migration, protein degradation, cytoskeletal organization, protein phosphorylation and transcriptional factor activity [16]. Recently, it has been shown that S100 proteins released from different cell types may serve as useful markers of disease activity including such diseases as asthma, chronic obstructive pulmonary disease, colitis, rheumatoid arthritis, Alzheimer's disease and cancer [17]. Furthermore, S100A8 and S100A9, with well-proven activity in inflammation, have been progressively recognized not only as markers, but also as new regulators with essential roles in modulating tumor growth and progression [18].

The S100 genes of the *A* series are sited in a region of chromosome 1 which is prone to rearrangements, linking these S100 proteins with cancer [19]. Marked changes in the expression of S100B, S100A2, S100A4, S100A6, S100A8/A9 and S100P have been reported for different types of cancer [20, 21]. For instance, serum S100B protein has been suggested as a biomarker of malignant melanoma [22], and serum S100A2 and S100A6 may have the potential for being used as a NSCLC biomarker [23]. Although it is known that S100A8 and S100A9 proteins can regulate the differentiation and function of different myeloid cells, including DC [24], new data allow speculating that other S100 proteins released in the tumor microenvironment may also affect DC activity. For instance, DC have been shown to require S100A4 for activating T cells [25].

Another well-established DAMP in cancer are *heat-shock proteins*, which function as intracellular chaperones and have been implicated in the activation and bridging of innate and adaptive immune systems. Studies based on molecular weight and phylogenetics have separated five major HSP families; however, only HSP96, HSP90, HSP70, HSP110 and HSP170 have proven immunogenic interactions as membrane-bound and extracellular components [26]. Stimulation of cross-presentation is achieved through binding of HSP to distinct cell surface receptors followed by antigen internalization, processing and presentation. For instance, HSP-CD91 binding on immune cells can assist in DC maturation, secretion of cytokines and T helper cell priming [27]. HSP70 binds to immature DC and induces their maturation as evidenced by an increase in CD40, CD86 and CD83 expression and enhanced ability to present model antigen to specific CTL [28]. Tumor-derived antigenic peptide or protein complexes with HSP can also be involved in immune activation via cross-presenting the chaperoned proteins to DC when they are released from necrotic tumor cells or secreted in response to cellular stress [29].

## Tumor-derived DC-suppressive factors

Dendritic cells, together with other immune cells, such cytotoxic T cells, macrophages, NK cells, γδ T cells and B cells, play an important role in cancer immunosurveillance—the ability to recognize and destroy newly ascending malignant cells. As cancer is linked to certain defects in immunosurveillance, newly appearing cancerous cells progressively gain a variety of mechanisms to escape immune recognition and elimination that favor further tumor survival and progression. Immune escape is the consequence of a direct or indirect cross talk between malignant cells and the immune system occurring in the local tumor microenvironment as well as at a systemic level. Soluble mediators produced by both tumor cells and stromal cells represent crucial performers in this cross talk (Table 1).

### Tumor-derived DC-suppressive factors: growth factors, cytokines and chemokines

Vascular endothelial growth factor (VEGF) is a secreted heparin-binding protein produced by the majority of tumors and responsible for the formation of tumor neovasculature

and tumor development [30]. The increased serum level of VEGF correlates with poor prognosis in patients with different types of cancer [31]. VEGF seems to be the first identified tumor-derived factor affecting DC: It inhibits its differentiation and maturation of DC via binding and activation of two tyrosine kinase receptors, VEGFR-1 and VEGFR-2 [32]. VEGF inhibits the development and maturation of DC in vitro and in vivo by blocking NF-κB activation in hematopoietic progenitor cells [33, 34]. Not only exposure of cultured DC to VEGF affects DC differentiation by induction of apoptosis, alteration of DC phenotypic profile and increasing CXCR4 expression, DC numbers in the peripheral blood of patients with cancer inversely correlate with VEGF serum levels [35]. VEGF molecules are also known to regulate DC migration and homing by recruiting immature myeloid cells and immature DC from the bone marrow to the tumor site [36].

As inhibition of the VEGF pathways has become an appreciated approach in the treatment of cancers, it is important to mention that inhibition of VEGF signaling by using VEGF-Trap, which significantly increased the proportion of mature DC in patients with refractory solid tumors, enrolled into a phase I clinical trials [37]. Direct in vitro studies showed that the inhibition of VEGF expression in breast cancer cells by small interfering RNA effectively recovered differentiation and maturation of DC inhibited by tumor cells and increased DC potential to induced tumor-specific cytotoxic T cells [38].

Different members of the transforming growth factor beta (TGF-β) superfamily have been shown to regulate activity and differentiation of DC [39]. Indeed, DC express both type-1 TGF receptors, including activin receptor 1 (ACVR1), ACVR1B, bone morphogenetic protein receptor (BMPR) 1A, BMPR1B and TGF-β receptor (TGFBR)1, and type-2 TGF receptors, including TGFBR2, BMPR2, ACVR2A and ACVR2B to respond to different TGF-β family ligands. DC also express all components of the principal signaling cascades, such as the R-SMAD, receptor-regulated SMAD—SMAD1/5/8 and SMAD2/3, and the Co-SMAD—SMAD4 [40]. However, with the exception of TGF-β, the role of different members of the TGF-β superfamily in DC regulation in the tumor microenvironment has not been yet established. TGF-β overexpression in the tumor milieu may be associated with suppressed DC maturation and function resulting in the defects of the tumor-specific immune responses [41]. Tumor-derived TGF-β has been shown to be responsible for downregulating the expression of DC maturation markers CD83, CD80, CD86 and MHC II molecules [42] and inhibiting the expression of proinflammatory cytokines inducing DC maturation, such as TNF-α, IL-1, IL-12 and IFN-α, while promoting the release of regulatory cytokines, including TGF-β itself [43]. TGF-β family ligands also affect DC motility and migration through the regulation of the expression of chemokines and chemokine receptors [39]. TGF-β might also induce apoptosis in DC [44].

These and other data showing decreased maturation of DC under the influence of TGF-β suggest that tumor-derived TGF-β can significantly suppress DC function and their ability to initiate antitumor immune responses. Additional results revealed that TGF-β can not only inhibit DC function, but may also polarize DC into immunosuppressive tolerogenic phenotype. These regulatory DC (regDC) display a strong ability to suppress proliferation of effector T cells and induce differentiation of T cells into regulatory (Treg) T cells [3, 5]. For instance, TGF-β has been shown to increase the expression of programmed death ligand 1 (PD-L1) and signal transducers and activators of transcription 3 (STAT3) in DC in both a time- and dose-dependent manner [45].

The DC-targeting effects of other members of the TGF-β superfamily produced in the tumor microenvironment are not well investigated. We have evaluated whether the ligands from the activin subfamily are expressed by tumor cell lines and can alter DC phenotype and function. We found that Nodal that is produced by different tumor cells and shares the SMAD2/3 signaling pathway with TGF-β1 can polarize DC into the regulatory phenotype by upregulating COX2 expression (Agassandian et al. in preparation).

Growth differentiation factor-15 [GDF-15, macrophage inhibitory cytokine-1 (MIC-1)], a divergent member of the TGF-β family of proteins, was detected in tissues and serum samples in patients with glioblastoma, and ovarian, prostate, gastric and colorectal cancers. GDF-15 was shown to inhibit the expression of CD83, CD86 and HLA-DR on DC, downregulate IL-12 and upregulate TGF-β1 production and activate phagocytic but inhibit T cell stimulatory activity of DC in vitro. Furthermore, GDF-15 suppressed DC potential to stimulate tumor-specific immune responses in vivo [46].

Interleukin-10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine primarily produced by monocytes and lymphocytes. However, IL-10 release has been reported from some tumors including melanoma, multiple myeloma and lung cancer [47, 48]. Tumor-derived IL-10 has been shown to have an inhibitory effect on DC maturation and the T cell stimulatory ability of DC [49]. In addition, increased serum levels of IL-10 also correlate with profound numerical deficiency and immature phenotype of circulating DC subsets in patients with hepatocellular carcinoma, indicating a dominant correlation between tumor-derived IL-10 and defects in DC differentiation [50].

The inhibitory effect of IL-10 on the expression of costimulatory and MHC molecules on DC has been well documented [51]. For instance, tumor-derived IL-10 not

only inhibits DC maturation and longevity and induces DC tolerance, but also inhibits CD40 expression, suppresses CD40-dependent IL-12 production, decreases chemokine receptor expression, blocks antigen presentation and induces upregulation of B7-H1 expression on DC [52, 53]. It is likely that p38 MAPK and STAT3 pathways are involved in the inhibition of DC by tumor-derived IL-10 [54]. Recent microarray studies showed that IL-10 not only inhibited DC function but also redirected differentiation of DC into cells with a different phenotype leading to a decreased pool of DC precursors [55].

*IL-6*, originally identified as a B cell differentiation factor, is known to display a plethora of effects on cell growth, differentiation, longevity and migration during immune responses, hematopoiesis and inflammation [56]. Overproduction of IL-6 is proved to be associated with a functional defect in DC from cancer patients [57]. For instance, increased plasma levels of IL-8 and IL-6 were detected in epithelial ovarian cancer patients, and production of both cytokines by cultured epithelial ovarian cancer cell lines was also reported [58]. Interestingly, immunosuppression of human DC by culture supernatant of ovarian tumor cells was reversed when the production of IL-6 and IL-8 was blocked. Furthermore, tumor-derived IL-6 affects the differentiation of hematopoietic progenitor cells and monocytes, including the macrophage and DC in vitro [59], and may be responsible for tolerogenic phenotype of DC [60]. It has been reported that IL-6-associated DC suppression could be normalized by JAK2/STAT3 inhibitor AG490 [54]. As STAT3 has been shown to be involved in the effect of IL-6 on the differentiation and maturation of DC, the tumor-induced phosphorylated STAT3 in DC could be regarded as a promising target for cancer immunotherapy [60].

Macrophage colony-stimulating factor (M-CSF), also known as colony-stimulating factor 1 (CSF-1), a major regulator of the mononuclear phagocytic lineage, is expressed in human breast and renal cell carcinomas, and its increased expression is a predictor of a poor prognosis [61]. CSF-1 not only modulates tumor progression and metastasis by recruiting and regulating macrophages, but also suppresses the differentiation of DC [62]. In addition, tumor-derived CSF-1 may inhibit the differentiation of hematopoietic progenitor $CD34^+$ cells into DC and induce cord blood monocyte to differentiate into tolerogenic DC [63]. Modulation of DC differentiation by CSF-1 is mediated by the PI3K-dependent pathway and delayed caspase activation in monocytes [64].

New data revealed receptor activator of nuclear factor κ-B ligand (RANKL), a TNF family member, as a DC-targeting tumor-derived factor that downregulated IL-12 and upregulated IL-10 production by DC and polarized DC into regDC that induce $FoxP3^+$ Treg cell differentiation [65].

It is well known that the recruitment of different subsets of myeloid cells varies according to the chemokine receptor expression profile and depends on the maturation stage of a particular cell population [53]. Several tumor-derived *chemokines* may target DC altering their migration and maturation statuses. Immature DC can be recruited into tumor inner location by tumor-derived chemotactic factors including CCL2, CCL20/MIP3a, CCL25, CCL5, CXCL12, CXCL1 and CXCL5, while mature DC reside in the surrounding areas of the tumor [66, 67]. These data suggest that the tumor-derived chemokines, produced by malignant or stromal cells, play an important role in the location and homing of tumor-infiltrating DC, as well as the maintenance of the immature status of DC. For instance, human ovarian epithelial tumor cells express high levels of CXCL12, also known as stromal cell-derived factor-1 (SDF-1), which binds to CXCR4 expressed on precursor of plasmacytoid DC and induces their chemotaxis, transmigration and adhesion [68]. The binding of CXCL12 to CXCR4 induces intracellular signaling through several different pathways initiating signaling cascades regulating chemotaxis, survival and proliferation [69]. Importantly, new data demonstrate that melanoma-derived factors can change maturation and activation of tissue-resident DC subsets and that the extent to which DC function is changed by these factors correlates with the in vivo tumorigenicity of melanomas [70].

## Tumor-derived DC-suppressive factors: tumor "antigens"

Prostate-specific antigen (PSA), a serine protease overexpressed in most prostate cancers, was the first tumor-associated antigen shown to inhibit maturation, longevity and function of DC [71]. Addition of active PSA to DC cultures resulted in significant inhibition of DC generation (dendropoiesis) and maturation, shown by the levels of expression of CD83, CD80, CD86 and HLA-DR molecules. The ability of DC to induce T cell proliferation was also inhibited by PSA-treated DC. Other study also showed that the endogenous factors presented in the serum of patients with prostate cancer inhibited the generation of functionally active DC from $CD14^+$ monocyte in vitro. This inhibition of DC maturation by serum from prostate cancer patients has a positive relationship with the levels of serum-free PSA [72], suggesting that PSA may be involved in impairment of resident DC in prostate cancer.

Cell surface-associated Mucin 1 (MUC1) is a glycoprotein overexpressed in many tumor cells. In normal cells, MUC1 forms a protective layer against the attack of microbes and toxic chemicals; however, oversecretion of MUC1 provides cancerous cells with an increased invasiveness, metastasis and resistance to effective immune

response [73]. It has been shown that MUC1 could chemoattract immature DC to the tumor site and induce semimaturation of DC subverting DC function. When cultured with MUC1 glycoprotein, human monocyte-derived DC displayed upregulated expression of D83, CD80, CD86, CD40 and MHC class II; however, these DC also produced greater amounts of IL-6, TNF-α and IL-10, but fail to make IL-12. When these DC were cocultured with CD4 + T cells, they induced production of IL-13 and IL-5 and lower levels of IL-2, thus failing to induce a type 1 response [74]. Other studies also showed that tumor-derived mucin profoundly affected the cytokine expression in monocyte-derived DC and transferred them into IL-$10^{high}$IL-$12^{low}$ regDC with a poor ability to induce protective Th1 responses [75]. These findings provide evidence that tumor-derived MUC1 may be responsible for the impaired DC maturation and function in certain types of cancer, identifying MUC1 as an additional mechanism of tumor escape from immune surveillance and disclosing the existence of tolerogenic DC in MAC1-positive cancers.

Finally, human chorionic gonadotropin (HCG), which serves as an important tumor marker for trophoblastic disease, choriocarcinoma and testicular cancer, has been shown to upregulate the expression of indoleamine-2, 3-dioxygenase (IDO) in DC [76]. IDO is the rate-limiting enzyme in the degradation pathway of tryptophan, an essential amino acid required for cell proliferation, was reported to be the mechanism of T cell suppression induced by IDO-expressing DC [77].

### Tumor-derived DC-suppressive factors: other molecules

*Gangliosides*, found predominantly in the nervous system, are also expressed by the neuroectodermal cell-originated tumors as membrane-bound or shaded glycosphingolipids and can be detected in the tumor microenvironment and the bloodstream. Gangliosides act as cell surface receptors and markers and also participate in intercellular communication, cell signaling, cell cycling and cell motility [78]. It is well documented that neuroblastoma-derived gangliosides regulate the development of the tumor immunity by inhibiting dendropoiesis, longevity and function of DC [79]. Melanoma-produced gangliosides were also reported to impair DC differentiation and induce their apoptosis [80, 81].

*Prostanoids*, a subclass of eicosanoids consisting of the prostaglandins, prostacyclins and thromboxanes, are known mediators of inflammatory, anaphylactic reactions and vasoconstriction. Prostanoids have been found elevated in many tumors and implicated in tumor-associated subversion of the immune functions. For instance, prostaglandin $PGE_2$ has been proposed as the principal prostanoid associated with colorectal tumors since $PGE_2$ levels and the activity of cyclooxygenases (COX) are elevated in patients with colon cancer and correlate with tumor size and patient survival [82]. Furthermore, $PGE_2$ was found to be responsible for the reduced differentiation of DC from $CD34^+$ precursors [83]. Furthermore, $PGE_2$ can serve as a mediator of DC tolerance since it upregulates the expression of IDO1 in DC resulting in the differentiation of Treg cells and in the inhibition of antigen-specific stimulatory potential of DC [84].

*Polyamines* (putrescine, spermidine and spermine) are naturally occurring aliphatic cations essential for cell growth and have been reported to be increased in prostate, colon and breast cancers [85, 86]. Spermine has been shown to induce altered maturation and impaired function in DC in vitro, while a significant inverse correlation between spermine level and the percentage of IL-12-expressing DC was found in patients with breast cancer [87].

Tumor-derived *lactic acid*, the end product of glycolysis, is known to affect cancerous cells, adjacent stroma and endothelial cells in the local tumor microenvironment reprogramming metabolism, promoting tumor inflammation and stimulating tumor angiogenesis [88]. On the other side, lactic acid is known as an important agent affecting DC by inhibiting IL-12 production and antigen presentation in the tumor environment, which may markedly support tumor escape from immune recognition [89]. Moreover, high lactate concentrations distress the differentiation of DC from monocytes decreasing the inflammatory phenotype of DC and inducing the production of IL-10 [90].

Recently, a metabolic stress- or hypoxia-associated *adenosine* accumulation has been suggested as one of the important drivers for an inhibition of antitumor immune response. Adenosine concentrations in tumor tissue are in the 50–100 μM range, while in normal tissues, they are found to be in the range of 10–100 nM [91]. After adenosine is released into the extracellular areas, it exerts numerous immunomodulatory effects via adenosine receptors expressed on different immune cells, including DC. Adenosine could alter differentiation of DC precursors into $CD11c^+Gr\text{-}1^+$ DC with a strong stimulatory effect on Th17 cells [92]. Adenosine-differentiated DC expressed a number of angiogenic, proinflammatory and immunosuppressive molecules, including TGF-β, IL-10, VEGF, IL-6, IL-8, COX-2 and IDO, and could support tumor growth if injected into tumors in mice [93]. Adenosine may also attract DC to Treg cells via Epac1–Rap1-dependent pathways rendering them less stimulatory [94].

New reports began to uncover an intricate role of *lipids* and lipid accumulation in DC functioning and how the triglycerides (triacylglycerol, TAG) in the context of tumors may alter DC activity and longevity. As DC develop and mature, they take on a "lacy" appearance composing an

amplified presence of fat and glycogen-containing lipid body droplets [95], and lipid production and consumption play critical roles in DC biology [96]. It is therefore of interest that elevated levels of lipids, particularly TAG, were described in substantial proportion of DC in mice bearing lymphoma and breast and colon cancers and patients with cancer [97]. Lipid accumulation in DC was due to an increased uptake of extracellular lipids induced by the upregulation of scavenger receptor A, and lipid-laden DC displayed a reduced potential to process antigens. This receptor is primarily responsible for the uptake of modified lipids, and several molecular species of oxygenated lipids in tumor-bearing animals responsible for their uptake and accumulation in DC via scavenger receptor A-dependent pathway have been recently identified [98]. Similarly, it has been recently reported that mesothelioma promotes lipid acquisition by DC, which was accompanied by reduced antigen processing and elevated expression of the costimulatory molecules and production of IL-10 [99].

Elevated expression of the lipoprotein lipase (LPL) and the fatty acid-binding protein (FABP4), as well as increased serum levels of triacylglycerol in radiation-induced tumors, may explain the mechanisms of lipid accumulation in DC in tumor-bearing hosts [100]. Furthermore, tumor-associated DC have been shown to display an activation of the unfolded protein response (UPR) seen as the appearance of high levels of an endoplasmic reticulum (ER) stress response factor XBP1 (X-box-binding protein 1). XBP1 activation, attributed to reactive oxygen species (ROS) in tumor, which induces lipid peroxidation, induced a triglyceride biosynthetic program in tumor-associated DC causing abnormal lipid accumulation and consequent suppression of DC ability to maintain antitumor T cell responses [101]. Interestingly, XBP1 is not only an important component of UPR, but also an essential nuclear transcription factor. Many XBP1 target genes are fatty acid synthesis enzymes. Enriched production of fatty acids results in the formation of lipid droplets inside the cytoplasm and extension of the ER compartment due to efficient intracellular membrane formation [102].

Many *neuropeptides* are known to be synthesized and released by tumor cell lines and primary tumor cells and are detected in the tumor microenvironment [103]. Interestingly, some of these regulatory peptides may also affect function of DC and influence the development of antitumor immune responses. For instance, substance P induces tumor cell proliferation, migration, invasion, intratumor angiogenesis and metastasis development [104], and suppresses phagocytic activity of monocyte-derived and resident DC [105]. Neuropeptide Y may function as a growth and angiogenic peptide controlling the inflammatory and immunologic tumor responses [106]; its expression was found to correlate with the progression of cutaneous melanoma upregulating tumor invasiveness [107]. Neuropeptide Y was also shown to induce a Th2 polarizing profile of DC through the increased expression of IL-6 and IL-10 [108]. Tumor-derived bombesin, neuromedin B and gastrin-releasing peptide were reported to inhibit maturation of DC assessed as downregulation of CD40, CD80 and CD86 expression, decreased IL-12 production and attenuated potential to stimulate T cell proliferation [109].

Interestingly, new data revealed that death receptor 6 (DR6), a member of the TNF receptor superfamily known to be overexpressed on many tumor cells, may affect DC generation and function. It was shown that DR6, which is expressed on tumor cells and may be cleaved from the surface of tumor cells by the membrane-associated matrix metalloproteinase (MMP)-14, could induce apoptosis in >50 % of monocytes differentiating into DC and changed phenotype and cytokine expression in the resulting immature DC [110].

*Tumor-derived microvesicles* are the heterogeneous group of membrane-bound particles that are shed from the surface of tumor cells into the extracellular environment. Proteins, lipids, glycoproteins, glycolipids, peptides, RNA, microRNA and DNA are included in this complex cargo, which suggests that microvesicles can use multipronged mechanisms to regulate cell interactions in the tumor milieu facilitating tumor progression [111]. The growing body of evidence demonstrates that tumor-derived microvesicles or exosomes can alter myeloid cell function in the tumor microenvironment by impairing monocyte differentiation into DC and promoting the generation of a myeloid immunosuppressive cell subset [112]. For instance, exosomes purified from the lung cancer biopsies and containing the epidermal growth factor receptor (EGFR) have been shown to induce tolerogenic DC, which stimulated the differentiation of tumor antigen-specific Treg cells that could suppress the tumor-specific CD8 + T cells [113]. Furthermore, pancreatic cancer-derived exosomal miRNA has been recently reported to inhibit mRNA expression in DC resulting in decreased expression of MHC molecules and induction of immune tolerance [114].

## Conclusions

Dendritic cells, the strongest functional antigen-presenting cells, essentially contribute to the induction and regulation of innate and adaptive immunity. By interacting with NK, NKT, T and B lymphocytes, macrophages, neutrophils, mast cells and various non-immune cells, DC play a central role in regulating immunologic and tolerogenic responses maintaining the stability of immune homeostasis. Furthermore, providing a critical link between the innate and adaptive immunity and regulating both the humoral and

**Table 1** DC-targeting tumor-derived inhibitory molecules and factors

| Factors | Effect on DC | Known signaling pathways | References |
|---|---|---|---|
| VEGF | Inhibition of differentiation, maturation, migration; induction of apoptosis | NF-κB | [32] |
| TGF-β | Suppression of maturation and function | SMAD, STAT3 | [40, 45] |
| GDF-15 | Inhibition of costimulatory molecule expression, IL-12 production, T cell stimulatory activity; increasing of TGF-β expression | | [46] |
| RANKL | Tolerogenic repolarization | | [65] |
| IL-10 | Inhibition of maturation, induction of tolerogenic phenotype, redirection of differentiation | p38 MAPK, STAT3 | [52, 54, 55] |
| IL-8 | Impaired migration | PI3K, AKT, PKC, MAPK | [115] |
| IL-6 | Effect on growth, longevity, differentiation, migration | MAPK, STAT3, NF-κB | [56, 60] |
| CSF-1 | Suppression of differentiation | PI3K | [64] |
| CCL2 | Regulation of migration and maturation | PI3K | [67] |
| MIP3a | | NF-κB, MAPK, JAK/STAT | [68] |
| SDF-1 | | | [69] |
| MUC1 | Regulation of chemotaxis, induction of semimaturation | | [74] |
| PSA | Inhibition of maturation, longevity and function | MAPK, STAT3, NF-κB | [71] |
| HCG | Induction of tolerogenic phenotype | | [76] |
| Gangliosides | Inhibition of dendropoiesis, longevity and function | IRAK-M | [79, 80] |
| Prostaglandins | Regulation of differentiation | RAS-MAPK, PI3K/AKT, PKA | [116] |
| Lactic acid | Inhibition of differentiation | NF-κB | [89, 90] |
| Adenosine | Alteration of differentiation and function and attraction to Treg cells | Epac1–Rap1-dependent pathways | [91] [94] [93] |
| Neuropeptides | Regulation of generation, function and longevity | Multiple pathways | [3, 109] |
| HLA-G | Induce tolerance | | [117] |
| Microvesicles | Impair differentiation | Multiple pathways | [112, 113] |

the cellular immune response, DC are primary involved in the developing and sustaining of cancer immunosurveillance and may profoundly impact tumor development and progression in patients. Therefore, it is not surprising that DC are also a key target and important player in the different pathways evolved by tumor cells to escape immune recognition and elimination. New insights gained over the last decades have revealed multiple mechanisms of immune regulation during tumor growth and progression, with DC likely to achieve a unique role in forming an immunosuppressive and tolerogenic milieu that supports cancer progression and blocks antitumor immunity. Although numerous studies identified and characterized various molecules produced in the tumor microenvironment that can suppress DC generation and function or polarize DC phenotype (Table 1), the most interesting and probably important question in this regard has not yet been answered—why do different tumors with quite diverse microenvironment utilize identical mechanisms to affect DC and why these pathways may be rather dissimilar in tumors of the same origin or the same type?

In relation to this question, there is an interesting fact that some of tumor-derived factors may display an opposite effect on DC depending on their concentration, the presence of other factors and cells or the stage of tumor development. Probably, TNF-α and prostaglandins are the most interesting examples from this category.

The balance between DC-stimulating and DC-suppressing factors in the tumor microenvironment at each particular time of tumor development and progression represents a unique parameter of maintaining immunologic activity in the tumor milieu (Fig. 1). Knowledge of

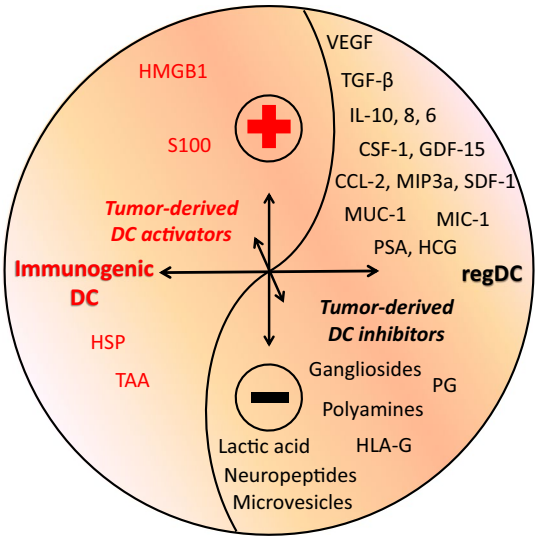


**Fig. 1** The balance between tumor-derived DC-activating and DC-suppressing factors directs the level of immunogenic and tolerogenic DC in the tumor milieu. The balance between DC-targeting factors in the tumor microenvironment at each particular time of tumor development and progression represents a unique parameter of maintaining immunologic activity in the tumor milieu. Agents affecting DC in cancer may be produced by malignant cells and stromal elements in the tumor environment. It is important to mention that there are a lot of other molecules that participate in the regulation of DC in patients with cancer: hormones associated with both physical and mental stress, and stress of surgery or therapy, non-tumor-derived cytokines and growth factors associated with other immune-mediated diseases and aging, environmental factors, such as nanomaterials in the air known to alter DC function and many drugs and medications that may also change DC activation in cancer patients. *HMGB1* high-mobility group box 1, *HSP* heat-shock proteins, *TAA* tumor-associated antigens, *VEGF* vascular endothelial growth factor, *CSF-1* colony-stimulating factor 1, *MIP3a* macrophage inflammatory protein-3, *SDF-1* stromal cell-derived factor 1, *PSA* prostate-specific antigen, *HCG* human chorionic gonadotropin, *PG* prostaglandins, *GDF-15* growth differentiation factor-15, *MIC-1* macrophage inhibitory cytokine-1

intercellular and intracellular circuits that shape immunogenic and tolerogenic phenotype of DC in cancer will provide necessary insights for developing adjuvant treatments to alleviate immunosuppression in the tumor microenvironment and improving the clinical efficacy of cancer vaccines and alternative immunotherapies for cancer.

**Acknowledgments** This work was supported in part by the National Institutes of Health (NIH), Grant RO1 CA154369 (to Shurin).

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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