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Dendritic cell defects in the colorectal cancer

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Abbreviations: CRC, Colorectal cancer; GM-CSF, granulocyte macrophage colony stimulating factor; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; DCs, dendritic cells; mDCs, myeloid dendritic cells; pDCs, plasmacytoid dendritic cells; DCregs, regulatory DCs; TIDCs, tumor-infiltrating DCs; NK, natural killer; MHC, major histocompatibility complex; PAMP, pathogen-associated molecular pattern; PRRs, pattern recognition receptors; TLR, toll-like receptor; Th, T helper; HNSCC, head and neck squamous cell carcinoma; APC, antigen presenting cells; TDLNs, draining lymph nodes; MDSCs, myeloid-derived suppressor cells; HMGB, high mobility group box; CTLA-4, anticytotoxic T-lymphocyte antigen 4; PD-1, programmed death 1

Colorectal cancer (CRC) results from the accumulation of both genetic and epigenetic alterations of the genome. However, also the formation of an inflammatory milieu plays a pivotal role in tumor development and progression. Dendritic cells (DCs) play a relevant role in tumor by exerting differential pro-tumorigenic and anti-tumorigenic functions, depending on the local milieu. Quantitative and functional impairments of DCs have been widely observed in several types of cancer, including CRC, representing a tumor-escape mechanism employed by cancer cells to elude host immunosurveillance.

Understanding the interactions between DCs and tumors is important for comprehending the mechanisms of tumor immune surveillance and escape, and provides novel approaches to therapy of cancer. This review summarizes updated information on the role of the DCs in colon cancer development and/or progression.

Introduction

Colorectal cancer (CRC) is one of the most common malignancies encountered in the population living a Western life style with over one million new cases diagnosed worldwide annually.[1-3] Rates of this cancer increase with industrialization and urbanization. CRC has been much more common in high income countries but it is now increasing in middle and low-income countries.[4]

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In Europe around 250,000 new colon cases are diagnosed each year, accounting for around 9% of all the malignancies.[4] Although surgical resection of the primary tumor is the first choice therapy worldwide, an effective approach for the treatment of metastasis and relapses has not been found yet.[2]

It is now widely accepted that cancer is a multi-step process resulting from the accumulation of both genetic and epigenetic alterations of the genome.[3,5,6] Growing lines of evidence suggest that accumulation of genetic and epigenetic alterations in malignant colonic cells progresses through at least 3 distinct pathways: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP).[7] In addition to cancer genome abnormalities, also the formation of an inflammatory milieu plays a pivotal role in tumor development and progression.[7-9]

In fact, the changes occurring in the tumor microenvironment during cancer progression resemble the process associated with chronic inflammation.[10,11] The primary role of the inflammatory response is to restrain and eliminate harmful body aggressors; such is the case of transformed cancer cells and the subsequent recruitment of antitumor immune cells to the cancer occurring tissue.[10,11] Thus, the tumor microenvironment is composed not only by tumor cells, but also by stromal and inflammatory cells that are recruited and/or locally induced to proliferate or differentiate by tumor cells or by normal cells "educated" by tumor cells. They communicate both directly through cell-cell contact and indirectly through paracrine signals.[12] These signals are predominantly constituted by cytokines and chemokines, key orchestrators of leukocytes trafficking under homeostatic conditions as well as during inflammation and cancer.[13-16]

The cellular component of the inflammatory microenvironment in the tumor includes the presence of host immune cells comprising monocytes/macrophages, dendritic cells (DCs), mast cells, neutrophils, natural killer cells, and T cells.[11,17-19] All these cells are differentially distributed within the tumor, reflecting the diversity in tumor biology and tumor-host interactions.[20]

The interactions between tumor cells and DCs are complex and have yet to be fully elucidated. Understanding the interactions between DCs and tumors is important for comprehending the mechanisms of tumor immune surveillance and escape and provides novel approaches to therapy of cancer.

This review summarizes updated information on the role of the DCs in colon cancer development and/or progression.

Biology of Dendritic Cells

Over the last few years several studies have focused on dendritic cells, the major antigen-presenting cells, which play a pivotal role in the induction of anti-tumor cytotoxic immune responses and further link the adaptive and innate immune systems.[21]

Characterization of DC populations in humans is challenging due to their low numbers in circulation (less than 1% of blood mononuclear cells) and limited availability of healthy tissues as opposed to animal models.[16]

Most findings of DC ontogenesis occurred about 20 y ago when the culture conditions to efficiently generate *ex vivo* large numbers of dendritic cells from mouse bone marrow were identified. Four years later, the corresponding DC production method from human monocytes was published, using a combination of granulocyte macrophage colony stimulating factor (GM-CSF) and interleukin (IL)-4.[22-25]

However, whether these observations reflect the in vivo characteristics of peripheral DCs is debatable. Moreover, the lack of DC specific markers has meant previous flow cytometric analysis relied on negative selection using a large panel of antibodies to remove lineage-specific cell populations.[26]

Peripheral blood dendritic cells comprise a heterogeneous group of cell types derived from haematopoietic precursors. They are frequently classified in 2 broad groups according to their lineage, myeloid dendritic cells (mDCs), often referred as conventional DCs, and plasmacytoid dendritic cells (pDCs),[22,25] and identified on the basis of different phenotypic markers and immunological activity.[27-29]

The characterization of pDC lineage has presented a considerable challenge, as pDC display molecular markers and features of several cell types and can be derived from multiple progenitors. Nevertheless, recent advances have firmly established their common developmental origin and genetic relationship with the dendritic cell lineage.[30] The pDCs originate in the bone marrow, from both myeloid and lymphoid precursors, although myeloid derivation is predominant, where a dendritic cell progenitor gives rise to both pDCs and classical mDCs.[31-33] The developmental pathways of DCs are summarized in **Figure 1**. **Figure 2** illustrates the immunophenotypic and functional hallmarks of blood DCs.

The mDCs express CD11c marker and require GM-CSF for growth and functions such as antigen uptake, T-cell activation and cytokine secretion (IL-6, IL-12 and IL-18). Recently, it has been demonstrated that the mDC subset can be further divided in CD1c+ and CD141+, which show a high level of similarity in protein expression and have also specific functions in the initiation of adaptive immune responses.[34] CD1c+ mDCs have been shown to readily stimulate naïve CD4+ T cells and to secrete high amounts of IL-12 in response to toll-like receptor (TLR) ligation, whereas CD141+ DCs do not secrete much IL-12 but they are well equipped to take up dead and necrotic cells for subsequent cross-presentation of derived antigens to CD8+ T cells.[34-36]

The pDCs express CD123 marker, depend on IL-3 for survival and produce high levels of interferon (IFN)-α,[37,38] reflecting their important function in anti-viral immune responses.[34,35,39] The released type I IFN by activated pDCs is a pleiotropic cytokine with not only antiviral properties, but it has also been reported to be important for pDC survival, mDC differentiation, mDC-mediated CD4+ and CD8+ T cell-responses, cross presentation, up regulation of co-stimulatory MHC molecules and activation of natural killer (NK), and B cells.[34,40-42] Furthermore it has been shown recently that IFN-α possesses also antitumoral activities against several types of cancers, both hematological and solid tumors, by affecting tumor cell survival, proliferation and spreading.[43] In addition to type I IFN, pDCs produce other cytokines, including TNF-α, IL-6, and CXCL8,[44,45] and inflammatory chemokines such as CXCL9, CXCL10, CCL3, CCL4,and CCL5.[33,46,47]

The mDC and pDC populations are in close contact *in vivo* at steady state as well as under inflammatory conditions, and it has been suggested that they act synergistically to induce more potent immuneresponses.[34,48,49]

DCs in their immature stage are ubiquitously distributed in all peripheral tissues, with a role of sentinels specialized in the uptake and processing of antigen. Upon detection of danger through their pathogen-associated molecular pattern (PAMP) receptors, they mature and migrate to the draining lymph nodes where they present antigens to T cells, generating an antigen-specific response by adaptive immune system.[29,50] Both mDCs and pDCs function as APCs following a similar maturation program: they lose immature characteristics, such as phagocytic activity, and acquire several phenotypic and functional features typical of mature DCs, including expression of the co-stimulatory markers CD40, CD80, CD83, and CD86 and the major histocompatibility complex (MHC) class I and II to interact with T cells.[29,34,51] However, there are complementary differences especially in the expression of pattern recognition receptors (PRRs) and thus in their response to pathogenic triggers.[34] For example, the toll-like receptor (TLR) family is differently expressed in mDCs and pDCs, being TLR7 and 9 selectively expressed in pDCs, and TLR1–6, 8, 10 in mDCs.[29,52,53] Both mDC and pDC cells are effective T cell-stimulators.[54] They direct the nature of T helper (Th) responses (Th1, Th2, Th17, Treg). It has been demonstrated that mDC cells primarily induce Th1 differentiation, whereas pDC cells mainly promote a Th2 response.[53,55]

DCs initiate immune responses in a manner that depends on signals they receive from pathogens, surrounding cells and their products.[34,56,57] In early studies it was believed that DCs were exclusively immunogenic, actively initiating or up-regulating immune responses.[53] More recent reports demonstrated that a

perturbation of the homeostatic condition can trigger either an immunogenic (immunostimulatory) or a tolerogenic (immunosuppressive) response, depending on the local circumstances and type of disease.[34,53,58] By default, immature pDCs are tolerogenic, whereas activated (mature) pDCs can have both immunogenic and tolerogenic capacities depending on the local environment in which they are activated.[34,59,60]

Recently new immune regulatory properties of DCs have been identified, so as they are defined regulatory DCs (DCregs). They show a weak capability to activate effector T cells, whereas they induce Treg lymphocytes proliferation and autoreactive T-cells anergy in order to promote immune tolerance.[61-63] Under physiological status, DCregs play a pivotal role in terminating inflammatory responses, but it has been shown that also immunogenic DCs can be directed toward the regulatory phenotype by several pathological conditions.[63] These findings suggest that DCregs are not a defined DC subset, but rather a functional state that can be acquired by several DC subsets. Over the past years molecules associated with the regulatory function of DCs have been identified, such as CD25, IL-10, TGF-β, IDO and PGE2, but molecular mechanisms involved in DCreg reprogramming are not fully understood.[63]

Clinical observations showed that DCs possess the ability to migrate directly to a neoplastic site and that the presence of tumor-infiltrating DCs (TIDCs) is associated with the delay of tumor progression and lymphonode metastasis in a variety of solid tumors; particularly the maturation state of DCs represents a potential clinical prognostic factor.[58,64-66] Although our views on the potential role of DCs in cancer have expanded remarkably, it is still not fully understood why DCs are unable to induce an efficient immune response. Therefore, understanding the functions of DCs in the tumor microenvironment might represent a rich field of investigation.[21]

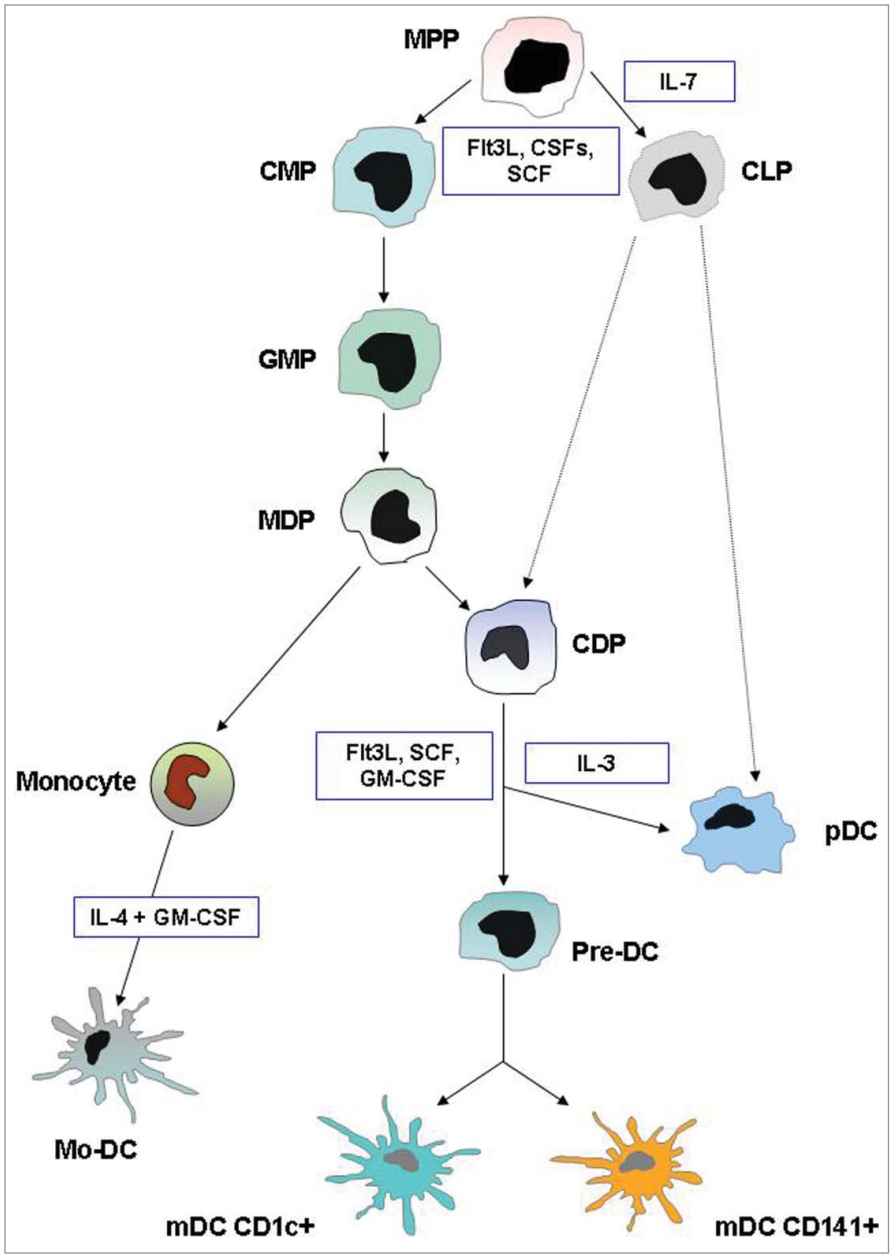

Figure 1. DC development. This illustration summarizes the current model of the developmental pathways of both myeloid and plasmacytoid DCs. Dashed lines indicate pathways that are likely but not yet definitively shown to operate in DC development. In humans, equivalents of mouse MDP, CDP, and pre-DC have not been found. Cytokines that are important in each transition are indicated. Abbreviations: MPP, multi potential progenitor; CMP, common myeloid progenitor; CLP, common lymphoid progenitor; MDP, macrophage DC progenitor; CDP, common DC progenitor; pre-DC, circulating DC progenitor; pDC, plasmacytoid DC; mDC, myeloid DC; Mo-DC, monocyte-derived DC.

Dendritic Cells in The Cancer Microenvironment

Quantitative and functional impairments of circulating DCs have been widely observed in several types of cancer,[38,67-72] and these represent a tumor-escape mechanism employed by cancer cells to elude host immunosurveillance (**Fig. 3**).[73,74]

Decreased numbers of mature DCs have been demonstrated in the circulation, tumor bed, and draining lymph nodes, in multiple tumor models.[75]

In vivo, blood DC numbers have been reported to be altered during the course of various types of hematologic malignancies,

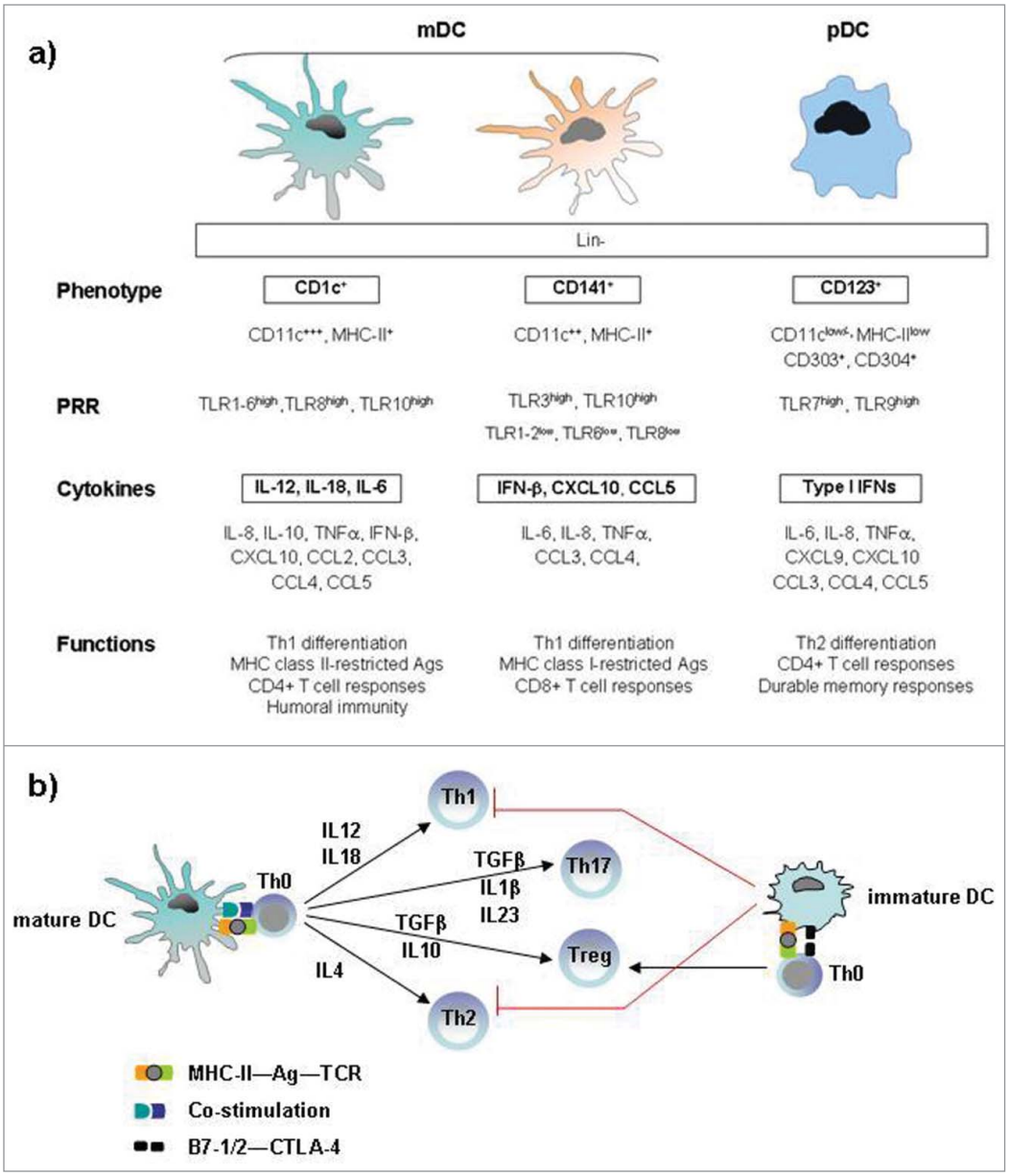

Figure 2. Immunophenotypic and functional hallmarks of DC subsets in blood and lymphoid tissue. (**A**) Both mDC and pDC cells are effective T-cell stimulators and direct the nature of Th responses, although mDC cells primarily induce Th1 differentiation, whereas pDC cells mainly promote a Th2 response. The archetypical antigen/cytokine of each subset is marked in bold. (**B**) Key cytokines involved in the DC-mediated polarization of naïve T cells into different T-cell subsets. Mature dendritic cells polarize naive Th0 cells into different Th effector cells through several signals: antigen presentation to the T-cell receptor, co-stimulatory signal and secretion of cytokines. Immature dendritic cells prime Th0 cells to make Treg cells. Abbreviations: pDC, plasmacytoid DC; mDC, myeloid DC; Lin, lineage markers; PRRs, pattern-recognition receptors; TLR, Toll like receptors Th, T helper cell; Treg, regulatory T cell; Ag, antigen, TCR, T-cell receptor; CTLA-4, cytotoxic T-lymphocyte antigen 4.

in patients with advanced solid tumors such as head and neck squamous cell carcinoma (HNSCC) and in patients with metastatic disease associated with breast cancer and colorectal, gastric, pulmonary, cervical, endometrial and renal cell carcinoma.[28,67-72,75-77] The studies analyzing circulating DCs in melanoma patients have reported conflicting data.[28,78-80] In a recent study[28] we detected a significant decrease of circulating DCs in melanoma patients, compared to healthy volunteers. This reduction mainly affected pDCs and was ascribable only to the more advanced stage of disease.[28]

DC subset analysis in patients with breast cancer and HNSCC has revealed that decreases in cell numbers are confined to DCs of the myeloid lineage, in comparison with those of the plasmacytoid or lymphoid lineage.[75,81] Minimal DCs are recruited to the tumor bed in patients with renal and prostate cancer, presenting low levels of costimulatory molecules and a decreased capacity to stimulate allogeneic T-cell proliferation.[75,82,83]

The majority of studies have described soluble factors derived from both tumors and associated cells within the tumor microenvironment that interfere with DC differentiation from precursors, thereby contributing to a loss of stimulatory APC activity in tumor-bearing hosts.[84] Tumor-associated DCs show decreased uptake, processing and presentation of antigens, lowered expression of costimulatory signal, inefficient motility and migration toward specific chemokines, suppressed endocytic potential and decreased production of IL-12.[58,76,85-88]

Regardless of the mechanism of inhibition, the loss of APC function associated with suppressing DC differentiation may significantly limit the induction of anti-tumor immune responses and greatly contribute to tumor immune escape.[84]

A variety of tumor-derived factors that disrupt DC maturation and function have been identified.[75] Among cytokines, IL-10 plays important role in DC defects.[53] It irreversibly blocks the monocyte-to-DC differentiation, driving the differentiation process toward the macrophage lineage and impair the potent APC

function of DC.[53,68,89] Beckebaum *et al.*[90] indicated that increased serum levels of IL-10 correlated with numerical deficiency and immature phenotype of circulating DC in patients with hepatocellular carcinoma.[68,90] IL-6 and M-CSF have been shown to block the differentiation of CD34+ progenitors into DCs and instead trigger their commitment toward CD14+ monocytes that express little to no MHC and costimulatory molecules and that fail to induce allogenic T cell proliferation in mixed leukocyte reaction (MLR) assays.[68,84,91,92]

Similar inhibition of CD34+ precursor cell differentiation into DC has been attributed to tumor-derived VEGF.[84,93] Moreover, elevated levels of VEGF associate with increased number of immature APC with a suppressive phenotype in the circulation of cancer patients.[68] Transforming growth factor (TGF)-β, produced by progressor tumors, has been demonstrated to immobilize dendritic cells within these tumors and inhibit DC migration from tumors to their draining lymph nodes (TDLNs), faciliting metastasis in the affected nodes.[94]

In addition to secreting cytokines, tumors may also secrete other factors, including gangliosides, prostanoids, and polyamines, that have been demonstrated to affect DC differentiation from progenitors, both in vitro and in vivo.[53,68] The gangliosides GD2 and GM3 secreted by human and murine neuroblastoma cell lines have been shown to inhibit differentiation of DC from CD34+ progenitors;[95] the gangliosides GM3 and GD3, secreted by human melanomas, have been demonstrated inhibit DC differentiation from monocytic precursors.[96]

Using both the in vitro and ex-vivo models, Esche *et al.*[97] reported that tumor-derived factors could induce apoptosis in murine and human DCs, and acceleration of DC turnover.[58,97,98] Among the above mentioned tumor-derived factors, gangliosides are also known as inducers of DC apoptosis at any step of DC differentiation in a dose-dependent fashion.[68,99]

In addition to the inhibitory effects of tumor-derived and tumor-associated factors on DC differentiation that preclude the development of cells with APC function, these factors can also promote the recruitment and accumulation of functionally deficient and frequently immature DCs.

It has been demonstrated that certain subsets of immature DCs fail to provide an appropriate costimulatory and cytokine signals to T cells, so tolerance or anergy may develop.[58,68] This might induce tolerance through abortive proliferation or anergy of antigen-specific CD4+ and CD8+ T cells in vivo or through the generation of regulatory T cells that prevent immune responses by producing IL-10 and TGF-β.[58,68,100,101]

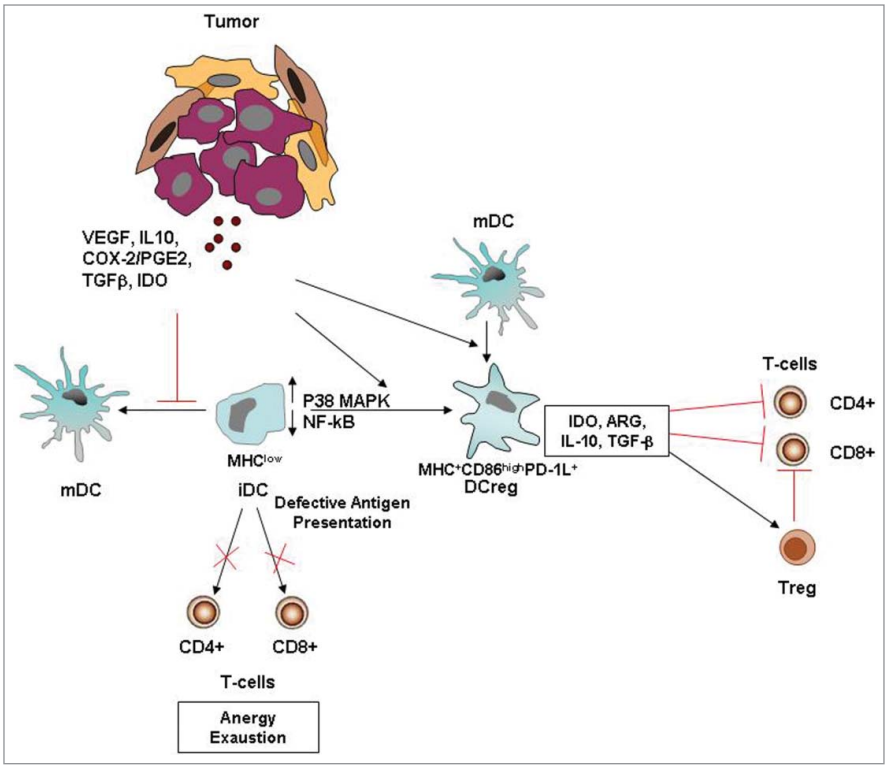

Figure 3. Tumor-altered DC function. Tumor-secreted factors can inhibit DC maturation. Immature DCs, displaying low NF-kB activation, low MHC class II and co-stimulatory molecule expression, are defective antigen presenting cells and induce T cell anergy and exhaustion. Tumor-derived factors can also induce the development of immunosuppressive regulatory DCs, which suppress T cell function through multiple mechanisms. More informations regarding the mechanisms by which tumors alter DC function and suppress host anti-tumor immunity are illustrated in the review of Hargadon.[84] Abbreviations: iDC, immature DC; MDC, mature DC; Reg DC, regulatory DC; Treg, regulatory T cell; PD-1L, programmed death 1 ligand.

The impairment of the differentiation program of DC precursors, can promote also the accumulation of an other subset of cells with immunosuppressive function, i.e. the myeloid-derived suppressor cells (MDSCs). These cells have been detected in various types of cancer, recovered at high levels from both tumors and tumor-draining lymph nodes and found to be associated with a poor prognosis and resistance to therapies.[28,102-105] MDSCs are arrested in an immature state and poorly differentiate along the DC or macrophage lineage even in the presence of cytokines or differentiating agents released by tumors and tumor-associated cells.[28,84,106,107] They are important immune regulators and play a key role in tumor-induced suppression of T-responses via multiple mechanisms.[28,102] It has been reported that they can induce a direct tolerization of anti-tumor T lymphocyte responses and also the development of Foxp^3+-regulatory T cells (Tregs).[84,103] In addition, it has been shown that MDSCs may also have indirect effects on T cells, by impeding the maturation and T-cell stimulatory capacity of DCs.[84,102] MDSCs also promote tumor progression by polarizing helper and cytotoxic T cells toward a type 2 response, through their cross-talk with macrophages by reducing IL-12 macrophage production and by increasing MDSC production of IL-10.[108,109] The type 2 responses are less robust in their anti-tumor efficacy.[84]

Tumors not only suppress DC maturation but they can also induce the development of DCs with regulatory function, that actively display immunosuppressive activity themselves.[84] In fact, it has recently demonstrated that the ovarian carcinoma progression is controlled by phenotypic changes in dendritic cells.[110]

Recently, several studies have shown a wide heterogeneity within DCs with regulatory properties, depending on the signals they receive from the microenvironment and on the immunological response they build up toward them. However they all share some characteristics in common, that are both modulating and inhibiting T-cell activation and inducing Treg proliferation and activity.[63] The high degree of plasticity of DCs toward the environmental milieu can determine a complete re-polarization of even fully mature DCs toward a tolerogenic phenotype.[58]

Moreover, it has been reported that high pDC infiltration can be observed in many types of cancer including melanoma, head and neck cancer, ovarian and prostate cancer, and these infiltrates mostly negatively correlate with patient survival.[34,48] pDCs have been documented also in tumor draining, whereas no data are available for pDCs in distant tumor metastasis.[48] These pDCs infiltrated in tumor microenvironment are mainly immature, and therefore seem to be predominantly immunosuppressive/tolerogenic.[34,43]

Conclusively, DCs play a relevant role both in the tumor microenvironment and systemic circulation, exerting differential pro-tumorigenic and anti-tumorigenic functions, which might be due to the plasticity of these cells capable of reacting to and integrating environmental signals.[63]

Dendritic Cells in Colorectal Cancer

Colorectal cancer has long been considered scarcely immunogenic, but several findings have shown that anti-tumor immune responses might occur in patients.[111,112] Similar to other malignancies, CRC antigens evoke DC recruitment, maturation, and cytokine release in order to generate effective Th1-type immune response.[65,113] However, CRC cancer cells use diverse strategies to inhibit the local tumor-specific immunity in order to escape attack and prolong cell survival resulting in an immune dysfunction in the tumor microenvironment.[113,114] The mechanism of colorectal cancer immune evasion is multifactorial and involves also defects of dendritic cells.

The infiltration rate and the local distribution of DCs in CRC tissue have been largely investigated.[65,111,115-117] It was reported that metastasis and tumor stage related with the infiltrating degree of DCs in the tumor tissue.[65,118]

Recently, Gulubova *et al.*[65] evaluated the association between the presence and maturation status of tumor-infiltrating DCs in different tumor compartments, with some clinical and pathological variables of the patients with colon cancer. They showed that patients with locally advanced tumors (T3–T4) had significantly lower infiltration with CD83+-matured DCs in tumor stroma, and in the invasive margin. The frequency of distant metastases was significantly associated with lower infiltration with CD1a-positive immature DCs in tumor stroma and lower infiltration with CD83-positive DCs in invasive margin.[65]

According with some previous observations,[114,119,120] it has been suggested that this apparent distribution pattern in tumor stroma of CRC might represent a moving of mature DCs from tumor nests to the peripheral lymph nodes for antigen presentation.[65]

The number of tumor infiltrating dendritic cells (TIDCs) in patients with colorectal cancer, as well as in other malignancies, was negatively correlated with lymph node metastasis, size of tumor, and survival time.[65,115,119]

The findings concerning DC's numbers correlated to patients' survival are controversial, sometimes being quite contradictory.[65,115,119,121]

Dadabayev *et al.*[119] found that the correlation between the degree of tumor infiltration of DCs and the prognosis depends on the level of maturation of these cells. In fact, only high intraepithelial infiltration with immature DCs tended to correlate with a longer disease-free survival, while the presence of mature (i.e., HLA-DR positive) DCs in the stroma showed an opposite effect on patient survival. Similar data have been reported also by Nagorsen *et al.*[115] Sandel *et al.*[121] showed that the number of immature DCs in the tumor did not affect the disease outcome; patients with a relatively higher number of mature (i.e., CD208-positive) infiltrating DCs in the tumor epithelium had a shorter overall survival and patients with higher numbers of immature (i.e., CD1a positive) DCs in the advancing margin of the tumor had a shorter disease-free survival.[65,121]

As discussed in the previous section, tumors can implement various mechanisms suppressing the activation of DCs in order to escape immune recognition and elimination. Altered immune cellular components and/or dysregulated cytokine levels might be present in the tumor microenvironment[122-124] and even in precancerous lesions such as colorectal adenoma.[114,125] Previous studies, reported decreased mature DC density in both human colon cancers and experimental rat colon cancer models.[114] Schwaab *et al.*[120] showed that the number of infiltrating mature DCs, in human primary colorectal cancer specimens, was 3 times lower than in normal colonic mucosa normal colonic mucosa and that DC density in metastases was fold6- lower than in colorectal primary tumors. The same Authors reported that the increase in the density of mature DCs was associated with the expression of VEGF.[120]

In addition to the density changes, multiple factors secreted by the tumor and at a systemic level can modulate also the function of tumor infiltrating DCs.[84,114,126] Recently, Michielsen *et al.*[127] found that tumor conditioned-media (TCM), obtained from cultured human colorectal tumor explant tissue, alters DC maturation and function. These Authors suggest that TCM components, such as CCL2, CXCL1, CXCL5 and VEGF may play a role in modulating the inflammatory response through inhibition of IL-12p70 secretion by DCs.[127,128]

It has been largely demonstrated that upregulation of COX-2, that is currently recognized as an important target for the prevention of CRC,[129,130] is associated to increased risk of CRC.[114,126,131] Yuan *et al.*[114] show that the DC infiltration

pattern is altered along the adenoma-carcinoma sequence and that the COX-2 increase might contribute to the functional defect of DCs in CRC. One potential mechanism evocated about the role of COX-2 in the CRC promotion is the inhibition of host anti-tumor immunity by suppressing DC differentiation, maturation and function through the downstream signal molecule PGE2 and its receptors EP2/EP4.[114,132] Apoptosis represents a mechanism of DC elimination in the tumor environment.[58]

Ishida *et al.*[133] demonstrated that MUC2 mucins purified from the conditioned medium of a colorectal cancer cell line increased the number of apoptotic cells in human monocyte-derived DC cultures. These authors suggested that the interaction between mucins and Siglec-3 expressed on monocytes/DCs may be partially related to this process.[133]

Moreover, the most important member of the high mobility group box protein family, HMGB1, a multifunctional cytokine secreted by cancer cells, has a role in cancer progression, angiogenesis, invasion, metastasis development and in inducing apoptosis in macrophages and DCs.[58]

HMGB1 is able to inhibit apoptosis by different pathways;[134] its overexpression suppresses caspase-3 and caspase-9 activity, thus, inhibiting significant steps in apoptosis. In colorectal cancer, cytochrome apoptosis inhibitor protein 2 (c-IAP2) levels are related to HMGB1 expression.[134,135] Kusume *et al.*[136] demonstrated that CD205-positive intra-tumor DC number decrease in patients with colorectal cancer with HMGB1 overexpression and lymph node metastasis, suggesting that HMGB1 produced by colon cancer cells suppressed nodal DCs.[58,134,136]

The tumor-induced inhibition of dendritic cells and other cells of the immune system may occur in the tumor microenvironment as well as in the systemic circulation.[53,72,74,75] However, few studies have been performed on the expression of DCs in CRC patients at circulating levels.[2,72,137,138]

An early study of Huang *et al.*[137] demonstrated that circulating DC levels in patients with colorectal cancer were reduced to about 60% of control levels, and complete colorectal cancer removal restored circulating DC levels to the normal range. This significant reduction in the level of circulating DCs was associated with an increased infiltration of Langerhans cells into colorectal mucosa, and it was correlated with a significant increase in the serum level of TGFβ1.

Della Porta *et al.*[138] reported a numerical and functional impairment of peripheral blood DC compartment, related to the stage of the disease and to VEGF levels, suggesting a possible effect of this cytokine in the numerical and functional impairment of DCs in colorectal cancer patients.

Recently, we focused on the quantification of circulating dendritic cells in CRC patients, categorized according to the stage of disease, at both pre- and post-operative time points.[72] In line with the above results, we found a significant reduction of the DC number in total and advanced stage-CRC patients compared to healthy controls. This significant reduction was totally recovered after complete tumor resection, suggesting a systemic immunosuppressive effect exerted by the tumor toward circulating DCs. Interestingly, the analysis of DC subset behavior revealed that the reduction in DCs was primarily due to changes in pDCs population.[72]

Concerning DC subsets, Bellik *et al.*[2] reported that both mDCs and pDCs in CRC patients, with and without metastasis, were significantly reduced compared to healthy subjects. However, they showed that the numbers of both DC subsets were significantly higher in metastatic than in patients without metastasis. Differences between our study and Bellik's one may be attributable to the different methodological approach used, because they isolated PBMCs before the flow cytometric DC counting.[72]

The observed decrease of circulating DCs may have functional consequences on the production of cytokines and on antigen presentation to T cells. However, data about the phenotype and function of circulating DCs in cancer patients, especially about the pDC subset, are still very limited.[48]

Interestingly, in our experimental approach we chose a DC gating strategy based on the expression of CD85 k, a DC antigen related to immunosuppressive and tolerogenic functions.[72,139] In the same study we showed that CD85 k expression on myeloid DCs was significantly higher in CRC patients compared with controls. This result suggested a more immunosuppressive nature of the myeloid DC subtype in cancer subjects that may contribute to affect the host immune reaction against the tumor.[72]

Several in vitro experiments have also demonstrated impairments of DC differentiation from CD14+ monocyte precursors, and of DC maturation in cancer patients; both mechanisms lead to dysfunctional DCs that cannot present antigens, thus inducing tolerogenicity.[111,140-142] However, these studies showed that there are differences in the quality of the monocyte-derived DCs dependent on the type of cancer, and that, in general, monocytes from cancer patients are less susceptible to cytokine stimulation compared to monocytes from healthy donors.[143] Conversely, few studies have been performed on the abilities of CRC patients to generate DCs from circulating monocytes.[2,98,111,144]

Recently, we showed an impaired *in vitro* differentiation of CRC patients' monocytes into immature DCs, compared to healthy subjects.[111] Furthermore, the cultured cells were characterized by persistent CD14 expression and higher endocytic activity, reduced ability to present antigens to allogenic T lymphocytes and to stimulate proliferation, together with a significantly altered co-stimulatory molecule expression compared to controls. Accordingly, we observed a markedly immunosuppressive cytokine profile in the patient DCs, characterized by increased IL-10, and reduced IL-12 and TNF-α secretion.[111] These results were in agreement with those of Michielsen *et al*,[127] which showed that CRC-conditioned medium negatively influenced DC maturation and IL-12 secretion, while augmented IL-10 secretion. Moreover, these negative effects exerted by the tumor on DC generation and maturation appeared correlate with the disease stage.[111]

Bellik *et al.*[2] reported an impaired developmental capacity of DCs from monocytes of both surgically-resected and CRC-bearing patients compared with healthy subjects. Furthermore, they showed that chemotherapy significantly affected both circulating

DC numbers and monocyte-derived DCs. Kvistborg *et al.*[143] observed that the maturation status of the monocyte-derived DCs correlated with the clinical status of the patients, but however resulting phenotypically and functionally superior to *in vivo* DCs in the same cancer patients. Thus the authors suggested that monocyte-derived DCs are good candidates for adjuvant cell-based cancer vaccine protocols, after an accurate selection of the cancer patients, based on their immune status.[143]

Conclusion

This review focus on dendritic cells as they are central players at the interface of the innate and adaptive immunity and play important roles in the establishment and persistence of cancer-induced immunosuppression. During the priming phase of the anti-tumor response, occurring in lymph nodes, DC dysfunction is due to inability to cross-presentation and to inadequate expression of costimulatory ligands. During the effector phase, operating within tumor mass, DC dysfunction involves: inadequate recruitment of activated effector T cells, presence of dominant immune inhibitory mechanisms capable of abrogating T cell effector function (e.g. the inhibitory receptors such as anti-cytotoxic T-lymphocyte antigen 4, CTLA-4, and programmed death 1, PD-1), extrinsic suppressive cells (Tregs, myeloid-derived suppressor cells), metabolic inhibitors (IDO, arginase), and inhibitory cytokines (IL-10, TGF-β).[145]

These data suggest that there could be potential biomarkers for checkpoint blockade therapy in cancer. Current preclinical studies are combining checkpoint blockade with tyrosine kinase inhibitors, radiation therapy and cancer vaccines (**Fig. 4**).[145]

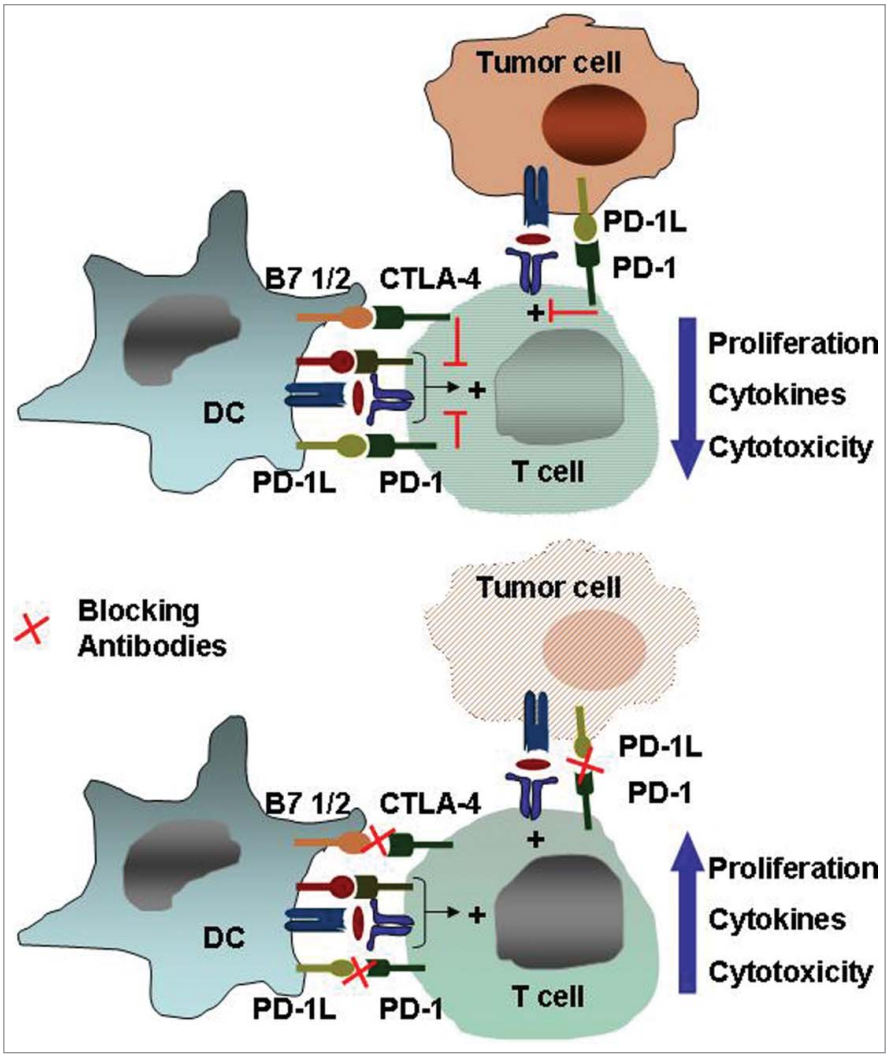

Figure 4. The immune checkpoints CTLA-4 and PD-1/PD-L1. Inhibitory receptors such as anti-cytotoxic T-lymphocyte antigen 4 and programmed death 1 expressed on tumor-specific T cells lead to compromised activation and suppressed effector functions such as proliferation, cytokine secretion, and tumor cell lysis. Modulating these receptors using monoclonal antibodies, an approach termed "immune checkpoint blockade," has gained momentum as a new approach in cancer immunotherapy. Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed death 1.

In the CRC, surgical resection is the primary treatment and is potentially curative. However, a significant proportion of patients present with disseminated disease and over half of all patients develop recurrence and die of their disease following surgery.[146] Thus, in the management of colorectal cancer alternative therapeutic strategies, such as the application of immunotherapy, are clearly needed.

The fully human anti–PD-1 mAb BMS-936558/MDX-1106/ONO-4538 (nivolumab), has demonstrated antitumor activity in phase 1/1 b studies in CRC, as well renal cell cancer, melanoma and non-small cell lung cancer. The humanized anti–PD-1 antibody MK-3945 (lambrolizumab) has also demonstrated antitumor activity in patients with advanced solid cancers, including CRC, in a phase 1 study.[145,147]

Dendritic cells are considered as promising candidates in cancer vaccines of CRC patients, to generate host immune responses against tumor antigens, and encouraging results have been obtained.[114] However, in spite of available information, many clinical protocols utilizing DC-based vaccines do not consider the fact that DCs administered in patients with cancer might quickly lose their activity in the cancer environment.[58] The existence of functionally defective DC in cancer patients strongly emphasizes the rationale of developing DC-based immune therapy to restore proper presentation of tumor associated antigens and T cell activation.[143] In fact, taking account of pivotal role of pDCs in ensuring an immune response, by strong IFN-α release and direct cell-cell interactions, Tel *et al.*[39] demonstrated that anti-cancer

immune responses may be initiated or boosted by vaccination with autologous tumor antigen loaded pDCs.[34,39]

Additionally, the DC-Treg interactions, by enhancing tumor-induced immunosuppression, represent a major barrier to successful immunotherapy. Targeting the generation of these 2 suppressive cell populations would be a desiderable goal in chemo- and immunotherapeutic approaches. Therefore, to achieve this objective there is a need to further improve strategies to simultaneously promote the full activation of DC using selective adjuvants such as TLR ligands or cytokines and impair Treg expansion, function and recruitment.[148]

The presence of TLR ligands as adjuvant in the vaccine strategy has the potential to increase the efficacy of immunization toward a given antigen. TLR activation strategies have been used in both established and experimental vaccines for infectious or non-infectious diseases, as well as for cancer treatment.[149] In a recent work, Fang et al,[149] demonstrate that danger-associated molecular patterns, released from chemically (oxaliplatin and/or 5-fluorouracil) stressed CRC cells, can induce mouse and human DC activation and maturation via TLR4 and enhance the induction of an anti-tumor T-cell immune response both in vitro and in vivo. Recently, the results of Gao et al,[150] indicate that DC vaccine combined with killer cells, generated ex-vivo by cytokines (IL-2, IL-1β, IFN-γ), may improve the disease-free survival in gastric and colorectal cancer.

In conclusion, the knowledge of the mechanisms, aimed to reverse the phenotype of DCs from an immunosuppressive to an immunostimulatory cell type, may be relevant to guide the design of more efficient protocols for cancer immunotherapy and to identify possible candidates for DC-based immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Author Contributions

All listed authors have reviewed and approved the final version of the manuscript. All authors contributed to the work presented in this paper.

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