Chapter 5
Immunobiology of Dendritic Cells in Cancer

Michael R. Shurin, Anton A. Keskinov and Gurkamal S. Chatta

Abstract Dendritic cells (DCs) play a crucial role in initiating immune responses against both foreign pathogens as well as tumors. DCs also control the type, potency, and extent of T-cell responses, contribute to natural killer (NK) and natural killer T-cell (NKT cell) antitumoral activity, as well as to B-cell-mediated immunity. However, antitumor immune responses are often deficient or suboptimal since tumor cells are able to exploit the functional roles of DCs for tumor progression. Suppression, dysfunction, and repolarization of DC function in cancer patients all contribute to the failure of antitumor immune responses and consequent disease progression. Subversion of tumor immunity by altering the tumor immunoenvironment and DC subset distribution and function is mediated by various malignant cell-derived and tumor stroma-derived factors, many of which remain to be identified. Molecular mechanisms of tumor-mediated dysfunction and repolarization of the DC system are under investigation, and several signaling pathways responsible for DC malfunction in cancer have been already described. Here, we summarize findings in the field of DC biology in cancer and discuss the importance of these data for designing novel DC-based vaccination strategies, as well as their applicability for combinatorial therapeutic approaches.

Keywords Dendritic cells · Dendropoiesis · Immunosuppression · Regulatory dendritic cells · Immunomodulation · Chemoimmunomodulation

M. R. Shurin (✉) · A. A. Keskinov
Department of Pathology, University of Pittsburgh Medical Center,
Pittsburgh, PA, USA
e-mail: shurinmr@upmc.edu

Department of Immunology, University of Pittsburgh Cancer Institute,
Pittsburgh, PA, USA

G. S. Chatta
Virginia Mason Medical Center Cancer Institute, Seattle, WA, USA

1 Introduction

Tumor development and progression are associated with suppression and malfunction of the immune system, of which dendritic cells (DCs) possess many key regulatory functions, especially those related to cytokine production, antigen presentation to naive T cells, and polarization and balancing T-helper subsets. DCs are professional antigen-presenting cells, strategically positioned for bridging innate and adaptive immunity. DCs can initiate T-cell responses against tumors due to their capacity to process and present tumor antigens and stimulate naive T cells. However, less is known about DC differentiation, behavior, and polarization in vivo in tumor-bearing hosts. Although neglected for many years, the importance of the tumor microenvironment in regulating immunology of DC is becoming more defined, as the dual role of DC in cancer was shown to play an important role in cancer progression [1].

Although alterations in DCs in the setting of cancer were described almost two decades ago, characterization of tumor-derived factors responsible for DC dysfunction and the molecular mechanisms of abnormal DC differentiation and activation are still not well understood. An understanding of how the tumor environment regulates the DC system and how it impacts the efficacy of DC vaccines and other immunotherapeutic approaches is far from complete and clinical trials focusing on the protection of DC from the detrimental effects of the tumor microenvironment are constantly being tested. In addition to the tumor/stromal cells and their interactions, the other factors impacting vaccine efficacy in cancer include (a) the psychological stress of both a potentially fatal disease as well as the stress associated with the treatment of the disease (Fig. 5.1) and (b) aging immune system, since more than 60 % of cancer arises in people older than 65 years of age. Thus, in patients with cancer, the DC system functions under the multidirectorial influences of various local and systemic tumor-derived and tumor stroma-derived factors, acute and chronic stress hormones, therapeutic agents and factors, as well as multifaceted conditions associated with aging, infections, autoimmune diseases, and other acute and chronic disorders (Fig. 5.1).

Modulation of DC generation and function by some of the above-mentioned factors or conditions has been partly described. However, a comprehensive and systematic analysis of the DC system in the tumor environment has not been reported. For instance, both tumor-derived factors (reviewed in [2], [3]) as well as nonmalignant cells in the tumor milieu (reviewed in [4]) have been reported to suppress DC maturation, function, and longevity. Psychological and physical stressors may affect the functional activity of DCs through a variety of hormones, neuro-mediators, and neuropeptides [5]–[7]. Indeed, modulation of DC maturation and function by glucocorticoids, neuropeptides, and biogenic amines has been described. Glucocorticoid-treated DCs show higher endocytic activity, lower antigen-presenting function, and a lower capacity to secrete cytokines [8]. Norepinephrine can impede interleukin-12 (IL-12) and stimulate IL-10 production in DCs, thus inhibiting their antigen-presenting capability and hampering their motility and chemotaxis [9], [10]. DCs also express receptors for and respond to calcitonin gene-related peptide, neuropeptide Y, opioid peptides, prolactin, bombesin-like peptides, substance P, and
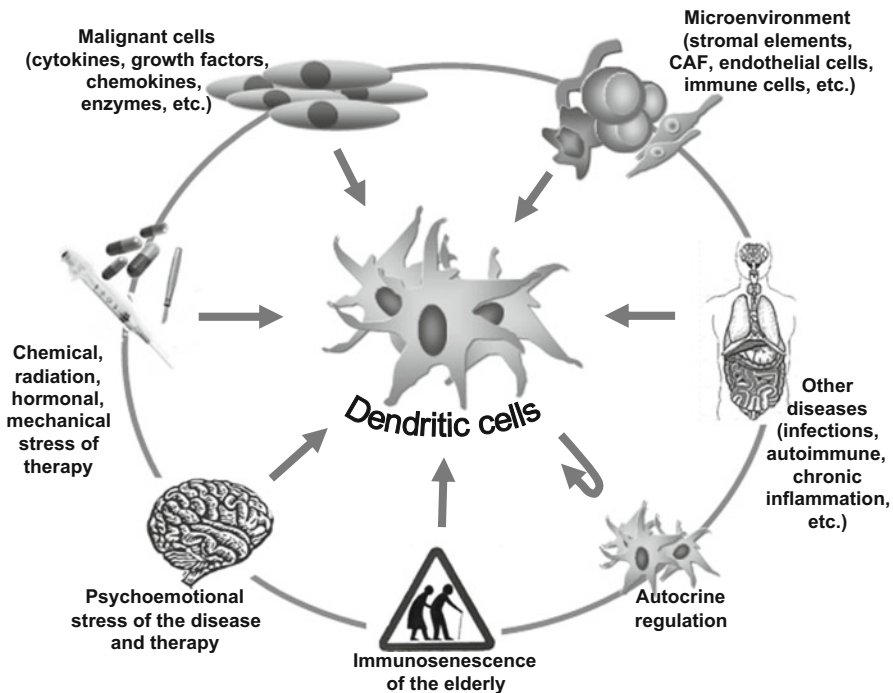
Fig. 5.1 Intrinsic and extrinsic mechanisms of dendritic cell regulation in cancer patients. DC generation, differentiation, polarization, and function are under constant, dynamic, and variable influences and regulatory pathways operating in patients with cancer. This includes numerous tumor-derived factors that affect all stages of DC development and may be represented by cytokines, chemokines, growth factors, prostaglandins, gangliosides, neuropeptides, and many other soluble and membrane-bound molecules on different cell types in the tumor microenvironment. Additional modulation of DC function in cancer may result from psychological stressors associated both with the diagnosis, as well as the effects of the treatment of a potentially fatal illness. Finally, DCs produce different factors, which may modulate cells in an autocrine and paracrine manner, and may also change DC responses to other molecules in the local environment. Thus, an understanding of the complex environmental conditions associated with DC function in cancer is necessary for harnessing the antitumor potential of these unique immunostimulatory and immunoregulatory cells

other neuropeptides, all of which may be involved in stress-related modulation of immunity [11]–[16].

As shown in Fig. 5.1, surgery, radiation, chemotherapeutic agents, and hormonal therapy might alter DC function and survival [17]–[20]. For example, many chemotherapeutic agents are known to suppress DC activity in therapeutic doses, but they may indirectly or directly upregulate DC maturation and function when used in low- or ultralow doses [21]–[25]. Interestingly, certain factors in the common environment, e.g., nanoparticles, may directly affect DC function in the lung or alter homing and function of other immune cells leading to dysfunction of antitumor immunity and tumor progression. For instance, it has been recently reported that in vivo exposure to single-walled carbon nanotubes (SWCNTs) modifies systemic immunity by

modulating DC function [26]. Furthermore, nanomaterials internalized by DCs differently affect their abilities to present antigens to T cells: While C(60)-fullerenes stimulated the antigen-specific major histocompatibility complex (MHC) class I-restricted T-cell response, graphene oxide (GO) impaired the stimulatory potential of DCs [27]. In contrast to C(60)-fullerenes, GO decreased the intracellular levels of low molecular mass polypeptide 7 (LMP7) immunoproteasome subunits required for processing of protein antigens. Interestingly, recent studies show that metastatic establishment and growth of lung carcinoma could be promoted by exposure to SWCNTs [28].

Furthermore, age-related alterations of DC maturity, function, longevity, and subpopulation composition also play a significant role in the ability of the DC system to interact with tumor cells and T cells and induce and maintain an antitumor immune response in patients with cancer (reviewed in [29]). For instance, increased levels of IL-6 and IL-10 repeatedly reported in old individuals might have a direct effect on dendropoiesis (i.e., DC generation) and maturation of DCs and, thus, on their motility and ability to process and present tumor antigens. Finally, exposure to different stimuli induces DCs to produce various endogenous mediators, including arachidonic acid-derived eicosanoids, cytokines, regulatory peptides, and small molecules like nitric oxide (NO). Many secreted products of DCs can act in an autocrine manner and modulate cell function; for instance, autocrine IL-10 can prevent maturation of DCs [30]. Interestingly, aging has been associated with immunological changes (immunosenescence) that mimic changes observed in the setting of chronic stress as well as changes seen with cancer [31], [32]. Thus, there may be common mechanisms of immune alterations in the DC system in cancer, aging, and chronic stress and numerous factors and agents can be involved in abnormal function of DCs in patients with cancer. These and many other issues related to differentiation, function, and clinical application of DCs in cancer have been discussed in the book *Dendritic Cells in Cancer* [33].

2 Alterations of DCs in Cancer

Regardless of the pathways and mechanisms responsible for tumor-associated changes of DCs, *functionally* three basic subtypes of DC can be seen in tumor-bearing hosts (Fig. 5.2): *normal* "unaltered" conventional DCs (cDCs) that can initiate and maintain immune responses, including antitumor responses; *functionally deficient* DCs with suppressed or blocked motility, antigen uptake/processing/presentation, or cytokine production or expression of costimulatory molecules; and *regulatory* or tolerogenic DCs that inhibit T-cell-mediated immune responses by different means. Because this classification is based strictly on DC function, there are no specific phenotypic markers to distinguish all functional subsets of DC seen in the tumor immunoenvironment [34]. In addition, DC function might be dynamically altered by the local microenvironment and surrounding cells. Functional plasticity of DC is a well-known phenomenon and different functional subsets of DC were repeatedly described in patients with cancer.
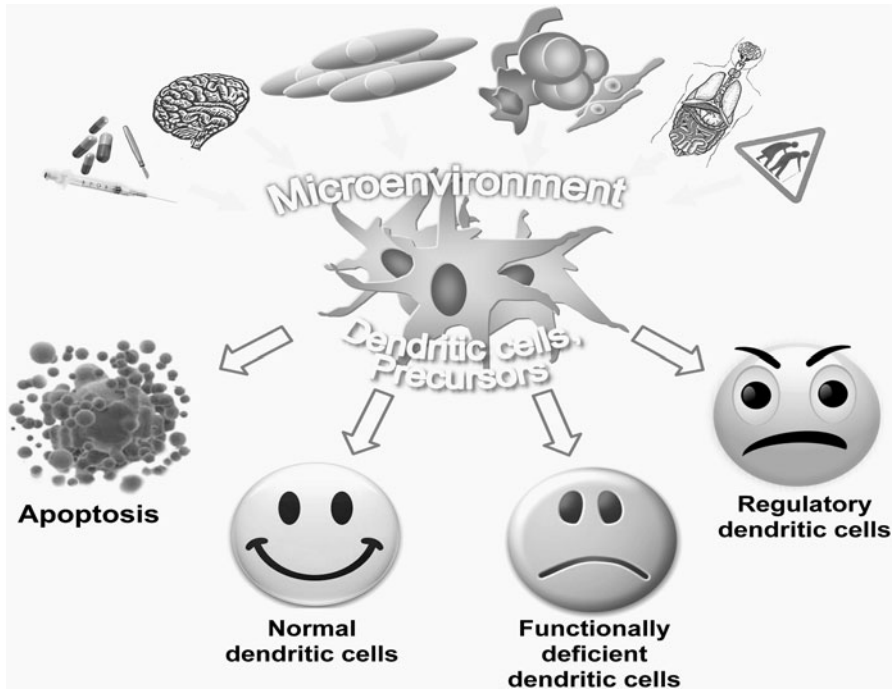
Fig. 5.2 Functional subsets of dendritic cells in cancer patients. The presence of numerous cells and factors affecting differentiation of DC precursors and activity of immature and mature DCs in the tumor environment results in formation of three basic functional subsets of DCs: normal "unaltered" immunostimulatory DCs, non-functional or functionally deficient DCs, and protumorigenic regulatory DCs. These DCs might belong to different or similar DC subpopulations (e.g., conventional or plasmacytoid), be on similar or different stages of maturation (e.g., immature, semi-mature, or mature), and express identical or different phenotypic markers (e.g., high or low MHC, CD80, CD86, CD40), but they act as inducers or suppressors of antitumor immune responses depending on the local and systemic environment

From the mechanistic point of view, most of the pathways that are responsible for altered functionality of DC in cancer can be also grouped in four categories: (1) *elimination* of functional DCs by blocking their production/differentiation/maturation or inducing apoptosis in DC or DC precursors; (2) *inhibition* of critical function of DCs; (3) *polarization* of DC subpopulations toward immunosuppressive or tolerogenic DC subsets; and (4) *avoidance* of the tumor contact with DCs by downregulating the expression of DC-attracting chemokines.

In 1988, Stene et al. revealed that melanoma-associated skin DCs (Langerhans cells) declined in number as melanoma progressed [35]. In 1989, Alcalay et al. described a decreased number and altered morphology of Langerhans cells in squamous cell carcinomas of the skin [36] and showed later (1991) that the antigen-presenting capacity of lymph node cells might be impaired during tumorigenesis [37]. Halliday et al. in 1991 demonstrated that tumor may regulate DC attraction and homing at

the tumor site and suggested that yet-unknown factors may inhibit DC function and thus induction of antitumor immunity [38], [39]. In 1992, Becker speculated that outcome of a primary tumor in patients depends on the ability of DCs to enter into tumors and that tumors might be different in their capacity to destroy or prevent DCs from entering the tumor site [40]. He also hypothesized that DCs and tumor cells interacted by releasing cytokines, which abrogate tumor cells or DCs, respectively [41]. In 1993, Tas et al. showed that DCs are functionally abnormal in patients with cancer [42]. Colasante et al. in 1995 studied the role of cytokines in the distribution and differentiation of DC lineage in primary lung carcinomas in humans and concluded on the potential role for granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), IL-1α, and IL-1β in DC modulation [43]. In 1996, Gabrilovich et al. reported that DCs isolated from tumor-bearing mice showed a significantly reduced ability to induce syngeneic tumor-specific cytotoxic T lymphocyte (CTL) and stimulate allogeneic T cells [44] and Chaux et al. revealed that tumor-associated DCs express low levels of costimulatory molecules [45]. Enk et al. in 1997 showed that melanoma-derived factors converted DC antigen-presenting function to tolerance induction against tumor tissue [46].

Following these initial findings, other teams demonstrated functional suppression in preparation of human CD34-derived and CD14-derived DCs, as well as murine bone marrow-derived DCs by both identified and unidentified tumor-derived factors (Table 5.1). For example, Ninomiya et al. (1999) reported that DCs propagated from patients with hepatocellular carcinoma expressed significantly lower levels of human leukocyte antigen-DR (HLA-DR), had significantly lower capacity to stimulate allogeneic T cells, and produced decreased amounts of IL-12 [47]. In vivo, Lissoni et al. (1999) revealed that the number of circulating DCs in the peripheral blood of cancer patients was also significantly decreased [48], and these results were confirmed by others, e.g., in patients with squamous cell carcinoma of the head and neck (HNSCC) [49], leukemia [50], hepatocellular carcinoma [51], lung cancer [52], and invasive breast cancer [53]. Metastasis development decreased the number of circulating DCs even further [18]. Furthermore, blood monocytes isolated from both patients with glioblastoma and intracranial metastases had significantly reduced expression of granulocyte macrophage colony-stimulating factor receptor (GM-CSFR) and showed a reduced capacity to differentiate into mature DCs [54]. Similar data were reported for other cancers [55]–[58]. Thus, local (at the tumor site) and systemic levels of DC might be markedly lower in cancer patients due to the inhibited or abnormal dendropoiesis [59], i.e., DC generation and differentiation.

Elimination of functional DCs in cancer may be also associated with the killing 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 [60] and confirmed by others [61]–[63]. Furthermore, the results were confirmed by documenting the presence of a significantly higher proportion of apoptotic blood DCs in patients with early-stage breast cancer compared to healthy volunteers [64]. Similarly, tumor-mediated cell death of DC precursors [65] and accelerated early apoptosis of DCs [58], [61], [66] were also reported.

Table 5.1 Abnormalities of the DC system in cancer

DC characteristics		Notes	Reference
I. *Elimination*	Quantitative inhibition of DC generation	From both CD34$^+$ hematopoietic precursors and CD14$^+$ macrophages in humans and bone marrow-derived precursors in mice	[54], [67], [166]–[168]
	Immaturity of DC at the tumor site	Low CD83, CD80, and CD86 expression	[157], [169], [170]
	Decreased number of circulating DCs	Low levels of DC1 in blood	[49], [85], [171]
	Low expression of CD40	In vitro and in vivo data	[55], [103]
	Downregulation of CCR7 on DCs	DCs prepared from tumor-bearing mice express low levels of CCR7 protein and mRNA	[172]
	Induction of DC apoptosis and acceleration of DC rate	Tumor-derived factors induced apoptotic death of DCs and increased rate of spontaneous apoptosis both in vitro and in vivo	[58], [60], [61], [64], [173]
	Apoptotic death of DC precursors	Tumor cells may kill DC precursors and decrease numbers of CFU-DCs	[65]
	Retention of DC inside the tumor lesions	Tumor-derived IL-8 might prevent DC emigration	[95]
II. *Inhibition*	Inhibition of DC motility	IL-8 and TGF-β1 as well as low CCR7 expression might prevent DC emigration from tumor lesions	[95], [174], [175]
	Inhibition of endocytic activity of DCs	Phagocytosis and receptor-mediated endocytosis were inhibited in DCs by different tumor cell lines	[58], [111], [131]
	Inhibition of antigen processing in DCs	Tumor suppress expression of MHC class I antigen-processing machinery proteins in DCs	[111]
	Inhibition of antigen presentation by DCs	Due to low MHC class I and II and costimulatory molecule expression	[58], [111], [176]
	Suppression of DC–T cell contact interactions	Decreased ability of DC to form clusters (rosettes) with T cells	[42] (Shurin, unpublished data)
	Low expression of costimulatory molecules on DCs	Downregulation of expression of B7 molecules	[123], [177]

Table 5.1 (continued)

DC characteristics		Notes	Reference
	Suppression of DC adhesiveness	Decreased adhesion of DCs to matrix protein-covered slides and tumor cell monolayers in vitro	(Shurin, unpublished data)
	Downregulation of cytokine production in DCs	For example, low IL-12 production by blood DCs in patients with breast cancer	[53]
III. *Polarization*	Dysbalance between cDC and regDC subpopulations	Decreased numbers of myeloid DCs (mDCs) in the blood	[49], [53], [82], [85], [87], [105], [139], [178]
		Low mDC/pDC ratio in blood	
		Decreased numbers of mDCs and increased numbers of lymphoid DCs (IDC) in the tumor milieu (e.g., peritoneal fluid in ovarian cancer patients)	
	Dysbalance between DCs, macrophages, and MDSCs	Tumor-associated increase in the levels of M2 macrophages and myeloid-derived suppressor cells	[179]–[181]
	Polarization of cDCs into regDCs	Tumor-induced conversion of proimmunogenic cDCs into pro-tumorigenic regDCs	[147], [160]
	Transdifferentiation of bone marrow-derived DCs into endothelial-like cells by tumor	Process of DC endothelialization is VEGF-dependent	[150]
IV. *Avoidance*	Loss of DC-attracting chemokines at the tumor site	Loss or downregulation of CXCL14 expression in tumor cells	[92], [182]

The second type of DC abnormalities in cancer includes the functional deficiency of DCs when compared to cells derived from healthy age-matched controls (Table 5.1). Decreased ability of DCs obtained from cancer patients' blood or lymph nodes, or DCs cocultured with malignant cells to stimulate allogeneic T cells, uptake, process, and present antigen(s), provide costimulatory signals, migrate toward specific chemokines, and produce IL-12 were repeatedly described for prostate, breast, renal, liver, lung cancer, HNSCC, melanoma, myeloma, leukemia, glioma, neuroblastoma, and other tumor types [65]–[74]. These and other results were also reviewed in [2], [3], [75]–[79] and therefore are not detailed here.

Polarization of DC subtypes represents the third type of the DC aberration in cancer (Table 5.1). For instance, there are substantial numbers of tumor-promoting functional plasmacytoid DCs (pDCs or lymphoid DCs by some classifications, but not cDCs or myeloid DCs) accumulated in tumor ascites in patients with ovarian carcinomas [80]. Similarly, estimating conventional and plasmacytoid subpopulations of DCs in the peritoneal fluid of women with ovarian tumors, Wertel et al. reported that the percentage of pDCs was higher in patients with ovarian cancer than in women with serous cystadenoma [81]. They also reported that the percentage of the peritoneal fluid myeloid DCs was significantly lower in patients with ovarian cancer in comparison to the group of nonmalignant ovarian tumors, while the percentage of the peritoneal fluid lymphoid DCs was higher in patients with ovarian cancer than in the reference group [82]. The presence of pDCs within primary breast tumors correlated with an unfavorable prognosis for patients [83]. Using fresh human breast tumor biopsies, the authors observed increased tumor-associated pDC rates in aggressive breast tumors and showed that these pDCs produced very low amounts of IFN-α. Interestingly, within breast tumors, pDCs colocalized with regulatory T cells (Treg cells); the selective suppression of IFN-α production endowed pDCs with the unique capacity to sustain Foxp3$^+$ Treg expansion [83]. The same team has recently identified transforming growth factor- β (TGF-β) and TNF-α as major soluble factors involved in pDC functional alteration in cancer [84]. These findings indicate that IFN-α-deficient tumor-associated pDCs accumulating in aggressive tumors are involved in the expansion of tumor-associated Treg cells in vivo, contributing to tumor immune tolerance and poor clinical outcome.

The levels of myeloid or cDC subsets in circulation may also be significantly lower, while the number of lymphoid or pDC subsets might vary, as was repetitively reported for patients with different tumor types compared to healthy donors [52], [85], [86]. Interestingly, these alterations were reverted by surgical resection of the tumor or by chemoradiotherapy [53], [85], [87], [88] suggesting that tumor-derived factors are responsible for redirecting DC differentiation (dendropoiesis) in the bone marrow, i.e., systemically. Indeed, microvesicles isolated from plasma of advanced melanoma patients, but not from healthy donors, mediated the effect of tumor on CD14$^+$ monocytes and skewed their differentiation from DCs toward CD14$^+$HLA-DR^{low} cells with TGF-β-mediated suppressive activity on T-cell functions [89]. A subset of these TGF-β-secreting CD14$^+$HLA-DR^{low} cells was found to be significantly expanded in the peripheral blood of melanoma patients compared with healthy donors.

Tumor-promoted redirection of dendropoiesis and its repolarization are also associated with increased numbers of immature DCs and the appearance of other related immature cells of myeloid progeny. For example, in addition to having fewer levels of DCs in the peripheral blood, patients with breast and prostate cancer as well as patients with malignant glioma showed significant accumulation of abnormal population of HLA-DR$^+$ immature cells (DR$^+$ICs), which in spite of HLA-DR, CD40, and CD86 expression had reduced capacity to capture antigens and elicited poor proliferation and IFN-γ secretion by T lymphocytes [86]. Immature DCs fail to provide an appropriate costimulatory signal 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 Treg cells that suppress immune responses by producing IL-10 and TGF-β [90]. Immature DCs were found at high levels within tumor-infiltrating leukocytes and increased circulating levels of immature DCs have also been observed in the peripheral blood of patients with lung, breast, head and neck, and esophageal cancer [91]. Immature myeloid precursors of DCs may also suppress T-cell activation as part of a population of myeloid-derived suppressor cells (MDSCs), a heterogeneous population of myeloid cells that comprises immature macrophages, granulocytes, DCs, and myeloid cells at early stages of differentiation, discussed in detail in other chapters of this monograph.

Finally, the last mechanism of decreased number of active DCs associated with the tumor progression is the loss of expression of DC-attracting chemokines at the tumor site (Table 5.1). For instance, it has been demonstrated that HNSCC cells do not express CXCL14 protein and messenger RNA (mRNA), a potent DC-attracting chemokine [92]. This resulted in low chemoattraction of DCs to the tumor bed, low numbers of tumor-associated DCs, and deficient induction of antitumor immunity; however, transduction of CXCL14-negative tumor cells with the CXCL14 gene was associated with increased DC infiltration, an antitumor immune response, and inhibition of tumor growth in vivo. Investigation of the mechanisms of loss of CXCL14 in prostate cancer cells revealed direct evidence for epigenetic regulation of chemokine expression in tumor cells [93]. Interestingly, melanoma cells might utilize an opposite approach and can effectively chemoattract DCs, modulate their phenotype, and, eventually, severely damage DC mobility: Melanoma-conditioned DCs exhibited an increased adhesion capacity to a melanoma cell line in vitro and did not migrate in response to DC chemokines [94]. The explanation for abnormal DC retention inside some human malignant lesions may come from another study where it was found that tumors from patients with hepatocellular carcinoma, colorectal cancer, or pancreatic cancer were producing IL-8 and that this chemokine attracted DCs that uniformly express both IL-8 receptors, CXCR1 and CXCR2 [95].

In summary, abnormal dendropoiesis, DC longevity and function, and DC migration toward or from the tumor site are the key characteristics of the local and systemic DC dysfunction in tumor-bearing hosts that have a crucial role in immune nonresponsiveness to tumors and tumor escape [34].

3   Mechanisms of Dendritic Cell Dysfunction in Cancer

3.1   *Factors*

Tumors exploit several strategies to evade immune recognition, including the production of a variety of immunosuppressive/immunomodulating factors, which might specifically block or redirect DC maturation, suppress DC survival, and impair function of DC in the vicinity of tumors [4] (Table 5.2). Historically, the first tumor-derived factor inhibiting DC differentiation in cancer was identified as vascular endothelial growth factor (VEGF) [96]. For instance, in patients affected by colorectal cancer, DC numbers inversely correlated with VEGF serum levels, suggesting a possible effect of this cytokine on the DC compartment. In cultures, the exposure of monocyte-derived DCs to VEGF produced a dramatic alteration of DC differentiation by induction of apoptosis, alteration of DC phenotypic profile, and increased CXCR4 expression [97]. VEGF blocks the functional maturation of DCs from hematopoietic progenitor cells by blocking nuclear factor kappa-B (NF-κB) transcription. The family of VEGF molecules also plays a key role in recruiting immature myeloid cells and immature DCS from the bone marrow to enrich the tumor microenvironment [98].

Tumor-derived TGF-β and IL-10 were shown to be responsible for downregulating CD80 expression on blood DCS in myeloma patients [68]. DC maturation, antigen presentation, and IL-12 production induced by inflammatory cytokines IL-1 and TNF-α or by lipopolysaccharide (LPS) might be inhibited by TGF-β [99]. TGF-β might also induce apoptosis in DCs [100]. Increased levels of IL-10 in serum from patients with hepatocellular carcinoma and tumor progression were shown to correlate with profound numerical deficiencies and immature phenotype of circulating DC subsets [101]. Murine bone marrow-derived DCs that were propagated in IL-10 and TGF-β (so-called alternatively activated DC) expressed low levels of Toll-like receptor 4 (TLR4), MHC class II, CD40, CD80, CD86, IL-12p70, and programmed death-ligand 2 (B7-DC; CD273) and were resistant to maturation [102]. They secreted much higher levels of IL-10 and efficiently expanded functional CD4$^+$CD25$^+$Foxp3$^+$ Treg cells. We have shown earlier that murine colon adenocarcinoma cells produce IL-10 and that IL-10 causes downregulation of CD40 expression on DCs and is responsible for inhibited CD40-dependent IL-12 production by DCs [103]. These and other studies also revealed the tumor-associated in vivo effects of IL-10 on DC function in eliciting a type 1 immune response in both allogeneic and tumor-specific responses [104]. Furthermore, analyzing pancreatic cancer-derived cytokines responsible for inhibition of DC differentiation, Bellone et al. (2006) reported that IL-10, TGF-β, and IL-6, but not VEGF, cooperatively affect DC precursors in a manner consistent with ineffective antitumor immune responses [105]. However, lung squamous cell carcinoma and adenocarcinoma have been shown to use different mediators to induce comparable phenotypic and functional changes in DCs: IL-6 versus IL-10$^+$IL-6$^+$ prostanoids, respectively [106]. Renal cell carcinoma (RCC)-derived IL-6 and VEGF were shown to block the ability of tumor antigen-loaded DCs to induce CTL in the autologous system [107].

Table 5.2 Mechanisms of DC dysfunction in cancer

Mechanisms and factors		Examples	Reference
Tumor/stroma-derived factors	Cytokines or their combinations	VEGF, M-CSF, IL-6, IL-10, TGF-β, and IL-8	[96], [103]–[105], [183]
	CCL2	Mediates the migration of myeloid suppressors to tumors	[184]
	CCL20/MIP3α	Involved in immature DCs and their precursors attraction	[158]
	Stromal-derived factor-1 and β-defensins	Attract proangiogenic DC subset	[80], [151]
	Prostanoids and prostaglandins	Regulate DC maturation	[109]
	Gangliosides	Suppress dendropoiesis and DC longevity	[63], [69], [111]
	Neuropeptides	Bombesin-like peptides (gastrin-releasing peptide (GRP) and neuromedin B (NMB))	[15]
	Tumor antigens	PSA is a serine protease; MUC1 subverts DC function	[113], [115]
	Other molecules	Lactic acid, hyaluronan, NO, and spermine	[53], [62], [112], [185]
	HLA-G	HLA-G might induce tolerogenic DCs by disruption of the MHC class II presentation pathway	[119], [146]
	Reactive oxygen species	Hydrogen peroxide may activate p38 and JNK in DC and induce apoptosis	[137]
	Tumor-derived microvesicles	Abnormal differentiation of monocytes into IL-6/TNF-α/TGF-β-producing cells	[89]
Affected signaling pathways in DCs	Upregulation of Bax and downregulation of Bcl-2 and Bcl-X$_L$	Both extrinsic and intrinsic pathways are involved in tumor-induced apoptosis of DCs	[60], [132], [133], [138]
	Ceramide	Mediates tumor-induced DC apoptosis by downregulation of the PI3K pathway	[134]
	Small Rho GTPases	Cdc42 and Rac 1 mediate tumor-induced dysfunction of DCs	[131]

Table 5.2 (continued)

Mechanisms and factors	Examples	Reference
STAT3	Tumor-mediated induction of STAT3 in DCs results in reduced expression of IL-12, MHC class II, and CD40	[123], [156], [186], [187]
SOCS1	SOCS1 functions as an antigen-presentation attenuator by controlling the tolerogenic state of DC and the magnitude of antigen presentation	[127]
p38 MAPK	Tumor activates p38 MAPK and JNK but inhibits ERK in DCs	[129]
H1 expression	Tumor-derived factors inhibit *h1* expression in DC precursors causing defective DC differentiation	[188]
PKCβII	Tumor-mediated inhibition of DC differentiation is mediated by downregulation of PKCβII expression	[130]
Epigenetic regulation of the CIITA type I promoter	Tumor-mediated downregulation of MHC class II in DC development is attributable to the epigenetic control of the CIITA type I promoter	[128]

To define the pathways limiting DC function in the tumor microenvironment, Sharma et al. assessed the impact of tumor cyclooxygenase (COX)-2 expression on DC activities and reported that inhibition of tumor COX-2 expression or activity could prevent tumor-induced suppression of DC capacity to process and present antigens and secrete IL-12 [108]. COX-1- and COX-2-regulated prostanoids and IL-6 were found to be solely responsible for the hampered differentiation of monocyte-derived and CD34$^+$-precursor-derived DCs by freshly excised solid human tumors (colon, breast, RCC, and melanoma) [109]. An important role for the EP2 receptor in prostaglandin E2 (PGE$_2$)-induced inhibition of DC differentiation and function and the diminished antitumor cellular immune responses in vivo has been also reported [110]. Finally, PGE$_2$ suppressed differentiation of DCs, it is a potent inducer of IL-10 in bone marrow-derived DCs, and PGE$_2$-induced IL-10 is a key regulator of the DC pro-inflammatory phenotype [109].

In addition to these "classic" tumor-derived antidendropoietic factors, other molecules were implicated in tumor-mediated dysfunction of the DC system (Table 5.2). Melanoma, neuroblastoma, RCC, and lung cancer were shown to produce and shed various gangliosides, which may suppress dendropoiesis, inhibit DC function, or induce apoptosis in DCs [63], [69], [111]. Tumor-derived lactic acid is also an important factor modulating the DC phenotype in the tumor environment, which may critically contribute to tumor escape mechanisms [112]. Interestingly, several tumor antigens were recently found to display antidendropoietic properties. Prostate specific antigen (PSA), which is a serine protease, was able to inhibit generation and maturation of DCs from CD34$^+$ hematopoietic precursors, assessed by the levels of expression of CD83, CD80, CD86, and HLA-DR, as well as the ability of DC to induce T-cell proliferation [113]. When cultured with the MUC1 glycoprotein, human monocyte-derived DCs displayed decreased expression of CD86, CD40, CD1d, HLA-DR, and CD83 and were defective in the ability to induce immune responses in both allogeneic and autologous settings. The modified phenotype of MUC1-treated DCs corresponded to an altered balance in IL-12/IL-10 cytokine production with a failure to make IL-12 and induce Th1 responses [114], [115]. Finally, human chorionic gonadotropin (hCG), which serves as an important tumor marker for trophoblastic disease, has been recently shown to upregulate expression of indoleamine-2,3-dioxygenase (IDO) in DCs [116].

HLA-G molecules, which are normally expressed in cytotrophoblasts and play a key role in maintaining immune tolerance at the maternal–fetal interface, were also reported to be expressed on malignant cells and they can be regulated by hypoxia [117], [118]. As DCs express immunoglobulin-like transcript 4 (ILT4), an inhibitory receptor capable of interacting with HLA-G, they 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 [119].

Finally, human tumors constitutively release endosome-derived microvesicles, transporting a broad array of biologically active molecules with potential modulatory effects on different immune cells. The first evidence that tumor-released microvesicles alter myeloid cell function by impairing monocyte differentiation into DCs and

promoting the generation of a myeloid immunosuppressive cell subset was probably published by Valenti et al. [89], [120] and then confirmed by other teams [121], [122].

3.2 Signaling Pathways

Many immunosuppressive factors produced by tumor cells induce signal transducer and activator of transcription 3 (STAT3) activation in DCs, blocking their normal functioning. For instance, treatment of DCs with melanoma-conditioned medium resulted in reduced expression of IL-12, MHC class II, and CD40 due to the increased induction of STAT3 [123]. The immunosuppressive effects of tumor-derived factors on DC differentiation were abrogated in cells from STAT3 knockout mice or by the treatment of DC precursors with a phosphopeptide that binds the STAT3 Src homology 2 (SH2) domain and blocks downstream STAT activation. Furthermore, IL-6-mediated suppression of DC maturation was also abrogated in STAT3-deficient DC precursors, indicating the significance of STAT3 in IL-6-mediated suppression of DC maturation and function [123]. Furthermore, constitutive STAT3 activation in tumor cells was shown to inhibit DC function by the increased induction of STAT3 in immature DCs. Thus, immunosuppression mediated by tumor cells results from a circuit of STAT3 signaling that begins in tumor cells and eventually activates inhibitory STAT3 signaling in DCs in part due to the production of cytokines that increase STAT3 activation in DCs (epidermal growth factor (EGF), VEGF, IL-6, IL-10, granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), and GM-CSF) [123]. In addition, STAT3 phosphorylation in DCs was regulated by IL-6 in vivo, and STAT3 was necessary for the IL-6 suppression of DC activation/maturation [124]. Interestingly, $CD4^+CD25^+Foxp3^+$ Treg cells from tumor-bearing animals may also impede DC function by activating STAT3 and inducing the Smad signaling pathway [125]. The suppression mechanism was also associated with downregulation of activation of the transcription factor NF-κB, required TGF-beta and IL-10, and resulted in strong inhibition of expression of the costimulatory molecules CD80, CD86, and CD40 and the production of TNF-α, IL-12, and chemokine (C-C motif) ligand 5 (CCL5 or RANTES—regulated on activation, normal T cell expressed and secreted) by DCs.

Many STAT family members are developmentally regulated and play a role in DC differentiation and maturation. For instance, the STAT6 signaling pathway is constitutively activated in immature DCs and declines as they differentiate into mature DCs. Downregulation of the STAT6 pathway is accompanied by dramatic induction of suppressors of cytokine signaling 1 (SOCS1), SOCS2, SOCS3, and cytokine-induced SH2-containing protein expression [126]. In contrast, STAT1 signaling is most robust in mature DCs. Thus, it is likely that cytokine-induced maturation of DCs is under feedback regulation by SOCS proteins and that the switch from constitutive activation of the STAT6 pathway in immature DCs to predominant use of STAT1 signals in mature DCs is mediated in part by STAT1-induced SOCS expression [126]. Recent studies also demonstrate that SOCS1 functions as an antigen-presentation

attenuator by controlling the tolerogenic state of DCs and the magnitude of antigen presentation [127]. Since SOCS1 restricts DCs' ability to break self-tolerance and induce antitumor immunity by regulating IL-12 production and signaling, it is quite possible that some products of tumor cells or other cells within the tumor milieu might induce SOCS1 expression in DCs. Although not proven experimentally, this pathway may operate in the tumor microenvironment limiting the ability of DCs to process and present tumor antigens and secrete IL-12.

Another interesting mechanism responsible for tumor-induced downregulation of MHC class II expression in DCs was reported by Choi et al. They found that STAT5 bound to the CIITA pI locus during DC differentiation and that the binding was markedly attenuated by a tumor-conditioned medium or by IL-10 [128]. IL-10 inhibited the expression of type I CIITA during DC differentiation: GM-CSF-mediated histone (H3 and H4) acetylation at the type I promoter (pI) locus of the CIITA gene was markedly increased during DC differentiation and this increase was blocked by IL-10. This suggests that IL-10-mediated MHC class II downregulation results from the inhibition of type I CIITA expression. This inhibition is most likely due to blocking of the STAT5-associated epigenetic modifications of the CIITA pI locus during the entire period of DC differentiation from bone marrow-derived precursors, as opposed to a simple inhibition of MHC class II expression at the immature/mature DC stage.

Wang et al. too speculated that tumor-induced p38 mitogen-activated protein kinase (MAPK) activation and extracellular signal-regulated kinase (ERK) inhibition in DCs might be a new mechanism of tumor evasion [129]. They showed that tumor supernatant-treated DCs were inferior to normal DCs at priming tumor-specific immune responses, but inhibiting p38 MAPK restored the phenotype, cytokine secretion, and function of tumor-treated DCs. Tumor-derived factors activated p38 MAPK and Janus kinase (JNK) but inhibited ERK in DCs. Interestingly, Farrent et al. have recently reported that tumor-mediated myeloid dysregulation may be mediated by Stat3-induced protein kinase C isoform βII (PKCβII) downregulation: they showed that tumors mediate both Stat3 activation and PKCβII downregulation in DC progenitor cells, a process mimicked by the expression of a constitutive active Stat3 mutant [130].

Since many functions of DCs, such as endocytosis, exocytosis, adhesiveness, and motility, depend on actin polymerization and membrane rearrangements, Tourkova et al. analyzed whether small Rho guanosine triphosphatases (GTPases: Cdc42, RhoA, and Rac1/2), which are primarily involved in regulating these functions in DCs [111], might be affected by tumor-derived factors. They found that impaired endocytic activity of DC cocultured with tumor cells was associated with decreased levels of active Cdc42 and Rac1. Transduction of DCs with the dominant negative Cdc42 and Rac1 genes also led to reduced phagocytosis and receptor-mediated endocytosis, while transduction of DCs with the constitutively active Cdc42 and Rac1 genes restored the endocytic activity of DCs that was inhibited by the tumors [131].

Less is known about signaling pathways that control DC longevity and DC sensitivity to tumor-induced cell death. Early studies showed that Bcl-X_L, Bcl-2, and mitochondrial cytochrome c release mediate resistance of DCs to tumor-induced

apoptosis [132], [133]. Other data demonstrated that downregulation of phospho-inositide 3-kinase (PI3K) is the major facet of tumor-induced DC apoptosis [134]. Interestingly, it is known that some cancer cells have increased production of hydrogen peroxide (H_2O_2) [135], [136] and, in DCs, hydrogen peroxide activates two key MAPKs, p38 and JNK. Activation of JNK, which is associated with inhibition of tyrosine phosphatases in DCs, is linked to the induction of DC apoptosis [137]. By targeting different antiapoptotic molecules, including FLICE-like inhibitory protein (FLIP), X-linked inhibitor of apoptosis protein or human IAP-like protein (XIAP/hILP), procaspase-9, and heat shock protein 70 (HSP70), Balkir et al. demonstrated that antiapoptotic molecules other than the Bcl-2 family of proteins were involved in tumor-induced apoptosis in DCs [138]. This suggests that tumor-induced apoptosis of DCs is not limited to the mitochondrial pathway of cell death and that both extrinsic and intrinsic apoptotic pathways play a role in DC survival in the tumor microenvironment.

4 Role of DCs in Tumor Escape Mechanisms

A growing body of evidence clearly demonstrates that different subsets of DC are directly and indirectly involved in controlling tumor growth and progression. However, with the realization that the DC lineage represents a varied collection of distinct populations, a question has arisen as to whether certain types of DC are dysregulated in tumor-bearing hosts, or whether the nature of immunological challenge and state of DC maturation define particular facets of innate/acquired/tolerogenic responses in the tumor environment. Numerous studies have revealed that specific DC subsets might be linked to immunological unresponsiveness and/or tolerance to tumor antigens. For instance, the clinical outcome of children with cancer has been shown to correlate with circulating pDC count: Children with high pDC counts at diagnosis showed significantly worse survival than those with low counts and the development of cancer was associated with low number of cDCs [139]. Elevated levels of pDC have been observed as breast cancer disseminates to the bone. The selective depletion of pDCs in mice led to a total abrogation of bone metastasis as well as to an increase in the T_H1 antitumor response [140]. Thus, tumor-associated pDCs contribute to the tumor immunosuppressive network. Tumor ascites pDCs induced IL-10$^+$CCR7$^+$CD45RO$^+$CD8$^+$ Treg cells, which significantly suppress myeloid DC-mediated tumor-associated antigen-specific T-cell effector functions through IL-10 [141]. pDCs in tumor-draining lymph nodes might create a local microenvironment that is potently suppressive of host antitumor T-cell responses and this mechanism may be mediated by immunosuppressive IDO.

IDO degrades tryptophan to kynurenine, which is further metabolized to 3-hydroxyanthranilic acid and thus initiates the immunosuppressive pathway of tryptophan catabolism (see Chap. 6 in this monograph). Emerging evidence suggests that Treg cells may be generated de novo against specific tumor-derived antigens, and thus they arise as a direct consequence of antigen presentation in the tumor-draining

lymph nodes [142]. IDO can also be expressed within the tumor itself, by tumor cells, or by host stromal cells, where it can inhibit the effector phase of the immune response [143]. Kynurenine pathway enzymes downstream of IDO can initiate tolerogenesis by DCs independently of tryptophan deprivation, as tolerogenic DCs can confer suppressive ability on otherwise immunogenic DCs in an IDO-dependent fashion [144]. IDO, i.e., tryptophan, kynurenine, or 3-hydroxyanthranilic acid, could also induce expression of the tolerogenic molecule HLA-G in DCs [145]. Thus, IDO and HLA-G can cooperate in the immune suppression, since HLA-G-expressing DCs might suppress or alter effector T cells as well. Indeed, activated $CD4^+$ and $CD8^+$ T cells could efficiently acquire immunosuppressive HLA-G from antigen-presenting cells through membrane transfers (a process called trogocytosis) and acquisition of HLA-G immediately reversed T-cell function from effectors to regulatory cells. These Treg cells were able to inhibit proliferative responses through HLA-G that they acquired [146]. Targeting IDO in regulatory DCs (regDCs) may represent a new approach for harnessing DCs in the tumor microenvironment [147].

In support of the concept that certain DC subpopulations play crucial roles in tumor escape, it was recently reported that tumor expansion could stimulate Treg cells via a specific DC subset. During tumor progression, a subset of DC exhibiting a myeloid immature phenotype may be recruited to draining lymph nodes and selectively promote proliferation of Treg cells in a TGF-β-dependent manner [148]. Importantly, tumor cells are necessary and sufficient to convert DCs into regulatory cells that secrete TGF-β and stimulate Treg cell proliferation. Regulatory DCs in cancer may directly and indirectly maintain antigen-specific and nonspecific T-cell unresponsiveness by controlling T-cell polarization, MDSC and Treg differentiation and activity, and affecting specific microenvironmental conditions in premalignant niches [149].

Another subset of DCs might contribute to neovascularization at the tumor site. Recently, Conejo-Garcia et al. reported that within 3 weeks of culture with tumor cell-conditioned medium, bone marrow-derived DCs could be transdifferentiated into endothelial-like cells in vitro [150]. They also identified a novel leukocyte subset within ovarian carcinoma that coexpressed endothelial and DC markers which may play a role in the formation of blood vessels [151]. Curiel et al. observed high numbers of pDC in malignant ascites of patients with untreated ovarian carcinoma and showed that tumor-associated pDC induced angiogenesis in vivo through production of TNF-α and IL-8 [152]. By contrast, cDCs, which might suppress angiogenesis in vivo through production of IL-12, were absent from malignant ascites. Thus, the tumor may attract pDCs to augment neovascularization while excluding myeloid DC to prevent angiogenesis inhibition.

Thus, one mechanism contributing to immunologic unresponsiveness toward tumors may be presentation of tumor antigens by tolerogenic/regulatory host DCs. Indeed, using bone marrow chimeras in transgenic mice, Mihalyo et al. have recently reported that DCs, but not $CD4^+CD25^+$ Treg cells, play a critical role in programming CD4 cell responses to tumor antigens during tumorigenesis [153]. Regulatory DCs could be produced from bone marrow precursors in the presence of GM-CSF, IL-10, TGF-β1, and LPS or TNF-α and they retained their T-cell regulatory

property in vitro and in vivo even under inflammatory conditions [154]. Another minor subpopulation of regulatory DCs has been recently described in murine spleen. These splenic CD19$^+$ DCs that did not express the pDC marker acquired potent IDO-dependent T-cell suppressive functions [155].

However, proponents of the "maturation" hypothesis suggest that the maturation state of the DC in the premalignant/inflammatory milieu or in the newly formed tumor setting predicts the development of an antitumor immune response or tumor tolerance. An increased proportion of immature DCs with reduced expression of costimulatory molecules was seen or isolated from tumor mass of patients with RCC, prostate cancer, basal-cell carcinoma, and melanoma or was found in the peripheral blood of patients with breast, head and neck, lung, or esophageal cancer [156]. Similar data have been obtained using several mouse tumor models. The maturation hypothesis was also bolstered by studies showing that in tumor tissues, immature DCs resided within the tumor, whereas mature DCs were located in peritumoral areas [157]. Immature DCs cannot induce antitumor immune responses and, most importantly, immature DCs can induce T-cell tolerance or anergy. Thomachot et al. showed that breast carcinoma cells produce soluble factors (chemokine (C-C motif) ligand 20 (CCL20) and TGF-β), which attract DC precursors in vivo and promote their differentiation into immature DCs with altered functional capacities, and that these altered DCs may contribute to the impaired immune response against the tumor [158]. Similarly, a medium conditioned by human pancreatic carcinoma cells induced monocyte-derived immature DCs with inhibited proliferation, expression of costimulatory molecules (CD80 and CD40) and HLA-DR, and functional activity as assessed by T-cell activation and IL-12p70 production [105]. Immature DCs generated from pancreatic carcinoma patients in advanced stages of the disease similarly showed decreased levels of HLA-DR expression and reduced ability to stimulate T cells. Direct ex vivo flow cytometric analysis of various DC subpopulations in peripheral blood from hepatocellular carcinoma patients revealed an immature phenotype of circulating DCs that was associated with increased IL-10 concentrations in serum and with tumor progression [47], [101].

To evaluate whether and to what extent the capacity of tumor-infiltrating DCs to drive immunization can be turned off by tumor cells, leading to tumor-specific tolerance rather than immunization, Perrot et al. have characterized the DCs isolated from human non-small cell lung cancer based on the expression of CD11c. All isolated DCs, including CD11c^{high} myeloid DC, CD11c$^-$ pDC, and a third DC subset expressing an intermediate level of CD11c, were immature and displayed poor antigen-presenting function even after TLR stimulation and reduced migratory response toward CCL21 and SDF-1 [159]. Interestingly, CD11c^{int} myeloid DCs, which represented approximately 25 % of total DC in tumor and peritumor tissues, expressed low levels of costimulatory molecules contrasting with high levels of the immunoinhibitory molecule B7-H1. These data suggest that immature tumor-associated DCs have an ability to compromise the tumor-specific immune response in draining lymph nodes in vivo. However, our data demonstrate that immature bone-marrow-derived DCs cannot suppress proliferation of pre-activated T cells without pretreatment with tumor-derived factors. Our recent data also reveal that different

tumor cell lines produce soluble factors that induce polarization of cDCs into regulatory DCs, both in vitro and in vivo. These regulatory DCs can suppress proliferation of pre-activated T cells and are phenotypically and functionally different from their precursors as well as the classical immature cDC [160]. Understanding the biology of regDCs and the mechanisms of their formation in the tumor immunoenvironment will provide a new therapeutic target for repolarizing protumorigenic immunoregulatory cells into proimmunogenic effector cells able to induce and support effective antitumor immunity.

In spite of multiple evidence supporting both "subpopulation"-based and "maturation"-based explanations of how the DC system is involved in tumor escape (Table 5.3), additional data suggest that the real situation might be significantly more complex. The first layer of complexity arrives from the results showing that DC subsets may induce both tolerogenic and immunogenic responses depending on the environmental stimuli. For example, although the general thought is that pDCs are usually tolerogenic, it appears that the functional role of pDCs in cancer immunity depends on cytokines that affect the balance between immunity and tolerance in the tumor and lymphoid organ microenvironment. In an analysis of draining lymph nodes in breast cancer, pDCs with a relative increase in IL-12 and interferon-γ (IFN-γ) were associated with a good prognosis, whereas pDCs with a relative increase in IL-10 and IL-4 were associated with a poor prognosis [161]. In confirmation of this conclusion, Kim et al. have reported that although pDCs recruited to the tumor site are implicated in facilitating tumor growth via immune suppression, they can be released from the tumor as a result of cell death caused by primary systemic chemotherapy and can then be activated through TLR9 [162]. Thus, synergistically with cDCs, pDCs may also play a crucial role in mediating cancer immunity. In fact, new results from a recent clinical trial indicate that vaccination with naturally occurring pDCs is feasible, with minimal toxicity, and that in patients with metastatic melanoma, it induces favorable immune responses [163]. Thus, we can conclude that pDCs, as well as myeloid cDCs, have a dual role not only in initiating immune responses but also in inducing tolerance to tumor antigens.

An additional layer of complexity of the DC subset versus the DC maturation problem in cancer comes from the data revealing different maturation patterns of different DC subsets and its differential regulation by other immune cells. For example, analysis of the maturation of human blood-derived cDCs and pDCs activated with TLR ligands in the presence of Treg cells revealed that pre-activated Treg cells strongly suppressed TLR-triggered cDC maturation, as judged by the blocking of costimulatory molecule upregulation and the inhibition of pro-inflammatory cytokine secretion that resulted in poor antigen presentation capacity. Although IL-10 played a prominent role in inhibiting cytokine secretion, suppression of phenotypic maturation required cell–cell contact and was independent of TGF-β and CTLA-4. In contrast, the acquisition of maturation markers and production of cytokines by pDCs triggered by TLR ligands were insensitive to Treg cells[164]. Therefore, human Treg may enlist conventional DCs, but not pDCs for the initiation and the amplification of tolerance in vivo by restraining their maturation after TLR stimulation.

Table 5.3 DC-mediated mechanisms of tumor escape

Mechanisms	Notes	Reference
Inability to present tumor antigens to T cells and induce tumor-specific CTL	Tumor-mediated suppression of critical functions of DCs	[2], [44], [107]
Immaturity of DC in the tumor environment	High levels of immature DCs can actively induce T-cell tolerance to tumor antigens and promote cancer progression	[47], [101], [105], [158]
Expression of IL-10	IL-10-producing DCs efficiently expand functional CD4$^+$CD25$^+$Foxp3 Treg cells	[148]
Expression of TGF-β	DCs exhibiting a myeloid immature phenotype may promote proliferation of Treg cells in a TGF-β-dependent manner	[71], [103], [105]
Low IL-12 production	DCs isolated from tumor-bearing animals or cancer patients produce low levels of spontaneous and inducible IL-12	[189]
Low IL-18 expression	Melanoma might block IL-18 synthesis in DCs and thus prevent activation of NK cells by DCs	[143], [190]
IDO-mediated mechanisms	Tolerogenic DCs can confer suppressive ability on otherwise immunogenic DCs in an IDO-dependent fashion	[191]
Immunoglobulin-like transcript 3 (ILT3) and ILT4 (human)	The HLA-G-ILT4 (immunoglobulin-like transcript) interaction leads to development of tolerogenic DCs with the induction of anergic and immunosuppressive T cells	
Paired immunoglobulin-like inhibitory receptor (PIR-B) (murine)		
Expression of HLA-G molecules	HLA-G on DCs induces immune suppression and tolerance	[145], [146]
Expression of B7-H1	Upregulation of B7-H1 on DCs in the tumor microenvironment downregulates T-cell immunity	[159], [192]
Attraction and protection of pDC precursors	Accumulation of pDCs in peritoneal fluid, ascites in ovarian cancer	[80], [81], [140]
Protumorigenic function of pDC	Depletion of pDCs in mice with breast cancer led to a total abrogation of bone metastasis and increase in Th1 antitumor response	
Stimulation of angiogenesis by tumor-associated pDC and DC precursors	Tumor pDCs produce high levels of TNF-α and IL-8 and induce neovascularization in vivo	[150], [152]
Induction of Treg	Tumor ascites pDCs induce IL-10$^+$CCR7$^+$CD45RO$^+$CD8$^+$ Treg	[141], [142]

Table 5.3 (continued)

Mechanisms	Notes	Reference
Induction of regDC	Tumor might induce a subpopulation of DCs which secrete TGF-β and support proliferation of Treg cells	[148], [154], [155], [160]
Inhibition of IKDC subset (?)	IFN-producing killer DCs (IKDCs) are B220⁺NK1.1⁺Gr1⁻ DCs that kill tumor cells through the TRAIL pathway	[193], [194]
Impairment of DC migration toward tumor site or lymphoid tissue	Decreased attraction of increased retention of DCs at the tumor site	[92], [95]
Anti-inflammatory and tolerogenic properties of tumor-induced immature DCs	Decreased production of IL-1, IL-6, and TNF-α and increased expression of IL-10 and TGF-β after capturing apoptotic tumor cells	[90]

In another study, evidence was provided that maturing cDCs and pDCs express different sets of molecules that drive distinct types of T-cell responses [165]. Although both maturing cDCs and pDCs upregulate the expression of CD80 and CD86, only pDCs upregulate the expression of inducible costimulatory ligand (ICOS-L) and maintain high expression levels upon differentiation into mature DCs. High ICOS-L expression endows maturing pDCs with the ability to induce the differentiation of naive CD4 T cells to produce IL-10 but not the Th2 cytokines IL-4, IL-5, and IL-13. These IL-10-producing T cells are Treg cells, and their generation by ICOS-L is independent of pDC-driven Th1 and Th2 differentiation. Thus, in contrast to cDCs, pDCs are poised to express ICOS-L upon maturation, which leads to the generation of IL-10-producing Treg cells [165].

As such, there is still a confusion in the field as to whether certain DC subpopulations have evolved to fulfill unique immunological roles in cancer (Th1/Th2/Th3/Th17 polarization, Treg induction, tolerance, etc.), or whether distinct DC subsets exist to uniquely respond to tumor-derived stimuli but each participates in maintaining tolerance or immunity in the immature or mature state. It is also somewhat undecided whether some of the diversity in the DC lineage as determined by cell surface-molecule expression represents genuine distinct DC subsets or particular developmental/activation states of the same DC subtype. However, collectively, an emerging view in the field is that DCs control the course of tumor immunity/tolerance on at least three levels: (1) the developmental repertoire of DC lineage populations which can dictate the nature of DC response to a particular stimulus in the tumor microenvironment, (2) the maturation stage of DCs when cells interact with other immune cells or respond to immunological signals (i.e., cytokines, chemokines, and TLR ligands), and (3) the environment within which DCs encounter tumor antigens, as defined by the tissue type, infiltrating leukocytes, and an inflammatory cytokine milieu.

Therefore, DCs in the tumor microenvironment serve as a double-edged sword and, in addition to initiating potent antitumor immune responses, may mediate genomic damage, support neovascularization, block antitumor immunity, and stimulate cancerous cell growth and spreading [149]. The importance of these issues and mechanisms controlling them is significant, as efforts to harness the power of DCs in vaccination strategies against tumors would ultimately aim to identify the correct type of DC for a particular approach and insure that these cells are appropriately activated or protected from tumor influence to elicit the desired response.

5 Concluding Remarks

Numerous experimental and clinical observations discussed above suggest that tumor-induced apoptosis or altered differentiation and function of DCs as well as accumulation of immature DCs or DC precursors with inhibitory and tolerogenic function could impair antitumor immune responses. For patients with cancer, the resulting dysfunction of the DC system would result in marked deficiency in

the induction of antitumor immunity, tumor progression, and probably, low response to immunotherapy [34]. This is really important for understanding tumor immunopathology as well as reevaluating tumor immunotherapeutic strategies since DCs prepared from patients with cancer are being evaluated as a cellular vaccine in multiple clinical trials worldwide. However, to date, DC-based immunotherapies have met with limited success for several reasons, including the restricted longevity and efficacy of administered DCs in a suppressive tumor environment. Therefore, alternative approaches, including protection of DC longevity, blockade of tumor-mediated inhibitory pathways, and prevention of DC dysfunction/polarization ex vivo, should be evaluated to potentiate the efficacy of DC-based cancer vaccines. Given that endogenous DCs might be important for fulfilling the potential of various cellular vaccines, gained knowledge in the area of DC immunobiology in cancer may help to find new drugs to selectively block suppressive pathways and restore the original function of DCs.

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