Chapter 2
Dendritic Cells in Cancer: Emergence of the Discipline

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Abstract Immunologic research, following the discovery of dendritic cells radically changed our understanding of the induction, maintenance, and emergence of immune-mediated inflammatory disorders, including malignant diseases. The mechanisms central to the etiology and pathogenesis of many of these chronic inflammatory conditions involve dendritic cells. Identification of dendritic cells in tumors as well as clinical evaluation of dendritic cell vaccines led to the realization that very complex interactions between dendritic cells and other cellular and extracellular components of the tumor microenvironment dictated clinical outcome. Dendritic cells interestingly either induce antitumor immune response or promote a wound repair phenotype including reparative epithelial tumor proliferation, resumption of "barrier function", promotion of the premetastatic niche, and metastases. The limited success of dendritic cell-based therapies suggests the need for a deeper understanding of immunobiology of these key cells of the immune system as they develop within the complex tumor microenvironment. Reanalyzing and reexamining the accumulated data and concepts in the field, as done in this chapter and the book overall, serve this important goal.

2.1 Discovery of Dendritic Cells

Dendritic cells (DC) are a critical component of immunity, previously underappreciated in a discipline dictated by the specificity and charm of specific antibodies and T cells. Immunologic research following the discovery of DC significantly changed our understanding of the induction and emergence of mechanisms central to the etiology and pathogenesis of many inflammatory disorders, including malignant diseases. DC were first described in the skin by

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M.R. Shurin, R.D. Salter (eds.), *Dendritic Cells in Cancer*,
DOI 10.1007/978-0-387-88611-4_2,

German pathologist Paul Langerhans (1847–1888) and provided the eponymic, Langerhans cells (LC). In 1868, still as an undergraduate, Paul Langerhans stained a sample of human skin with gold chloride and analyzed epidermal skin cells as part of an open competition organized by Berlin University. He identified the cells, which from their appearance, Langerhans believed were nerve cells. The "branched skin cells resembling neuron", described in his 1868 paper entitled "On the nerves of the human skin" (Langerhans 1868), remained an enigma for over a century before their immunological function was recognized. Even after this, the biological and clinical significance of LC has been a matter of conjecture for many years.

In the nineteenth century, in discussing the nature of the cells recently described by Langerhans, Ranvier in 1875 expressed the opinion that they were neither nervous elements nor branched pigmentary cells, but rather lymphatic cells that had migrated into the epidermis (Ranvier 1875). As quoted by Ranvier, Eberth was the first to contest the neural origin of the cell described 2 years earlier by Paul Langerhans. He thought in 1870 that these cells were either branched pigmentary cells or migratory cells (Eberth 1870). It is, indeed, surprising that that opinion has remained ignored for many years.

A hundred years after the discovery of LC in the skin, these cells were identified in the lymph nodes and thymus (Olah et al. 1968; Jimbow et al. 1969; Kondo 1969; Van Haelst 1969). In the 1960s, some investigators believed that LC were skin macrophages (Tarnowski and Hashimoto 1967; Hashimoto and Tarnowski 1968; Prunieras 1969; Hashimoto 1971) and their capability to uptake foreign particles was proven (Wolff and Schreiner 1970; Sagebiel 1972). Interestingly, LC were also suggested in the 1960s – early 1970s to be lymphoid cells which are capable of producing antibody (Billingham and Silvers 1965; Kuwahara 1971). Based on these and other results, it has been proposed that LC being the skin "dendritic cells" (as in (Prunieras 1969)) may capture antigenic material and thus play a role in the primary immune response (Prunieras 1969; Hashimoto 1971; Vernon et al. 1973). In the early 1970s, Silberberg et al. based on the electron microscopy analyses postulated that if "LC are shown to possess antigen on or near their surface and in the course of the contact allergic reaction reach lymph nodes, they may very well participate in immune responses (i.e., immunoproliferative processes) in the lymph nodes as well as locally in the skin" and concluded that "Langerhans cells are a previously unrecognized cell population of immunologic importance" (Silberberg 1971, 1972, 1973; Silberberg et al. 1974, 1976). It is interesting to note that it was also suggested by the same group that LC might interact with sensitized lymphocytes and "release substances which lead to further inflammatory changes in the skin".

LC thus were known to be DC, but the term was only based on "the dendritic nature": for example, according to Michael Birbeck in 1961, "the perikarya of these cells appear characteristically dendritic" (Birbeck et al. 1961). There are also several interesting terminological issues. Although "dendritic cells" were described in the skin in the 1960s (Zelickson 1965; Zelickson and Mottaz 1968;

Prunieras 1969; Mishima and Kawasaki 1970) (e.g., Michael Birbeck's et al. paper from 1961 (Birbeck et al. 1961)), they included different cell populations. In addition to using the term "dendritic cells" for LC, it was used for melanocytes and an unusual cell population described as non-keratinocytic cells (α-cells) that have neither premelanosomes nor Langerhans (Birbeck) granules (Mishima and Kawasaki 1970; Kidd et al. 1971). These cells were also known as α-DC (Mishima et al. 1972).

It was not until 1973, however, that the term "dendritic cells" was used by Ralph M. Steinman and Zanvil A. Cohn for a new class of white blood cells with a number of distinctive features and functions (Steinman and Cohn 1973). Their publication is commonly accepted as the beginning of the modern era of dendritic cell science. Today, the term *dendritic cell* defines a diverse and multifunctional group of cells that serve as sentinels, adjuvants, and conductors of many immune functions, including the host defense against pathogens, both infectious and neoplastic.

2.2 Dendritic Cells in Cancer: Recognition of Their Functional Significance

Understanding of the functional significance of DC in initiating and maintenance of antitumor immunity and in cancer immunosurveillance began with the identification of LC at the tumor site, first in the skin tumors and later in other solid malignancies. From the early 1970s, an increased number of LC has been reported in benign epidermal tumors, whereas contradictory findings of the presence and the number of LC have been reported in squamous cell carcinomas both of cutaneous and mucosal origin (Lisi 1973; Wilborn et al. 1978; Loning et al. 1982; Fernandez-Bussy et al. 1983; Gatter et al. 1984). Basset et al. (1974) reported "Large numbers of dendritic cells similar in structure to Langerhans cells of normal epidermis and other epithelia were observed within nodules of a tumour identified as a bronchiolar-alveolar tumour of primary alveolar origin". Interestingly, although the overall function of LC was not yet proven at that time, the authors speculated that their presence at the tumor site "might be regarded as part of a defense process, since their occurrence in lymph nodes, thymus, and spleen could suggest they may have some function in this connection".

Functional studies on LC have always been hampered by the fact that these cells represent only a very small subpopulation of epidermal cells and it was therefore not possible to separate them from other epidermal cells. Only in the late 1970s, the functional role for LC was reported in direct in vitro studies and the ability of LC to present antigen was directly proven. Based on the contemporary identification of Fc receptors on LC in 1977 (Stingl et al. 1977), LC were isolated by rosetting and gradient centrifugation. Stingl et al. asked whether LC could act as antigen-presenting cells for either soluble protein

antigens (PPD, OVA) or for simple chemical haptens (TNP). The results clearly demonstrated that LC-induced antigen-specific T-cell proliferative responses comparable in magnitude to that induced by macrophages (Stingl et al. 1978a). Following the identification of Ia molecules on LC (Klareskog et al. 1977; Rowden et al. 1977), their ability to stimulate allogeneic T-cell proliferation in MLR assay was also tested and compared to that of macrophages (Stingl et al. 1978a). The authors reported that Ia-dependent ability of LC to stimulate allogeneic T cells was similar to that of macrophages in the same assay. Although this study has dealt exclusively with epidermal LC, the authors concluded "It is conceivable that all nonlymphoid organs contain a small percentage of cells with similar immunologic properties" (Stingl et al. 1978a).

Based on morphological, ultrastructural, immunohistochemical and biochemical analyses, "a relationship between Langerhans cells and the monocyte–macrophage system" was repeatedly suggested (Stingl et al. 1978b; Sterry and Steigleder 1979). Thus, by the late 1970s, it was accepted that "Langerhans cells represent specific granule-containing dendritic cells . . . , occur in the squamous epithelium, and also in the corium, lymph node and thymus. . ., are able to phagocytize antigens. . . as well as to migrate through the lymph vessels into the regional lymph nodes. . ., [and display] the antigen-presenting and lymphocyte stimulating functions. . ." (Haustein 1979). At the same time, in ongoing studies utilizing the in vitro MLR assay as a model of T-cell recognition and response to cell surface alloantigens, it was shown that splenic adherent cells, called SAC or A-cells, and "lymphoid dendritic cells", represent the same cell population (Steinman and Witmer 1978; Ahmann et al. 1979, 1981). Furthermore, the ability of LC to induce CTL responses similarly to SAC has been also reported (Pehamberger et al. 1983). Based on various similarities, LC of the skin and "indeterminate dendritic cells" as well as interdigitating cells (IDC), first described by Veldman (Veldman et al. 1978), of the normal tonsils, spleen, and thymic medulla were suggested to be related (Heusermann et al. 1974; Kelly et al. 1978; Hoefsmit et al. 1979). The latter cell subset circulates and was referred to as "veiled cells" in the lymph and "macrophages with ruffled membrane" in the peritoneal exudates (Kelly et al. 1978; Spry et al. 1980). Thus, several types of irregularly shaped *dendritic cells* have been identified, including dendritic cells and interdigitating cells in lymphoid tissues, epidermal Langerhans cells, follicular or germinal center dendritic cells, and veiled cells in lymph (Van Voorhis et al. 1983b). Interestingly, in 1982, Stella C. Knight suggested that veiled cells resemble DC described by Steinman or may be the precursors of DC (Balfour et al. 1982; Knight et al. 1982). At that time, the "DC of Steinman" were considered to be in vitro equivalents of LC and IDC (Hoefsmit 1982). While LC, IDC, and veiled cells were believed to belong to a subpopulation of the macrophages and could be developed from monocytes, DC described by Steinman and Cohn were considered to be bone marrow derived as a separate cell subset (Steinman and Nussenzweig 1980). DC that were originally identified in rodents were soon seen in and isolated from human tissues and their role "as inducer cells in the immune response" was also confirmed (Van Voorhis et al. 1983a; Richtsmeier et al. 1984).

In relation to the tumor, clusters of Langerhans and lymphoid cells in the inflammatory peritumoral infiltrate in basal cell carcinoma, for instance, were described in the 1970s and based on the similarity between "Langerhans' and interdigitating reticulum cells" it was thought that this specific microenvironment might be "favourable to certain immunological activities of T-lymphocyte populations" (Macadam 1978; Porfiri et al. 1979). "Dendritic cells similar to Langerhans' cells of normal epidermis" were recognized at the same time in specimens from cutaneous T-cell lymphoma (CTCL), oral squamous cell carcinoma (SCC), salivary gland adenoma, malignant melanoma, and other tumor types (Rowden et al. 1979; David and Buchner 1980; Schenk 1980; Szekeres and Daroczy 1981; Thomas et al. 1984). For instance, HLA-DR positive DC were shown in the infiltrate and between the melanoma cells (Poppema et al. 1983). Analyzing individual mononuclear cell populations at the tumor site, including antigen-presenting DC, CD4+ T helpers, and CD8+ cytotoxic T lymphocytes, the authors concluded that they might play a role in immune defenses against malignant cells.

In 1981, LC were shown to express S-100 antigen (Cocchia et al. 1981) and soon S-100-expressing DC were identified and characterized in various neoplastic tissues (Nakajima et al. 1982). For instance, S-100 antigen-containing cells with dendritic features, recognizable by morphological and immunohistochemical criteria as belonging to the Langerhans' cell type, have been found in undifferentiated nasopharyngeal carcinoma and in lymph node metastases. S-100+ DC appeared to be few or absent in most SCC of both mucosal and epidermal origin. The presence of these cells, which have a special function of antigen presentation in immune responses, was speculated to be involved in host–tumor interactions (Lauriola et al. 1984). Similar results were reported for S-100+ DC in many different tumor types, including lung, oral, and cervical cancer as well as others (Kurihara and Hashimoto 1985; Nakajima et al. 1985; Tay et al. 1987).

Thus, soon after identification of DC at the tumor site, it was accepted that they may play an important role in tumor–host interactions and may be involved in initiation of antitumor immune response (Fig. 2.1A). This concept was primarily supported by functional studies modulating DC activity at the tumor site and by direct experiments demonstrating antitumor potential of DC in pre-clinical models. For example, in the middle 1980s it was shown that DC can pick up tumor antigens and modulate antitumor immunity in vivo (Knight et al. 1985): DC isolated from the spleen and pulsed with tumor antigens caused inhibition of tumor growth when injected into tumor-bearing mice, thereby serving as antitumor vaccines. At the same time involvement of LC in antitumor immunity was also suggested: Muller at al. (1985) showed that the chemical carcinogen DMBA induced skin tumors and depleted LC from treated skin, which however repopulated the skin upon cessation of the DMBA treatment (Muller et al. 1985). During this repopulation of the skin by LC, the tumors decreased in size. The authors concluded that since LC function as local cutaneous APC, their depletion during tumor induction may allow DMBA-transformed cells to circumvent the immune system and form tumors. Their reappearance associated with tumor regression suggested that the LC are

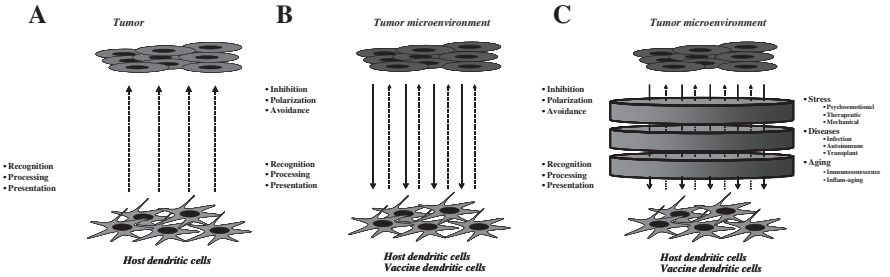

Fig. 2.1 Emergence of understanding of dendritic cell–tumor cell interaction. Dendritic cells (DC) were recognized as important mediators, inducing specific immune responses. Identification of DC within the tumor mass supported the notion that they played a consequential involvement in initiating antitumor immunity (**A**). This view has received additional support in numerous reports demonstrating a direct correlation between the number of tumor-infiltrating DC and prognosis. However, from the very early reports it became clear that the morphological appearance of DC in the tumor environment, as well as phenotypic maturation and function of tumor-associated DC or DC isolated from patients with cancer could be compromised or deficient. Tumor-derived factors suppress differentiation, activation, and longevity of DC precursors and DC themselves in vitro and in vivo provided sustaining evidence of tumor-mediated repression of DC. These findings suggested that tumor-induced inhibition of DC differentiation (dendropoiesis), functioning, and survival represents pathophysiological mechanisms by which tumors survive immunological recognition and elimination (**B**). Nevertheless, novel experimental and clinical data reveal additional layers of complexity of existing concept of DC functioning in the setting of cancer (**C**). First of all, common psychologic stressors in patients diagnosed with malignant diseases, as well as those associated with therapy (e.g., chemotherapy and radiation) or mechanical disruption (e.g., surgery and biopsy), strongly affect dendropoiesis and DC activation via release of glucocorticoids, catecholamines, neuropeptides, and inflammatory cytokines and chemokines. Secondly, infectious, allergic, and autoimmune diseases, especially in the pediatric and elderly populations of cancer patients drastically modulate the state of the DC and its ability to respond to tumor-derived or therapy-associated stimuli. Cell and organ transplantation and related immunosuppressive treatments may both account for unusual behavior of DC within the tumor milieu. Thirdly, as has been recently proven, immunosenescence of the elderly arises in part due to the altered differentiation and function of individual subpopulations of DC and, thus, might also compromise development and sustaining of DC-mediated antitumor immunity in cancer patients. Most of these factors that modify the DC in patients with malignancies should be applied not only to endogenous host DC, but also to exogenously administered DC vaccines. The interaction between injected DC and resident DC may compromise the induction of effective antitumor immune responses. Understanding of DC behavior in the tumor environment in a particular patient is crucial for designing and applying efficient therapy for cancer treatment

involved in an immune response against the tumors (Muller et al. 1985). Moreover, DC receiving TA were also shown to induce protective immunity against a subsequent tumor challenge (Gyure et al. 1987).

Furthermore, the role of DC in the development of antitumor immunity (Fig. 2.1A) was supported by a growing number of clinical and pathological data analyzing a correlation between the levels of tumor-infiltrating DC and the patients' outcomes. For instance, Igisu et al. (1983) found in CTCL, the fewer

the number of intratumoral LC, the poorer the prognosis. Survival time in patients with the advanced stage of gastric carcinoma correlated well with the density of LC. In patients with a marked infiltration of LC, survival time was longer than in cases of only a slight infiltration (Tsujitani et al. 1987). Patients with many S-100+ DC in colorectal adenocarcinomas survived longer than did those with few, most often in those patients with no metastases (Ambe et al. 1989).

In addition, Nomori et al. (1986) found that the degree of density of T-zone histiocytes (i.e., DC) was significantly related to prognosis in primary site of biopsy specimens of nasopharyngeal carcinoma. Furukawa et al. found similar results in stage 1a adenocarcinoma of the lung (Furukawa et al. 1985) and reported that LC were present more frequently in moderately to well-differentiated adenocarcinoma than in poorly differentiated adenocarcinoma of the lung. Cochran et al. (1987) also showed that DC were infrequent in lymph nodes infiltrated by melanoma or located near melanoma but were numerous in nodes located farther from tumor. Interestingly the appearance of LC seemed to be related to the presence of chronic inflammation: Very few LC were observed in carcinomas in which inflammatory cells were rare (Nakajima et al. 1985). Many subsequent reports confirmed the conclusion that survival of patients whose tumors contain high density of DC is more favorable when compared to those whose tumors have a low density of these cells in different types of cancer. Altogether these and similar results allowed wide acceptance of the prevalent concept that LC/DC in immunological defense mechanisms of the host against the tumor may be clinically effective during the early phases of tumor development.

2.3 Dendritic Cells in Cancer: Recognition of Their Role in Tumor Escape

By the mid-end 1980s, with only a few exceptions, analyzing S-100+ and HLA-DR+ DC and LC in human tumors, most investigators commonly concluded that there was a significant decrease of these cells in tumors when compared with non-malignant or surrounding tissues. Also, the distribution of DC in the tumor tissues and regional lymph nodes could be considered as a reference indicator of tumor histologic grade and clinical prognosis of patients with different tumor types, and thus could reflect the degree of tumor immunity induced in the tumor-bearing host. However, pathogenetic and immunologic mechanisms regulating DC distribution and homing at the tumor site were still unknown. Soon a clue appeared with the accumulation of data suggesting first morphologic then functional abnormalities of LC/DC in the tumor mass. In characterizing distribution of LC in human skin tumors, "A striking finding to emerge was that in benign skin lesions Langerhans' cells were increased, whereas in malignant tumours they were not only markedly depleted or absent

but also grossly stunted and deformed in outline" (Gatter et al. 1984). This is probably the first report describing tumor-associated abnormalities in DC. Similar alterations were seen in LC in the skin of patients with basal cell carcinoma (BCC): "Perturbations of ATPase-positive, dendritic LC were evident in all specimens. These perturbations included various degrees of disruption of the usually uniform LC network and alterations in the morphology of LC. Many LC had rounded, deformed cell bodies, dendrites that were shortened or completely absent" (Azizi et al. 1987). The authors speculated that the perturbations could reflect an effect of the tumor cells on LC morphology. It took, however, almost a decade before direct experimental evidence of tumor-mediated inhibition of DC functioning was reported.

Early attempts to identify potential alterations of function of DC isolated from patients with cancer or from growing tumors were inconclusive (Stene et al. 1992; Chaux et al. 1993; Tas et al. 1993), in spite of well thought-out predictions of tumor cell capability of abrogating the anticancer activity of the DC (Becker 1992) through, for instance, tumor-derived IL-10 (Becker 1993b). In fact IL-10 production by tumor cells has been soon shown to represent one of the mechanisms involved in the modulation of the antigen-presenting cell function of tumor-associated DC and in tumor immunological escape (Chaux 1995). In the early 1990s, a growing number of studies reported deficiency of DC function in the tumor microenvironment, whereas only a few reports failed to detect DC abnormalities in cancer. For instance, the capability of DC prepared from the blood to form cellular clusters with allogeneic cells was shown to be impaired in 26/44 patients with head and neck squamous cell carcinoma (HNSCC) (Stoger et al. 1993), which could be explained by defects in expression of various molecules on tumor-associated DC (Chaux et al. 1995) or small-Rho GTPase-mediated inhibition of actin polymerization and associated cell functions including motility and adhesiveness (Shurin et al. 2005b; Tourkova et al. 2007). In 1996, Gabrilovich et al. in a series of in vivo and in vitro experiments demonstrated that DC from tumor-bearing mice had a reduced ability to present antigens and stimulate T-cell proliferation (Gabrilovich et al. 1996a, b). Decreased expression of CD80 and CD86 on tumor-infiltrating DC was also reported (Chaux et al. 1996). Enk et al. (1997) revealed that melanoma-derived factors convert DC-antigen-presenting cell function to tolerance induction against tumor tissue, changing antitumor DC to "silencers" of antitumor immune responses.

These and other early reports supported the notion that inadequate presentation of tumor antigens by host DC is one potential mechanism of tumor-mediated inhibition of DC function as antigen-presenting cells (Fig. 2.1B). At the same time, it was shown that tumor-derived factors might suppress differentiation and functional maturation of DC (Gabrilovich et al. 1996a) resulting in a decreased pool of active DC capable of inducing antitumor immune responses in the tumor environment. Progressing skin tumors produce factors that inhibit LC migration from the epidermis to lymph nodes, which may enable tumors to evade the activation of protective immunity (Lucas and

Halliday 1999). Furthermore, in 1999, we reported that not only may tumors suppress DC differentiation and function, but they could also actively induce apoptotic death of DC and DC precursors both in vitro and in vivo (Esche et al. 1999; Shurin et al. 1999; Katsenelson et al. 2001). All of these early findings were confirmed later in several reports (Kiertscher et al. 2000; Pirtskhalaishvili et al. 2000, 2001; Shurin et al. 2001; Peguet-Navarro et al. 2003; Pinzon-Charry et al. 2006). Because conventional DC are the primary cell population responsible for initiating antitumor immunity, it is not surprising that tumors develop mechanisms for inhibiting DC function and longevity. The important interplay between DC and tumor cells in regulating tumor progression and antitumor immunity was first predicted (Becker 1993a) and then proven in numerous pre-clinical and clinical studies (Fig. 2.1B). Thus tumor-mediated interference with DC generation, function, and survival represents one pathway by which tumors escape host immune mechanisms via inhibiting the activity of DC (Fig. 2.1B).

Other than inhibiting DC, tumor cells are able to redirect or re-polarize differentiation of hematopoietic precursors from the conventional DC lineage to regulatory or tolerogenic DC subpopulations, protumorigenic endothelial-like DC, or to myeloid-derived suppressor cells (MDSC) and monocyte/macrophages. For instance, several reports demonstrated accumulation of tumor-supporting plasmacytoid DC (pDC or DC2) in tumor ascites in patients with ovarian cancer (Zou et al. 2001; Curiel et al. 2004; Wertel et al. 2006). Melanoma cells also induced immunosuppressive DC (McCarter et al. 2007). Interestingly, a low circulating pDC count in cancer patients, as well as low number of tumor-infiltrating pDC, was reported as a good prognostic sign (Vakkila et al. 2004; O'Donnell et al. 2007). There is evidence that tumor cells may also skew monocyte differentiation from DC to macrophage-like cells: DC generated in the presence of soluble factors produced by lung SCC and adenocarcinoma were phenotypically and functionally more similar to macrophages than to untreated control DC (Avila-Moreno et al. 2006). The accumulation of MDSC, which could precede their development into immature DC (Rossner et al. 2005) or be a separate differentiation pathway (Auffray et al. 2008; Geissmann et al. 2008), is also associated with immune suppression in tumor-bearing mice and in cancer patients. These cells exhibit a protumorigenic role due to their pleiotropic activities that include, in addition to well-defined immunosuppression and tolerance, support of mutagenesis in the tumor microenvironment, promotion of angiogenesis and metastasis, as well as directly sustaining both neoplastic growth and inflammatory reaction (Marigo et al. 2008). Thus, re-polarization of myeloid progenitor cells or macrophage DC progenitors (MDP) (Fogg et al. 2006) induced by the presence of tumor-derived factors is a second mechanism of tumor escape from immune recognition limiting DC (Fig. 2.1B).

A recently described third mechanism of tumor evasion, so-called avoidance, is the loss of expression of DC chemokines in tumor cells. DC chemoattractants are produced by all normal tissues, but their expression may be down-regulated upon transition to malignancy. Absence of the chemokine CXCL14 is the best known factor enabling the avoidance pathway. Constitutive CXCL14 (BRAK)

expression was described in all tested non-malignant tissues and cell lines, but not in tumor cell lines or tumor tissues (Hromas et al. 1999; Frederick et al. 2000). Thus CXCL14 is a strong chemoattractant for immature DC and an activator of DC maturation. Expression of CXCL14 correlates with DC attraction and homing, and its absence could make tumor cells "invisible" for recruitment of DC and should be considered as an additional mechanism of tumor escape from the immunological recognition (Shurin et al. 2005a) (Fig. 2.1B).

Conventional or myeloid DC (DC1) are a fundamental part of the immune defense mechanism, which can promote specific immunity by inducing T-cell activation, expansion, and ultimately recruitment to the tumor site. Despite this, their presence within the tumor microenvironment has been associated with enhanced antitumor immunity, while tolerogenic regulatory DC populations have been shown to promote tumor cell growth and spreading, angiogenesis, and immunosuppression. This paradoxical role of DC in cancer can be explained by their functional plasticity. It may result in the polarized expression of either pro- or anti-tumorigenic functions. Key players in the setting of DC phenotype are the tumor microenvironmental signals to which DC are exposed and which selectively tune their functions within a functional spectrum encompassing the DC1 and DC2 extremes (Shurin et al. 2006).

2.4 Dendritic Cells in Cancer: Recognition of the Diversity of Regulatory Roles

That an impaired or re-directed functionality of DC in the tumor environment plays a crucial role in tumor proliferation, spreading, and metastasis, i.e., in tumor escape mechanisms (Shurin and Gabrilovich 2001; Shurin et al. 2003; Shurin and Chatta 2008) is no longer in doubt. Specifically, abnormalities of DC that allow tumor progression include defective MHC class I (Tourkova et al. 2005) and class II (Gerner et al. 2008) presentation of tumor antigens; immaturity of DC and low level of expression of co-stimulatory molecules (Chaux et al. 1996; Shurin et al. 2001); induction of regulatory DC producing IL-10 and/or TGF-β that promote regulatory T cells (Ghiringhelli et al. 2005; Lan et al. 2006); low levels of IL-12, IL-15, and IL-18 production by DC (Shurin et al. 2002; Bellone et al. 2006; Capobianco et al. 2006); expression of immunosuppressive molecules HLA-G and B7-H1 (Curiel et al. 2003; Lemaoult et al. 2007) and IDO (Hou et al. 2007); production of TNF-α and IL-8 and induction of neovascularization (Conejo-Garcia et al. 2004; Curiel et al. 2004); impaired migration (Shurin et al. 2005b) and endocytic activity (Tourkova et al. 2007); and, probably, inhibited killing activity of DC (Taieb et al. 2006) in the tumor environment. Multiple tumor-derived and stroma-derived factors are responsible for altering the DC found at the tumor site and systemically. The list of these molecules includes but is not limited to VEGF, M-CSF, IL-6, IL-10, IL-8, TGF-β, CCL2, CCL20, SDF-1, prostaglandins, gangliosides, neuropeptides, tumor antigens

(e.g., PSA and MUC1), lactic acid, NO, spermine, hyaluronan, reactive oxygen species, and other largely unknown factors (Shurin and Chatta 2008). These factors could be produced by various cells in the tumor microenvironment, including not only tumor cells themselves but also fibroblasts, endothelial cells, macrophages, lymphocytes, neutrophils, and other tissue-specific cells depending on the tumor location. This suggests that cellular interactions within the tissue at the tumor site are primarily responsible for the state of DC maturation, activation, functioning, and survival and, thus, for supporting tumor progression or antitumor immunity. Furthermore, other signals generated during the course of tumor process also alter the activation of DC and include extracellular acidosis, oxidative stress, and fever-like temperature. Understanding of how DC are regulated in the tumor microenvironment and how this impacts the efficacy of DC vaccines and other immunotherapeutic means is far from complete. Only a few clinical trials focusing on protection of DC from the harmful effects of the tumor environment have been tested.

In addition to a direct regulation of DC functionality by local factors in the tumor milieu, important factors and associated conditions may influence the functional state of DC. The activity of administered DC vaccines in patients with cancer may depend on these factors. Psychological stress associated with the diagnosis of cancer, selection of the treatment options, and the prognosis of individual diseases (Fig. 2.1C). Stress-associated hormones, neuropeptides and neuromediators, such as glucocorticoids, ACTH, substance P, and catecholamines, are well documented to alter differentiation, maturation, and activity of DC. In addition to the psychoemotional stress, patients with cancer commonly experience a variety of physical/mechanical stresses linked to the treatment procedures, such as surgery, radiation, and chemotherapy. These stressors also cause an influx of common stress hormones, as well as mediators related to pain, trauma, tissue destruction, and specific effects of radiation and chemotherapy, which all strongly affect the functional state of DC (Saint-Mezard et al. 2003; Elftman et al. 2007; Goyarts et al. 2008; Kawasaki et al. 2008; Kleyn et al. 2008). Thus analyzing the behavior of DC in the tumor milieu is contingent on recognition of the acute and chronic stress conditions, which might substantially limit or exacerbate DC response to tumor/stroma-mediated signaling.

Another level of complexity is due to the pathogenic modifications of DC function in infectious, autoimmune, allergic, and other immune-mediated diseases sometimes associated with tumor development or tumor therapy (Fig. 2.1C). Alterations in DC homeostasis have been implicated in various human inflammatory, autoimmune, and allergic diseases (Adler and Steinbrink 2007; Blanco et al. 2008). Both in vitro and in vivo studies have shown that tolerogenic DC contribute to prevention of autoimmunity and allergic reactions. These cells might thus worsen the course of cancer and certain infectious diseases. Furthermore, immunosuppressive drugs used the following organ transplantation impair DC function, resulting in an increased incidence of viral associated malignancies (Sebelin et al. 2006). Mixed DC populations with a diverse spectrum of activities might be a common feature in cancer patients

with mixed diseases. On the other hand, prevalence of "pro-dendritic" or "anti-dendritic" stimuli, i.e., immunogenic vs tolerogenic pathways, may determine the course of tumor progression and its response to therapy.

More than half of cancers arise in individuals older than 65 years of age. Age-related alterations of DC should be considered as a third layer of complexity in understanding the DC–tumor cell interplay in patients with cancer. It seems reasonable to suggest the existence of both pathways: (i) DC in the elderly are involved in the increased incidence of cancer and (ii) tumor-induced modulation of DC might direct appearance of various immune-mediated diseases in the elderly (Shurin et al. 2007; Agrawal et al. 2008). For instance, increased levels of IL-6 and IL-10 reported in older individuals (Caruso et al. 2004; Maggio et al. 2006) may directly affect dendropoiesis and function of DC and thus their potential to induce and maintain antitumor immunity. Thus, design of DC vaccines for elderly patients with cancer might differ from DC vaccines prepared for the younger patient population and should take into account specific behavior and immunological state of DC in aged individuals, especially if they suffer from other diseases. This simple conclusion sounds logical and reasonable, but unfortunately it is hard to transfer into modern clinical trials. Hopefully, new experimental and pre-clinical studies will demonstrate an undeniable demand for designing combinatorial DC vaccine-based therapy that accounts for specific medical conditions of cancer patients, including their age, psychoemotional status, and the presence of other immune-mediated diseases.

Cancer, arising in adults in the setting of chronic inflammation, thus can be envisioned as a network of interacting cells, emerging as a property of tissues with continuous autocrine growth as well as perpetual stress signaling. DC, as integrants of such signals arising from epithelia, stroma, endothelia, and recruited inflammatory cells, can thus play varying roles during the evolution of a tumor, in some instances impeding their development and in others actively promoting immune tolerance and impotence in the tumor microenvironment, responding to ambient microenvironmental nutrients, redox status, and oxygenation. Together, these observations suggest the existence of multiple means by which the activation, suppression, or polarization of DC can be induced in patients with cancer, supporting the view that in spite of a multiplicity of roles, the coherent manipulation of endogenous DC and rational preparation of DC vaccines could elicit robust antitumor immune responses leading to clinically significant outcomes. Full explication and development of DC-based strategies will require the emergence of a more mature perception of the tumor microenvironment in which they, and interacting inflammatory/immune cells, play their role.

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http://www.springer.com/978-0-387-88610-7

Dendritic Cells in Cancer
Shurin, M.R.; Salter, R.D. (Eds.)
2009, XVIII, 396 p. 26 illus., Hardcover
ISBN: 978-0-387-88610-7