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Dendritic cells and tumor microenvironment: a dangerous liaison:

Dendritic cells and tumor microenvironment

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Abstract

The fact that the immune response to cancer is compromised has been convincingly demonstrated in murine tumor models as well as in cancer patients. The unresponsiveness of the host immune system is one of the major mechanisms of tumor escape as well as an important factor that limits the success of cancer immunotherapy. Inadequate function of professional antigen presenting cells dendritic cells (DC) in cancer is one of the major elements of compromised anti-tumor immune response. Despite substantial progress in recent years, the mechanism of inadequate DC function in cancer still remains unclear. The tumor microenvironment has emerged as an important component contributing to DC malfunction. In this review we will discuss the potential role of tumor microenvironment in DC dysfunction.

Introduction

Dendritic cells (DC) are considered the most powerful antigen presenting cells (APC) and therefore viewed as critical regulators of adaptive immune responses. DCs are a highly heterogenic population of cells with high plasticity sharing common features like morphology and functional characteristics (Banchereau, et al. 1998,Lanzavecchia, et al. 2001). DCs arise from $CD34^+$ bone-marrow stem cells and are classified in two different developmental stages: **immature** (iDC) and **mature** (mDC) cells. iDC are localized primarily in peripheral tissues and perform the specialized functions of antigen uptake and processing. On the other hand, mDCs reside in lymphoid organs, where they interact with antigen-specific T cells and initiate immune responses. The chemokine receptor repertoire of iDCs is distinct from mDCs, and this regulates their migration into tissue sites.

Two main populations of DCs are recognized in mouse and human tissues: ***myeloid DCs*** (MDCs) and ***plasmacytoid DCs*** (PDCs) (Colonna, et al. 2004,Kaech, et al. 2001,Lanzavecchia, et al. 2001,O'Neill, et al. 2004). Early work in humans identified plasmacytoid monocytes (now called plasmacytoid DCs [PDCs]) as cells present in inflamed lymph nodes surrounding high endothelial venules (Facchetti, et al. 1989). These cells have a characteristic phenotype distinct from that of monocytes and myeloid DCs ($CD123^+$, $CD45RA^+$, $CD4^+$, $CD11c^-$, $ILT3^+$, $ILT1^-$, Lin^-) and are present at low levels in peripheral blood (where they express additional markers BDCA-2 and 4) (Dzionek, et al. 2000,Grouard, et al. 1997,Olweus, et al. 1997). Experiments using cultured human stem cells, as well as retroviral transduction with genes that interfere with lymphocyte development, indicate that PDCs may have a lymphoid origin (Blom, et al. 2000,Spits, et al. 2000). Recent studies indicate that freshly isolated PDCs stimulated by viruses produce extremely high levels of type I IFNs (Cella, et al. 1999,Siegal, et al. 1999) and selectively prime T cells to produce IFN-γ and IL-10 (i.e. cells with a T_H1-like phenotype) (Cella, et al. 2000,Kadowaki, et al. 2000). In humans, the expression of Toll-

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like receptors TLR7 and TLR9 are restricted to PDC (Edwards, et al. 2003). The path of PDC development and their molecular regulation are not completely understood. The main cytokine required for the development of PDC from hematopoietic stem cells is Fms-like Tyrosine Kinase 3 Ligand (Flt3L) (Blom, et al. 2000,Chen, et al. 2004,Gilliet, et al. 2002). Administration of Flt3L to human volunteers resulted in an increase of PDCs in peripheral blood (Pulendran, et al. 2000). Additionally, Flt3L-deficient mice displayed a smaller amount of PDC whereas Flt3L-transgenic mice had increased levels (Brawand, et al. 2002). Granulocyte colony stimulating factor is also important in PDC biology because it promotes their mobilization from bone marrow (Arpinati, et al. 2000,Pulendran, et al. 2000).

Myeloid DC are characterized through their expression of CD11c, CD33 and absence of CD45RA, CD123 and lineage marker (Kadowaki, et al. 2001,Sieling, et al. 2002). Furthermore, human MDC express a different TLR-repertoire (TLR1, 2, 3, 4, 5, 6, 8, 10) and do not secrete interferon I after viral challenge. According to phenotypical and functional characteristics MDC can be further divided into subpopulations (Grabbe, et al. 2000). Previously, it was believed that PDC (also called DC2) induce a T_H2 response, whereas MDC (also termed DC1) induce a T_H1 type response (Rissoan, et al. 1999,Vieira, et al. 2000). Now it is accepted that DC are capable of promoting either T_H1-, T_H2- or T_H0/T_R1 responses depending on culture conditions and/or origin of activation signal rather than on the ontogeny of DC (Kalinski, et al. 1999).

In early studies it was believed that DCs were exclusively immunogenic, actively initiating or up-regulating immune responses. More recent reports demonstrated that DCs may cover dual functions, and can also exhibit regulatory (suppressive) activity. DCs are able to actively down-regulate an immune response or to induce immune tolerance by influencing the activity of other cell types. It has been seen particularly within the tumor microenvironment that DCs acquire a regulatory function (Curiel, et al. 2004,Curiel, et al. 2003,Gabrilovich, et al. 1996,Munn, et al. 2004a,Zou, et al. 2001). This regulatory capacity is probably not a part of intrinsic nature of a defined DC subset but rather the result of the influence of tumor microenvironment.

Myeloid DCs share the same progenitor cells as monocytes/macrophages, and express myeloid lineage surface markers (Banchereau, et al. 1998). Mature MDCs are potent inducers of T helper 1 (T_H1)-type immune responses and also are considered as powerful initiators of tumor associated antigen (TAA)-specific immunity. However, the appearance of functional competent myeloid mDCs inside the tumor is rare as described for human ovarian (Zou, et al. 2001), breast (Bell, et al. 1999,Iwamoto, et al. 2003), prostate (Troy, et al. 1998a) and renal-cell cancers (Troy, et al. 1998b). Multiple factors may be responsible for this phenomenon, such as defective DC recruitment, differentiation, maturation, and survival. There are strong data demonstrating profoundly suppressed differentiation and maturation of myeloid DCs in the presence of factors present in the tumor microenvironment. Tumor cells are able to produce large amounts of vascular endothelial growth factor (VEGF) among other factors (Carmeliet, et al. 2000,Kryczek, et al. 2005). Lack or low levels of IL-12 and/or IFN-γ create an aberrant cytokine pattern in the tumor environment (Freedman, et al. 2004,Kryczek, et al. 2000). The imbalance of cytokines in the tumor microenvironment impairs DC differentiation and maturation. While *in vivo* myeloid mDCs can induce strong TAA-directed immunity (Labeur, et al. 1999), immature or partially differentiated MDCs induce either T-cell unresponsiveness (Dhodapkar, et al. 1999,Hawiger, et al. 2001) or suppressive regulatory T cells (T_{reg}) (Dhodapkar, et al. 2001,Jonuleit, et al. 2000). Homing of suppressive T_{reg} cells to draining lymph nodes may induce systemically disabled TAA-specific immunity. Incomplete differentiated or immature myeloid DCs therefore can be regarded as regulatory DCs and may function as an important component of the immunosuppressive networks in the tumor microenvironment.

General characteristics of tumor microenvironment and potential role of dendritic cells

Solid tumor is not solely composed of malignant cells, but also includes several non-malignant cell types including endothelial cells, fibroblasts, adipocytes, lymphocytes, macrophages, granulocytes, and immature myeloid cells. This creates a unique microenvironment, which can modify the neoplastic properties of the tumor cells. Studies have shown that the nature of the surrounding cells can modify the outcome of primary oncogenic events in epithelial cells (Coussens, et al. 2000,Coussens, et al. 2002,Iyengar, et al. 2003,Krtolica, et al. 2001,Lin, et al. 2001). It was noted that within the tumor, primarily iDC not mDC (Troy, et al. 1998a,Troy, et al. 1998b) were present while mDC were detected in the marginal zones (Sandel, et al. 2005). Furthermore, labeling experiments revealed that most of the intratumoral DCs remain inside the tumor instead of migrating out (Feijoo, et al. 2005).

An important factor for the tumor development is angiogenesis, a function widely attributed to factors produced by macrophages (Carmeliet, et al. 2000). This process involves a wide range of soluble mediators that are both stimulatory and inhibitory, including basic fibroblast growth factor (bFGF), VEGF, the angiopoietins (ANG1 and ANG2), IL-1, IL-8, tumor necrosis factor-α (TNF-α), thymidine phosphorylase (TP; also known as vascular-derived endothelial growth factor), the matrix metalloproteinases MMP-9 and MMP-2, and nitric oxide (NO) (Boudreau, et al. 2003,Carmeliet, et al. 2000). These molecules, which are expressed in a coordinated spatial and temporal fashion, result in the proliferation and migration of endothelial cells, matrix remodeling and the eventual formation of stabilized vessels (Hanahan, et al. 1996). Macrophages are perfectly designed to promote these processes, as their precursors can migrate into sites where they differentiate into macrophages. These cells can synthesize the required angiogenic molecules on demand in specific locations (Bando, et al. 2000).

Human myeloid DCs, but not plasmacytoid DCs, are the major producers of IL-12. This fact may contrubute to the suppression of tumor neoangiogenesis by myeloid DCs (Curiel, et al. 2004), which is essential for tumor growth and metastasis (Carmeliet, et al. 2000). However, tumor environment seem to lack angiogenesis-inhibitory myeloid DCs, whereas angiogenesis-stimulatory DCs, such as plasmacytoid DCs are present (Conejo-Garcia, et al. 2004,Curiel, et al. 2004). This could be due to the tumor-derived chemokine CXCL12, which attracts and protects plasmacytoid DCs in the tumor microenvironment. These cells in turn are capable of inducing vascularization by spontaneously producing TNF-α and IL-8 (Curiel, et al. 2004). Coukos *et al.* demonstrated that vascular DCs are recruited by β-defensin, and induce vasculogenesis under the influence of VEGF in mice. Vascular DCs are also found in ovarian tumors (Conejo-Garcia, et al. 2004). Therefore, DCs are relevant not only in tumor immunopathogenesis, but also in tumor vascularization. Optimal vascularization of tumors might require the simultaneous accumulation of vascular DCs and the absence of anti-angiogenic myeloid DCs, as is observed in ovarian tumours. Furthermore, as recently observed, tumor vascularization and growth can also be mediated by DC precursors. These cells can be attracted to the tumor sited by β-defensins and under the influence of VEGF-A may differentiate into endothelial-like cells expressing both DC and endothelial cell markers (Conejo-Garcia, et al. 2004). Therefore, DCs are relevant not only in tumor immunopathogenesis, but also in tumor vascularization.

Modulating factors released by the tumor microenvironment

Ideally, DCs should be recruited to the tumor site to initiate and drive immune responses that would lead to the rejection of the tumor. However, there is now enough evidence indicating that the tumor microenvironment is immunosuppressive (Elgert, et al. 1998,Ohm, et al. 2001). A number of factors that contribute to this suppression are discussed below.

1. Cytokines/chemokines

***GM-CSF* (granulocyte macrophage colony stimulating factor)—**Naba *et al*. reported that granulocytes, macrophages, and DCs can develop from a common MHC class-II-negative progenitor in the presence of GM-CSF (Inaba, et al. 1993). The concept that DCs can be derived from myeloid precursors was definitively shown by Sallusto and Lanzavecchia (Sallusto, et al. 1994) in a report indicating that human DCs can be differentiated *in vitro* from monocytes, and has been strengthened more recently by Randolph *et al.* using an *in vivo* approach in mice (Randolph, et al. 1999). GM-CSF is released by a large number of tumor cell lines (Bronte, et al. 1999). In mice, chronic exposure to GM-CSF leads to the generation of a cell population expressing the granulocyte and monocyte markers Gr-1 and CD11b (Bronte, et al. 1999,Young, et al. 1991). Most of these cells are immature myeloid cells able to directly suppress antigen-specific T-cell responses (Kusmartsev, et al. 2005). Interestingly, Gr-1^+ $CD11b^+$ cells isolated from tumor bearing mice could be differentiated into fully competent mature DC in the absence of tumor-conditioned medium. Furthermore it is important to note that that GM-CSF had been shown to have therapeutic potential as a component of cancer vaccines. The amount of GM-CSF released seems to be the important factor. Serafini *et al.* showed a strong accumulation of immunosuppressive immature myeloid cells (ImC) in animals vaccinated with a high GM-CSF producing tumor cell line (Serafini 2004).

M-CSF and IL-6—Macrophage colony-stimulating factor (M-CSF) and IL-6 are produced by a large number of tumors and have also been reported to be involved in the tumor-mediated regulation of DC differentiation (Gabrilovich, et al. 1996,Menetrier-Caux, et al. 1998). Renal-cell carcinoma cell lines were shown to release soluble factors that inhibit the differentiation of $CD34^+$ progenitor cells into DCs and instead trigger their differentiation towards monocytic cells. Both neutralizing IL-6- and M-CSF-specific antibodies abolished the impact of renal-cell carcinoma conditioned medium on DC differentiation (1998, Menetrier-Caux, et al. 2001) and the combination of IL-6 and M-CSF displayed a similar effect on inhibition of DC differentiation (Menetrier-Caux, et al. 2001). IL-4 as well as IL-13 improved differentiation of $CD34^+$ cells into DCs affected by the presence of either renal cell carcinoma conditioned medium, IL-6, or M-CSF. It was found that IL-4 rapidly blocked the expression of M-CSF and the IL-6R-transducing chain (gp130), as well as decreased the secondary production of M-CSF, thereby preventing the loss of GM-CSF receptor α-chain expression, which normally occurs during the differentiation of $CD34^+$ cells (Menetrier-Caux, et al. 2001). IL-6 plays an important role in abnormal DC differentiation in multiple myeloma (Ratta, et al. 2002). Furthermore, sera from patients with multiple myeloma inhibited the generation of DCs, which could be reverted by anti-VEGF and/or anti-IL-6 antibodies (Hayashi, et al. 2003). In another recent study, IL-6 was found to suppress DC maturation *in vivo* and play a major role in maintaining immature DCs (Park, et al. 2004). The suppressive role of IL-6 could be attributed to activation of the transcription factor STAT3.

***VEGF* (Vascular endothelial growth factor)—**VEGF was the first tumor-derived factor described to inhibit DC differentiation. VEGF plays an important role in neovascularization and hematopoiesis during embryogenesis. VEGF is produced by most tumors and increased plasma levels of VEGF in cancer patients correlate with an unfavorable prognosis (Ellis, et al. 1996,Toi, et al. 1996). Involvement of VEGF in tumor-induced defects in DC differentiation was demonstrated *in vitro* where abrogation of the negative effect of tumor cell conditioned medium on the differentiation of DCs could be achieved by neutralizing VEGF-specific antibodies (Gabrilovich, et al. 1998). These initial findings were confirmed *in vivo* by administration of recombinant VEGF to tumor-free mice resulting in inhibited DC development and association with increased production of Gr-1^+ ImCs (Gabrilovich, et al. 1998). Furthermore, the stimulatory effect of Flt3L on DC production was also abrogated by VEGF (Ohm, et al. 1999). Consequently, in tumor-bearing mice the application of neutralizing

VEGF-antibodies resulted in improved DC differentiation and increased number of mDCs (Gabrilovich, et al. 1999,Ishida, et al. 1998). Assembled clinical data supported the important role of VEGF on the observed DC dysfunction: expression of VEGF inversely correlated with DC numbers in tumor tissue (Saito, et al. 1998) and peripheral blood (Almand, et al. 2000,Lissoni, et al. 2001) of cancer patients. Additionally, for patients with gastric cancer or non-small-cell lung cancer, DC differentiation was demonstrated to be negatively affected by VEGF (Fan, et al. 2003,Takahashi 2004). A recent report attributes the inhibitory effect of VEGF on DC to Flt-1 signaling. In the presence of VEGF during culture, DC from wild-type mice displayed an inhibition of antigen presentation capacity, which was not observed for DC from $Id1^{-/-}$ mice under the same experimental settings. Furthermore, addition of neutralizing anti-Flt-1 antibody abrogated the inhibitory effect of VEGF on wild-type DCs (Laxmanan, et al. 2005).

***IL-8* (CXCL8)—**IL-8 acts as a direct autocrine growth factor for malignant melanoma (Schadendorf, et al. 1993), liver and pancreatic tumors (Miyamoto, et al. 1998), and for colon carcinoma cells (Brew, et al. 2000). Interestingly, in ovarian cancer, the receptors for CXCL8, namely CXCR1/2, have been shown to cross-talk with the epidermal growth factor receptor (EGFR) (Venkatakrishnan, et al. 2000), which links this growth factor pathway with chemokines. Besides its function as a growth factor, IL-8 also exerts chemotactic activity on polymorphonuclear neutrophils (PMNs) (Baggiolini 1998), monocytes (Bonecchi, et al. 2000) and endothelial cells (Schraufstatter, et al. 2003). Both receptors for the CXC chemokine IL-8, CXCR1 and CXCR2, are expressed on monocyte derived DCs. IL-8 was recently reported to be produced by a variety of tumors (hepatocellular carcinoma, colorectal, and pancreatic cancer), which attracts monocyte derived DCs. This effect could be blocked by neutralizing antibodies and the authors suggested involvement of IL-8 in the retention of DCs inside malignant lesions and impairment of DC migration toward lymphoid tissue (Feijoo, et al. 2005).

IL-10—IL-10 plays important role in DC defects in cancer. DCs derived from transgenic mice with IL-10 overexpression have suppressed ability to stimulate allogeneic T-cell and CTL responses as well as IL-12 production (Sharma, et al. 1999). IL-10 might contribute to the conversion of iDC into tolerogenic APCs by decreasing the expression of co-stimulatory molecules (Steinbrink, et al. 1997). Treatment of human DC with IL-10 was found to induce suppression of antigen-specific proliferation of $CD4^+$ and $CD8^+$ T cells via cell-cell contact (Steinbrink, et al. 2002). Furthermore, the blockade of differentiation of monocytes to DCs could be attributed to IL-10, which drives the differentiation process towards a macrophage cell type rather than DC (Allavena, et al. 1998,Buelens, et al. 1997). IL-10 also inhibits the function of Langerhans cells (Beissert, et al. 1995,Enk, et al. 1993,Peguet-Navarro, et al. 1994), monocyte derived DCs, or $CD34^+$ progenitors (Caux, et al. 1994,Steinbrink, et al. 1997). A mouse tumor model revealed that tumor derived IL-10 was responsible for DC dysfunction *in vivo*. DC function was not affected in IL-10 deficient tumor bearing mice (Yang, et al. 2003). Even though different tumor cells might produce and release IL-10, the majority of IL-10 is probably produced by tumor-associated macrophages (TAM) with some contribution from tumor-infiltrating lymphocytes (Seo, et al. 2001,Sica, et al. 2000).

Gangliosides—Gangliosides are sialic-acid-containing glycosphingolipids that are implicated in the regulation of cellular proliferation and differentiation (Hakomori 2003). A broad range of different gangliosides have been detected in different tissues; including GD2, GD3, and GM3, which seem to be involved in tumor progression. In comparison to the corresponding normal tissues, an abnormal expression pattern of gangliosides was described for neuroblastoma, melanoma, leukemia, lymphoma, and breast tumors (Birkle, et al. 2003). Besides the surface expression on tumor cells gangliosides are also secreted and likely to

circulate in the peripheral blood. Tumor-derived gangliosides can inhibit the generation of DCs from mouse bone-marrow progenitors or from human $CD34^+$ precursors (Peguet-Navarro, et al. 2003,Shurin, et al. 2001).

***TGF*-β (transforming growth factor-β)—**Cytokines of the TGF-β family are essential factors in embryonic development and tissue repair. This family includes three types of TGF-β (β1, β2 and β3), inhibins and activins, as well as various bone morphogenetic proteins (BMPs) and mullerian inhibiting substance. Activin βA and TGF-β1 share functions in inflammatory reactions including tissue repair and suppression (Munz, et al. 1999,Rosendahl, et al. 2001). Both cytokines share SMAD2/3 and SMAD4 as intracellular signalling targets of their receptors (Itoh, et al. 2000). In an adoptive transfer model TGF-β revealed its capability of inducing T_{reg} by its ability to generate DCs that promote tolerance in a manner dependent on MHC class II molecules (Alard, et al. 2004). Specifically, generation of T_{reg} cells was attributed to immature DCs, and TGF-β prevents the maturation of DCs by maintaining a low expression of co-stimulatory molecules (Geissmann, et al. 1999,Roncarolo, et al. 2001).

2. Altered glycosylation pattern of tumor associated antigens

MUC1 was shown to transform monocyte derived DC into IL-10^{high} IL-12^{low} producing cells with limited capacity to induce T_H1 responses in T-cells. Furthermore, the DC lost the ability to fully mature and rendered T cells anergic or to become suppressor/regulatory cells (Monti, et al. 2004). Previously it was reported that O-glycosylation of MUC1 is responsible for preventing its proteolysis (Hanisch, et al. 2003) and escape of this molecule from processing and presentation (Hiltbold, et al. 2000). Recently, similar results were obtained with a recombinant produced MUC1, which was as strongly sialylated as that expressed by epithelial tumors. This recombinant MUC1 also induced high levels of IL-10 and low levels of IL-12 in monocyte derived DC as well as impaired their development. Furthermore, these DCs had a decreased ability to stimulate allogenic and autologous T cells (Rughetti, et al. 2005).

3. Reactive oxygen species

Reactive oxygen species (**ROS**) include superoxide, hydrogen peroxide (H_2O_2), hydroxyl radicals and a variety of their reaction products. Activation of NADPH oxidase, a multicomponent enzyme system which catalyses the NADPH-dependent reduction of oxygen to the superoxide anion (O_2^-), is the precursor of the other ROS. In resting cells, this multicomponent enzyme system is inactive, and its components are dispersed between the cytosol and the membranes. The flavocytochrome b558 component, which is composed of two subunits, gp91*phox* and p22*phox*, is located in the plasma membrane and in specific granules. The other components of the NADPH complex (p47*phox*, p67*phox*, p40*phox* and small G protein Rac2) are cytosol proteins. The activation triggers the phosphorylation of the p47*phox*, p67*phox* and p40*phox* cytosolic components and their translocation to the plasma membrane, where they interact with flavocytochrome b558 (Ago, et al. 1999,Babior 1999,Chanock, et al. 1994,Park, et al. 1992). Concomitantly, Rac2 is dissociated from its inhibitor, RhoGDI, and then interacts with flavocytochrome b558 to form a binding partner for p67*phox* (Bokoch, et al. 2002). The complete assembly of NADPH oxidase components is crucial for O_2^- production (Babior 2004).

While low levels of ROS are attributed to be important in proliferation of normal cells and regulation of cellular signaling (Burdon 1995), increased ROS were observed in cancer cells. The biological effects of ROS vary widely in different cells and include modulation of signaling pathways by directly altering the activity of protein kinases and protein phosphatases (PTPases) (Denu, et al. 1998,Monteiro, et al. 1996). Elevated ROS levels during tumor progression leads to constant activation of transcription factors (NFκB and AP-1). Furthermore, the accumulation of ROS in the tumor environment seems to have a strong impact on the development of immune

cells infiltrating the tumor tissue by creating a milieu of constant oxidative stress. It is known that oxidative stress triggers expression of Heme oxygenase-1 (HO-1). During the maturation of DC *in vitro,* expression of HO-1 drastically decreases. Whereas in human tissue the expression is only found in iDC but not in mDC (Chauveau, et al. 2005). Furthermore, the authors could show that chemical-induced oxidative stress inhibited LPS-induced phenotypic maturation and secretion of proinflammatory cytokines, resulting in the inhibition of alloreactive T-cell proliferation, although retaining the ability of these DC to produce IL-10 (Chauveau, et al. 2005). As recently reported, only balanced NF-κB and JNK/AP-1 activity is associated with prolonged DC survival. Low NF-κB and high JNK/AP-1 activity signals cell death in DCs (Kriehuber, et al. 2005). Moreover, this study showed that limiting ROS loads is a major NF-κB function that results in the control of JNK activity in DCs. A current study showed that hydrogen peroxide, at low concentrations, activated p38 but did not alter DC phenotype (Handley, et al. 2005). However, increased concentrations of hydrogen peroxide activated both p38 and JNK, leading to inhibition of tyrosine phosphatases by JNK in DC and induction of apoptosis. JNK inhibitors partially protected the DC from the proapoptotic effects, whereas hydrogen peroxide and LPS synergized in inducing JNK activation and DC apoptosis (Handley, et al. 2005).

Peroxynitrites ($ONOO^-$) are another category of ROS formed as a by-product of the reaction between O_2^- and NO. They represent an highly potent oxidizing agent that damages biological targets (Radi 2004,Schopfer, et al. 2003) and are able to cross membranes within or between cells faster than they decay (Denicola, et al. 1998). Peroxynitrites can therefore function as unusual intra- and intercellular messengers, because they can induce post-translational protein modifications including the nitration of tyrosine residues in proteins like transcription factors.

4. Indoleamine-2,3-deoxygenase

The expression of ***IDO*** (indoleamine-2,3-deoxygenase) in myeloid DC has been described for human as well as murine DC (Munn, et al. 2002). Appearance of IDO^+ DC could be demonstrated *in vivo* in breast tumor tissue as well as draining lymph nodes in patients with melanoma, breast, colon, lung and pancreas cancers (Mellor, et al. 2004b). Catabolism of tryptophan is catalyzed by IDO via oxidation. Tryptophan is essential for proliferation and differentiation of T cells and IDO^+ DC contribute to reduction of free environmental tryptophan. This may prevent the clonal expansion of T cells and promote T cell death by apoptosis, anergy, or immune deviation. In studies using immunohistochemistry to detect IDO protein expression *in vivo*, treatment with CTLA4–immunoglobulin fusion protein was found to upregulate the levels of immunoreactive IDO only by certain subsets of mouse APC in the spleen. This response was restricted mainly to cells in the $B220^+$ (plasmacytoid) and $CD8\alpha^+$ populations of splenic DCs (Mellor, et al. 2003). Studies with APC fractions that were isolated from mice exposed to CTLA4–immunoglobulin confirmed that IDO-dependent T cell suppression was confined to specific DC subsets that express these markers (Mellor, et al. 2004a). Further evaluation will be needed to clarify whether these results describe a single 'IDO-competent' population of cells that expresses both markers (that is, $B220^+$ $CD8\alpha^+$ DCs (O'Keeffe, et al. 2002)) or several different populations within the complex mixture of DC subtypes in the spleen. However, an important point is that many more cells express the target ligands for the CTLA4–immunoglobulin fusion protein than actually showed up-regulation of IDO expression. A detailed analysis of IDO-mediated T cell suppression in tumor-draining lymph nodes (Munn, et al. 2004b) showed that although a significant fraction of DCs expressed detectable levels of IDO protein by immunohistochemistry, the functional IDO-mediated suppression was mediated almost entirely by a small, well-defined $CD19^+$ subset among the $B220^+$ plasmacytoid DCs. Furthermore, in humans an IDO^+ DC subset could be detected, which also expressed CD123 and CCR6 (Munn, et al. 2002). Whether this particular DC phenotype is a specialized feature of tumor-draining lymph nodes or is a more general

phenomenon remains to be elucidated, but these data emphasize that the biologically relevant population of IDO-expressing DCs might be a minor subset. Even within the population of IDO-competent DCs there can be a considerable degree of functional plasticity. Certain pro-inflammatory signals might down-regulate the expression of IDO by cells that would normally express it (Grohmann, et al. 2003,Grohmann, et al. 2001). In contrast, different tolerogenic stimuli might induce IDO expression by different DC populations (Fallarino, et al. 2003,Grohmann, et al. 2003).

5. Stroma-mediated effects on DCs

Recently, it became obvious that the analysis of the tumor stroma is important to better understand tumor biology. At a certain stage of tumor progression, cancer cells start altering residing tissue cells and induce an inflammatory response in order to recruit stromal cells, which are required for tumor progression (Bissell, et al. 2001,Elenbaas, et al. 2001,Tlsty, et al. 2001,Wiseman, et al. 2002). The tumor stroma is a composition of those cell types necessary to built and sustain a tissue. It provides growth factors, blood supply, extracellular matrix, and removes waste and dead cells. The stroma can keep pre-malignant cells in check, and the phenotypically abnormal stroma can support tumor development. The latter point is illustrated by the recent demonstration that the loss of tumor growth factor-β responsiveness in fibroblasts resulted in epithelial neoplasia (Bhowmick, et al. 2004). The released factors also activate surrounding stromal cell types, such as fibroblasts, smooth-muscle cells (De Wever, et al. 2003), and adipocytes (Manabe, et al. 2003), leading to the secretion of additional growth factors and proteases. Concomitant with the altered growth-factor expression, and often induced by their autocrine effect on the tumor cells, cancer cells also start producing proteolytic enzymes (Mueller, et al. 2003,Stetler-Stevenson, et al. 2001), which remodel the extracellular matrix (ECM) and the basement membrane creating a pro-migratory and pro-invasive environment. In addition, degradation of ECM molecules exposes obscure protein domains and generates specific new molecule fragments that can have pro-migratory as well as pro- and anti-angiogenic functions (Kalluri 2003). The remodelled ECM contains matrix metalloproteinases (MMPs) (Brinckerhoff, et al. 2002), which activate cell-surface and ECM-bound growth factors (Egeblad, et al. 2002,McCawley, et al. 2001). These contribute to the extensive crosstalk between the microenvironment and the cancer cells. However, in benign and malignant tumor, no difference in the levels of protease expression was detected. Only when cultured in the presence of stromal fibroblasts did these features correlate with increased expression of MMP1 and MMP9. Interestingly, when co-cultured with stromal cells, only malignant, but not benign, tumor cells exhibited MMP1 and MMP9 production (Borchers, et al. 1997). Furthermore, transplantation of benign tumor cells to mice abolished MMP1 expression, whereas transplantation of tumor cells increased MMP1 expression. Tumor cells also induced production of interstitial collagenase by the host stroma, whereas benign cells did not (Airola, et al. 2001).

Because of these tremendous changes in the tumor stroma, it is conceivable that the stroma also exerts a negative effect on DC development. Recently, it was shown that spleen-derived stromal cells promote the selective development of lin^{-} $c\text{-}kit^{+}$ progenitor cells into $CD11c^{low}CD45RB^{+}$ regulatory DC, which primarily produce IL-10. These DC had the ability to suppress T cell responses and induce IL-10-producing regulatory T cells *in vitro* and antigen-specific tolerance *in vivo* (Svensson, et al. 2004). Furthermore, it could be demonstrated that contact with stromal cells promoted mature DCs to proliferate in a fibronectin-dependent way. Both stromal cell contact and stromal cell-derived transforming growth factor-β induced their differentiation into a new regulatory DC subset, whose *in vivo* counterpart could be identified in the spleen with similar phenotype and functions. These differentiated DCs secreted nitric oxide, which mediated the suppression of T cell proliferation in response to antigen presentation by mature DCs (Zhang, et al. 2004).

Molecular mechanism involved in DC dysfunction in cancer

Despite the wealth of information regarding various tumor-derived factors affecting DC differentiation, little is known about the molecular mechanisms responsible for DC dysfunction in cancer. One important family of proteins involved in the transition of the immature to mature stage of DC is the STAT family. A fundamental component of several signal-transduction pathways is the Janus activated kinase (JAK) family of tyrosine kinases and signal transducer and activator of transcription (STAT) proteins. These molecules are actively involved in cellular survival, proliferation, differentiation, and apoptosis. In mammals, four members of the JAK family are known (JAK1, JAK2, JAK3 and TYK2) (Rane, et al. 2000). Signal transduction by most of the factors implicated in defective DC function in cancer is mediated by JAKs. Receptor oligomerization induced by cytokine binding to its receptor triggers JAK activation by either auto- or transphosphorylation. The same set of JAKs can be activated by different cytokines though JAKs are not supreme determinants of the specificity of cytokine-mediated signalling (reviewed in Imada, et al. 2000). Subsequent to ligand binding, activated JAKs phosphorylate receptors on target tyrosine residues, generating docking sites for STATs through the STAT Src homology 2 (SH2) domain. Activated JAKs recruite and phosphorylate STATs, which leads to their dimerization and nuclear translocation, where they modulate the expression of target genes. The STAT transcription factor family is comprised of seven members (STAT1, -2, -3, -4, -5A, -5B and -6).

A number of cytokines involved in DC maturation transduce their extracellular signals to the nucleus through activated STAT proteins (Bromberg, et al. 2000,Darnell 1998) and the duration or intensity of the cytokine induced signal is under feedback regulation by a newly described eight-member family of intracellular proteins called suppressors of cytokine signaling (SOCS) (Naka, et al. 1999). SOCS proteins are characterized by the presence of an Src homology 2 domain and a C-terminal conserved domain called the SOCS box, and their inhibitory effects derives from direct interaction with JAKs, thereby preventing recruitment of STATs to the signaling complex (Naka, et al. 1999). SOCS proteins have recently been shown to modulate macrophage effector functions and negatively regulate LPS-induced macrophage activation (Baetz, et al. 2004,Berlato, et al. 2002,Kinjyo, et al. 2002,Nakagawa, et al. 2002), suggesting that they may also be involved in the regulation of DC differentiation and/or maturation.

In mouse DCs, STAT6 plays an important role in regulation of transition from the immature to mature stage. Activation of STAT6 signaling was not detected in freshly isolated precursor DCs (pDCs), while it was found to be constitutively expressed in iDC and its expression disappears in mDC accompanied by increased expression of SOCS1, SOCS2, SOCS3, and Src homology 2-containing protein (Jackson, et al. 2004). STAT6 expression as an early event of activation could also be demonstrated by immunohistochemistry in a subpopulation of human $CD1a^+$ DC in rheumatoid arthritis (Walker, et al. 2005). STAT5 was shown to be constitutively activated at all stages of DC maturation, whereas STAT1 and STAT6 pathways are preferentially used at different stages of DC differentiation and maturation (Jackson, et al. 2004). However, STAT1 activation was detected at all stages of DC development. The tyrosine phosphorylated STAT1 protein was detected mainly in mDCs, implicating the requirement of a more robust STAT1 signaling pathway for functionally mature DCs. The complex function of STAT1 in DC development was explored by analyzing hematopoietic precursor cell (HPC) from STAT1 null mice differentiated into DC. Although STAT1 inhibits CD86 expression in cells at the pDC stage, its inhibitory effects were overridden in mDCs, presumably by maturation signals, such as LPS. In contrast, the STAT1 signaling pathway appears to have no effect on CD40 expression at the pDC stage, but is required for optimal expression of CD40 in mDCs. Contrary to the regulatory effects on CD86 and CD40 expression, STAT1 has no effect on MHC class II expression (Jackson, et al. 2004). Furthermore, STAT1 involvement

could be demonstrated in TLR mediated maturation of DC (Hoshino, et al. 2002). Activation of human PDC by CpG was impaired by p38 mitogen-activated protein kinase (MAPK) inhibitor. In the presence of p38 inhibitor, the STAT1 phosphorylation of Y701 as well as S727 in activated PDC disappeared (Takauji, et al. 2002). However, up regulation of SOCS did not affect signaling of STAT1 suggesting that STAT6 and STAT1 are individually regulated during DC maturation (Jackson, et al. 2004).

In vivo, another critical factor for the regulation of DC maturation seems to be IL-6, because IL-6 knockout (KO) mice displayed increased amounts of mDC. Furthermore, IL-6 treatment of DC was shown to abrogate the LPS maturation of DC, which was mediated by its STAT3 activation. Additionally, STAT3 was required for the IL-6-mediated suppression of bone marrow-derived DC activation and/or maturation Thus the IL-6-gp130-STAT3 axis may represent an important regulatory component in DC activation/maturation mechanism (Park, et al. 2004).

Further evidence for the importance of the STAT3 to STAT1 switch on DC maturation was shown by *in vitro* experiments where overexpression of STAT3 through viral transfection of DC resulted in less IL-2 production by T cells/DC co-cultures (Cheng, et al. 2003). Interestingly, even the development of immature myeloid cells (ImC) into DC seems to be coupled to the transition of STAT3 levels to a more prominent STAT1 milieu. As it was shown *in vitro*, factors released by tumor cells strongly induce JAK2/STAT3 activation in ImC, which prevented their transition into DC. This blocking effect of the tumor supernatant could be reverted by adding antibodies against tumor-derived factors (Nefedova, et al. 2004).

Summary

Unfortunately, tumors are very effective in evading immune responses. One of the major mechanisms limiting immune recognition is suppression of immune responses. Further insights into the role of dendritic cells during the effector phase of the immune response and the complex interplay of stromal, immune, and tumor cells in the tumor microenvironment represent the future challenges to be conquered in tumor immunology. Gained knowledge in these areas may help to find new drugs to selectively block suppressive pathways and restore the original function of DC. Although the DC system is highly heterogeneous, the differentiation and function of DC populations is largely regulated by exogenous factors. A possible approch to overcome the tumor induced malfunction of DC may be to “override“ the tumor induced signals by a more prominant danger signal such as pathogen derived factors or peptides including CpG, bacterial cell wall component, or viral compounds to actively strenghten the immune response, an area for future research.

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