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Dysfunction of Antigen Processing and Presentation by Dendritic Cells in Cancer

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Abstract

The ability to mount an effective anti-tumor immune response requires coordinate control of CD4 T cell and CD8 T cell function by antigen presenting cells (APCs). Unfortunately, tumors create an immunosuppressive microenvironment that helps protect tumor cells from immune recognition. In many cases this defect can be traced back to a failure of APCs (most importantly dendritic cells (DCs)) to recognize, process, and present tumor antigens to T cells. In this review, we will summarize work addressing the role of different DC subsets in anti-tumor immunity and the various mechanisms used by tumor cells to suppress the ability of APCs to stimulate potent anti-tumor T cell responses.

Keywords

antigen processing and presentation; cancer

1. Introduction

The immune system is composed of a variety of specialized cell types that fight not only pathogen-infected cells but also oncogenic cellular components. To initiate this fight, “foreign” antigens must first be recognized and presented to effector cells of immune system. Although endogenous antigens can be presented on major histocompatibility complexes (MHC) class I (MHC-I) by most nucleated cells, specific immune responses to endo- and exogenous antigens requires naïve T cell priming by APCs [1]. DCs are highly specialized “professional” APCs that link antigen-independent innate immunity *(microbe and danger sensing)* and antigen-specific adaptive immunity *(T cell and B cell priming)* [2]. While immunotherapies are now showing great promise in treating cancer patients [3], there is growing evidence that the efficacy of “traditional” therapeutic methods of radiation/chemotherapy largely depend on the host immune system [4, 5]. Whereas T cell priming by DCs is essential for the initial generation of antitumor T cells, it fails in more advance stages of cancer. This review will focus on the antigen presentation properties of DCs in the context of cancer and how the tumor microenvironment impairs antigen presentation, thereby

suppressing anti-tumor immune responses. For the purposes of this review “antigen processing and presentation” refers not only to the ability of an APC to process and present antigenic peptides to antigen-specific T cells, but also includes additional signals provided by the APC, which lead to an effective immune response.

2. DC subtypes in cancer

2.1. cDC1 and cDC2

Since their identification by Steinman and Cohn in 1973 [6], DC development and the capacity of DCs to present antigens to naïve T cells has been extensively investigated. DCs originate in bone marrow from macrophage/DC progenitors (MDP) [7] that give rise to common DC progenitors (CDP) that differentiate into two major categories: classical DCs (cDCs) and plasmacytoid DCs (pDCs) [8]. Murine cDCs consist of two subtypes currently described as cDC1 and cDC2 with their human counterparts being $BDCA3^+$ DC and $BDCA1^+$ DC, respectively [9]. These two subtypes of DC differ functionally and phenotypically. cDC1 specialize in presenting internalized antigens bound to MHC-I to CD8 T cells in a process termed cross-presentation [10]. These cells do not express CD11b and reside in both lymphoid tissues (as $CD8\alpha^+$ cDC1) and in non-lymphoid tissues (as $CD103^+$ cDC1) [11].

The differentiation of both $CD8\alpha^+$ and $CD103^+$ cDC1 subsets is driven by a common transcription factor Batf3 [12]. Both cDC1 subsets (as well as the human homologue of $CD8\alpha^+$ DCs [13]) are characterized by surface expression of the chemokine receptor XCR1 that has a unique ligand, XCL1. This chemokine is produced by CD8 T cells and the XCR1-XCL1 axis provides communication between cross-presenting DCs and antigen-specific CD8 T cells [13, 14]. The importance of cross-presenting cDC1 for anti-tumor immunity has been revealed by several groups. $CD103^+$ DCs can produce large amounts of IL-12 and are very efficient for antigen cross-presentation and crucial during initial priming of CD8 T cells [15–17]. Expression of CCR7 regulates the ability of $CD103^+$ DCs to migrate from the tumor environment to the draining lymph node (LN) where they initially prime naïve CD8 T cells [18]. Due in part to their low expression of lysosomal enzymes, $CD103^+$ DCs deliver intact tumor antigens to draining LNs [19, 20] and “hand off” tumor antigens to other DC subsets in LNs (including $CD8\alpha^+$ DCs) [18], further highlighting the importance of this DC subset in tumor immunity. Furthermore, tumor-resident $CD103^+$ DCs play a crucial role in recruiting CD8 effector T cells and CD4 T_H1 helper cells to the tumor site by the virtue of their production of the CXCR3 ligands CXCL9 and CXCL10 [21]. Since $CD103^+$ DCs seem to play a role both at the tumor site and in the tumor-draining LN, it has been suggested that $CD103^+$ DCs present in the tumor microenvironment migrate to the LN to prime naïve CD8 T cells, however some of these cells remain at the tumor side and secrete CXCR3 ligands to recruit T cells that were primed in the draining LN [22]. Not surprisingly, expansion of cross-presenting $CD103^+$ DCs in the tumor environment can stimulate anti-tumor immune responses [20] and higher numbers of these DCs in human tumors correlates with improved clinical outcome [23].

Unlike cDC1 cells, lymphoid tissue resident cDC2 express CD11b and these cells play a critical role in presenting internalized exogenous antigens bound to MHC class II (MHC-II)

to CD4 T cells [24]. cDC2 are the main APC subtype that prime naïve CD4 T cells in LNs [25], an essential first step in acquired immunity. The importance of these cells in anti-tumor responses has recently been highlighted in a study by Ma *et al*, in which neutralization of $CD11b^+$ DCs blocked chemotherapy-induced anti-tumor immunity [26].

2.2. inf-DC

Bipotent MDP also gives rise to monocytes that differentiate in peripheral tissues into a special DC subset called “inflammatory DCs” (inf-DC) [27, 28]. As their name implies, these cells are generated by inflammatory stimuli and are present in the tumor microenvironment. Inf-DCs induce T_H17 responses that are important not only in autoimmune/inflammatory disorders but also in the tumor-associated immune environment, making them a target of interest in the context of cancer therapy [28, 29]. In addition to promoting antigen-specific CD4 T cell responses, inf-DCs are also able to cross-present antigens to CD8 T cells and their presence has a positive impact on treatment success [30]. In a recent study of adoptive T cell therapy, a novel subset of inf-DCs, termed TIP-DCs, was shown to produce large amounts of TNF-α and nitric oxide (NO), factors that promoted anti-tumor T cell expansion [31].

2.3. pDC

A second major subset of DCs that differentiates from CDP are pDCs. This relatively small cell population specializes in production of type I interferon (IFN) and participates in antiviral immune responses, but these cells can also secrete IL-12, IL-6, TNF-α and other pro-inflammatory cytokines [32, 33]. pDCs are present in the tumor environment as well as in tumor-draining LNs. Although less efficient than cDC as APCs, pDC can present antigens to T cells [34], however their role in cancer is thought to be tolerogenic [35] and high tumor infiltration by pDC is associated with poor prognosis [36]. Through production of the tryptophan-depleting enzyme indoleamine 2,3-dioxygenase (IDO), pDCs contribute to the generation of immunosuppressive regulatory T cells (Tregs) in the cancer environment and in tumor-draining LNs [37, 38]. pDCs can also stimulate Treg generation by their expression of ICOS-L [36, 39]. Unfortunately, ICOS-L and OX40L-expressing pDCs promote tumor-supporting T_H2 responses in melanoma patients [40], revealing a deleterious role for pDCs in the host response to tumor cells.

Surprisingly, pDCs have been reported to have the capacity to promote antitumor responses. Activation of pDCs with the TLR7 agonist imiquimod (used for the treatment of skin tumors) results in their expression of TRAIL and acquisition of cytotoxic activity against tumor cells *in vitro* [41]. A similar finding was shown in a mouse model of melanoma, demonstrating that the cytolytic potential of pDCs in eradicating tumor cells can be independent of adaptive immunity [42]. pDCs can also present melanoma-derived antigens to CD8 T cells and indirectly support anti-tumor responses through type I IFN secretion [43, 44]. It is worth noting that adoptive transfer of tumor-antigen loaded pDCs has been reported to induce anti-tumor T cell responses in patients suffering from melanoma [45], revealing a potent role for this DC subtype in controlling cancer. Given the apparent contradictory role that pDCs play in anti-tumor immune responses, additional studies must be performed to fully understand the importance of this DC subset in modulating anti-tumor immunity.

3. Tumor-antigen processing and presentation by DCs

For immunotherapy to be effective, tumors must be immunogenic, meaning that tumor-associated antigens (TAAs) must be recognized and processed by APCs to stimulate anti-tumor T cell responses. Studies in mouse models of cancer showed that tumor-antigen presentation, particularly by DCs, is essential for induction of anti-tumor immunity [46, 47]. Anti-tumor immune responses are induced in three consecutive steps: a) tumor-antigen processing and presentation, b) priming of tumor-antigen specific T cells by APCs, and c) eradication of tumor cells by effector T cells at the tumor site [48]. Failure of any of these steps suppresses anti-tumor immune responses, and therefore there is intense interest in understanding these processes both under normal and pathophysiological conditions. Different subsets of DCs (summarized above) are equipped to induce different types of T cell responses. In addition, the location and ability to capture tumor antigens also regulates antigen processing by DCs and subsequent T cell responses.

Antigens associated with neoplastic cells are processed and presented as complexes with MHC molecules on the surface of both APCs and transformed cells themselves. Tumor antigens presented by APCs are essential to prime antigen-specific T cells that subsequently recognize MHC-peptide complexes on target neoplastic cells [49]. Cell-associated antigens at the tumor site are captured by tissue-resident DCs that can either present them to T cells *in situ*, or after migration of the DCs through afferent lymphatics, in tumor-draining LNs [50]. Necrotic or apoptotic tumor cells, or even fragments of tumor cells, are engulfed by DCs by phagocytosis. Phagosomes fuse with lysosomes to become phagolysosomes, compartments in which complexes of tumor antigen-derived peptides bind to MHC-II molecules [48]. Soluble tumor-associated antigens can also directly travel via lymphatic vessels to LNs for uptake by macropinocytosis by DCs, are processed into peptides, and presented by LN-resident DCs to either CD4 or CD8 T cells [25]. cDC2 cells are very efficient in generating pMHC-II from internalized foreign antigens, and this is essential for stimulation of naïve CD4 T cells. As mentioned previously, cDC1 are specially equipped with the machinery required to load internalized exogenous protein antigens on MHC-I for stimulation of CD8 T cells by cross-presentation [51]. This pathway also applies to presentation of antigens derived from apoptotic tumor cells that are engulfed by DCs [48]. Antigen cross-presentation by MHC-I is especially important in eradication of tumors as it induces CD8 T cells that differentiate into cytotoxic T lymphocytes (CTL) that recognize exogenous tumor-derived antigens.

4. Tumor-derived factors suppress DC maturation

A primary mechanism by which tumors escape the immune system is by suppressing antigen presentation [1]. Based on their distinction as “professional” APCs, DCs should be able to promote antitumor immunity. However, as cancer progresses, DCs fail to activate anti-tumor immunity and eventually immune suppression ensues. For antigen presentation to be efficient in stimulating anti-tumor T cell responses, several requirements must be met, including a) the appropriate type of DC acquire and process tumor antigens, b) efficient antigen processing and delivery of pMHC to the DC surface, c) and sufficient enhancement of DC costimulatory/homing molecules to ensure efficient T cell activation [52]. Malignant

cells can unfortunately impact DCs at each of these stages by a variety of mechanisms that either disable generation of tumor-associated antigen-specific T cells or promote immune cell tolerance to the tumor [53].

To induce potent T cell responses, antigen-MHC interactions with antigen-specific T cell receptors (TCR) must be accompanied by costimulatory signals provided by the binding of receptors on T cells (such as CD28) with complementary ligands on APCs (such as B7). Resting DCs express low amounts of costimulatory molecules on their surface, however DC activation enhances expression of costimulatory molecules [54]. DC activation can occur by recognition of “classical danger” signals [54] or “sterile/homeostatic danger” signals [55]. TCR stimulation by DCs in the absence of costimulation results either in T cell anergy or induction of Tregs, processes that play critical roles in the suppression of anti-tumor immunity [56–58]. T cell activation is also disrupted when the DC costimulatory molecule B7 interacts with the T cell inhibitory receptor CTLA-4 instead of the stimulatory receptor CD28 [59, 60]. In normal physiology, the B7/CTLA-4 inhibitory pathway is thought to protect from excessive T cell activation, however this pathway is exploited by tumors to escape detection by the immune system.

4.1. Inhibition of DC function by IL-6 and IL-10

An important mechanism of immune escape by tumors is by maintaining DCs in an immature state, thereby rendering these cells unable to stimulate an anti-tumor T cell response. The environment created by tumor-derived factors (including IL-6, IL-10, and VEGF) impairs DC maturation and ultimately their function as APCs. Tumor cells can interfere with the antigen presenting properties of DCs by secreting IL-10, a cytokine that inhibits DC maturation and their ability to secrete IL-12 [56]. IL-10 signaling has been reported to directly suppress DC activation by a variety of mechanisms [61]. IL-6 is also produced by tumor cells and other cell types present in the tumor microenvironment, and in cancer patients high serum level of IL-6 is usually correlated to poor disease outcome [62]. IL-6 is a proinflammatory cytokine that normally supports cell proliferation and inhibits apoptosis. While promoting survival of inflammatory cells is helpful for acute immune responses, dysregulated expression of IL-6 leads to chronic inflammation and oncogenesis [63]. Like IL-10, IL-6 has immunosuppressive effects on DCs including down-regulating expression of both MHC-II [64, 65] and the LN-homing receptor CCR7 [66]. Both IL-10 and IL-6 activate STAT3, a transcription factor that is activated in many types of cancer [67] and whose activation is linked to DC dysfunction [68]. Tumors induce autocrine secretion of IL-6 and IL-10 by DCs themselves, further contributing to immune suppression and revealing cell-intrinsic factors that reduce DC function in cancer [69]. Increased sensitivity to IL-6 and IL-10 is thought to be due to increased expression of IL-6 receptors and IL-10 receptors by activating TLR2 ligands [69], thereby enhancing STAT3 signaling and suppressing DC activation.

4.2. Generation of regulatory DCs by tumors

In addition to maintaining DCs in a non-functional “immature” state, tumors promote the generation of “mature” DCs possessing immunosuppressive instead of immunostimulatory properties. Regulatory DCs, a DC subset dependent on the transcription factor Satb1, are

activated not by pattern recognition receptor (PRR) ligands but are activated instead by inflammatory mediators such as IL-1β, TNF-α, type I IFN, and prostaglandin E2 [70]. Activation by these factors, or by ligation of membrane-bound CTLA-4 or CD200, can trigger the expression of the tryptophan catabolizing enzyme IDO in tumor-infiltrating DCs [71], thereby depleting this essential amino acid required for T cell proliferation [72]. Phenotypically mature DCs that inhibit anti-tumor T cell immunity can also be found in the tumor microenvironment and these cells suppress CD8 T cell function by depriving them of the essential amino acid L-arginine [73], however whether these cells are Satb1-dependent regulatory DCs remains to be determined.

4.3. T_H skewing alters anti-tumor CD8 CTL function

An additional mechanism used by tumors to subvert immune detection is by influencing the ability of DCs to skew T cell differentiation. Differentiation of naïve CD8 T cell into cytotoxic effector cells and differentiation of CD4 T cells into distinct subsets of T helper cells depends on cytokine signaling during antigen presentation. DCs producing large amounts of IL-12 preferentially induce T_H1 cells, low IL-12-producing DCs induce T_H2 responses [74], and secretion of TGF-β and IL-6 leads to the generation of T_H17 cells [75]. As mentioned previously, immature DCs presenting antigen to CD4 T cells in the absence of costimulation [76] or IDO- or ICOS-L-expressing pDCs [37, 39] can also guide differentiation of Tregs. By altering DC maturation and cytokine secretion, tumors are therefore able to interfere with T cell differentiation. The quality of T cells induced by DCs ultimately modulates the outcome of immune responses to cancer by either supporting tumor growth or anti-tumor immunity.

T_H1 T cells promote anti-tumor CD8 T cell responses by supporting their expansion into long-term memory cells [77, 78]. T_H17 cells are also recognized as potent anti-tumor cells due to their support of anti-tumor CTL-responses and recruitment of cross-priming DCs to tumor-draining LNs [79]. Unlike T_H1 and T_H17 cells, T_H2 cells actually promote tumor survival by cytokine-dependent suppression of T cell function or by induction of T cell anergy [50]. T cell differentiation towards T_H2 is enhanced by several factors present in the tumor microenvironment. For example, tumor-derived cytokine thymic stromal lymphopoietin (TSLP) upregulates expression of OX40L on DCs, thereby instructing them to generate CD4 T_H2 cells that produce the tumor-supporting cytokines IL-4 and IL-13 [80, 81]. These cytokines stimulate cancer cell growth both directly and indirectly (by attracting alternatively-activated macrophages that might contribute to angiogenesis) [80]. Tumor-infiltrating DCs modulate the T cell repertoire by their production of IL-6, IL-10, and galectin-1 [82]. As discussed in section 4.1, IL-6 and IL-10 impair the ability of DCs to mature, thereby suppressing DC secretion of IL-12 and leading to the generation of T_H2 responses. These immature DCs also promote the generation of pro-tumorigenic Tregs by a TGF-β-dependent mechanism [83]. Production of the immunosuppressive lectin galectin-1 by tumor infiltrating DCs also supports Treg generation and diminishes T_H1 and T_H17 T cell differentiation, also inhibiting anti-tumor immune responses [84].

5. Dysfunction in antigen presentation machinery in cancer

Tumor cell escape from immune surveillance is primarily based on disabling the process of tumor-antigen presentation. As discussed above, inhibition of DC activation by cytokines present in the tumor microenvironment profoundly reduces tumor-antigen processing and presentation. However, specific alterations of the molecular machinery controlling antigen processing and presentation in tumor cells themselves can also profoundly inhibit anti-tumor immunity. Antigen presentation in anti-tumor immunity is important at two distinct stages: firstly, when naïve T cells are primed by APCs presenting tumor-associated antigens and secondly, when primed cytotoxic effector T cells must find their target antigen presented by MHC-I on tumor cells themselves.

5.1. MHC-II-pathway

As mentioned above, a variety of tumor-derived factors (such as IL-6 and IL-10) impact the function of DCs in cancer but further studies are necessary to explain the mechanisms of these tumor-induced defects. Curiously, intracellular accumulation of lipids has been identified as one of the causes of DC dysfunction in cancer. Upregulation of the scavenger receptor Msr1 by unknown tumor-derived factors leads to increased uptake of extracellular lipids by DCs in the tumor-bearing host. Although their activation status appeared normal, high lipid-laden DCs did not efficiently present soluble protein antigens to antigen-specific CD4 T cells but presented preprocessed antigenic peptides normally, revealing defective MHC-II antigen processing ability in lipid-laden DCs [85]. Therefore, dysfunction of antigen processing caused by lipid accumulation could attribute to antigen presentation defects in immune responses to cancer.

MHC-II expression is controlled by the APC-specific regulator of transcription CIITA [86]. APCs such as B cells, DCs and macrophages can be targets of different types of malignancies. DC neoplasms are extremely rare tumors that include Langerhans cell (LC) histiocytosis, LC sarcoma, interdigitating DC sarcoma and follicular DC sarcoma [87]. We are unaware of any reports demonstrating defects in the antigen presentation properties of DC tumors. Unlike DC neoplasms, dysregulation of antigen presentation has been broadly defined for largely common B cell malignancies. In diffuse large B cell lymphoma, MHC-II expression is reduced by downregulation of CIITA [88] and by mutations within the *MHC-II* locus itself [89]. In addition to affecting overall MHC-II expression, there have been reports of dysregulation of peptide binding to MHC-II. MHC-II molecules are assembled in ER with invariant chain (Ii) and traffic to endocytic compartments [90]. In endo/lysosomes MHC-II-bound Ii is degraded and ultimately a small Ii-derived “CLIP” peptide is removed from the MHC-II peptide binding groove by HLA-DM [91, 92]. Malignant cells in Hodgkin’s B cell lymphoma have been shown to express large amounts of surface MHC-II still containing the Ii-associated CLIP peptide instead of antigenic peptides [93], suggesting that there is a failure of HLA-DM to remove CLIP from the MHC-II peptide binding groove in these cells.

A common feature of B cell lymphomas is increased activation of the oncogene c-myc. A recent study in Burkitt’s lymphoma cells correlated high levels of c-myc with poor antigen presentation to CD4 T cells [94]. This was reportedly due to alterations in HLA-DM-

catalyzed peptide loading onto MHC-II as well as altered expression of the IFN-γ-induced thiol reductase GILT in endo/lysosomal antigen processing compartments [94]. Aberrant MHC-II expression has also been reported in some non-lymphoid cancers [95], however expression of MHC-II in tumor cells themselves seems to actually support tumor eradication and is associated with relatively good prognosis.

5.2. MHC-I pathway

The immune system, especially in the early stages of cancer development, is still able to generate tumor-antigen specific CD8 T cells [96, 97], and therefore tumor cells must clearly use additional approaches to escape immune recognition. Like many viruses, tumor cells attempt to become “invisible” to the immune system by modifying the MHC-I antigen loading and presentation pathway [98]. Tumor cells at early stages of disease express MHC-I, but this is downregulated or lost as cancer progresses. The selective pressure of CD8 T cells on tumor cells themselves, as well as immunoediting by malignant cells, helps limit T cell attack of tumor cells [99, 100]. Tumors can also suppress the function of the proteasome, thereby reducing the supply of antigenic peptides for binding to MHC-I both quantitatively and qualitatively [101]. Downregulation of ER-resident aminopeptidases (ERAP) that shape the repertoire of MHC-I-binding peptides [102] and deficient expression of TAP in tumor cells have also been reported to limit tumor-antigen binding to MHC-I [103, 104]. Tumor-induced changes in the MHC-I machinery can be restored by incubation of tumor cells with cytokines such as IFN-γ, a known transcriptional regulator of the MHC-I peptide binding machinery [105]. Unlike IFN-γ, IL-10 expressed in the tumor microenvironment reduces TAP function on tumor cells [106, 107], thereby diminishing presentation of MHC-I-associated antigens. Whereas disruption of MHC-I function in tumor cells is a common way tumors attempt to subvert T cell recognition, we are not aware of dysregulation of MHC-I expression in DCs in the tumor microenvironment.

Curiously, tumor-derived IL-10 can subvert the immune system by promoting the expression of the non-classical MHC molecule HLA-G on tumor cells themselves [108]. HLA-G is normally expressed during pregnancy where it functions to protect the fetus from rejection by the maternal immune system [109]. Similarly, tumor cell expression of HLA-G induces tolerance when tumor cells interact with T cells or DCs that express ILT receptors, inhibitory receptors that recognize MHC-I [110]. Expression of HLA-G can also be induced on the surface of DCs by IDO, leading to the generation of DCs that promote the development of immunosuppressive CD4 T cells [111, 112].

6. Overcoming the antigen presentation defects for immunotherapy

In recent years, immunotherapy based on DC vaccines has complemented T cell-based cancer therapies. Many approaches of improving immunotherapies have focused on the priming phase of the anti-tumor immune response. For efficient T cell-priming, however, tumor-induced defects in DC function need to be remedied, regardless whether the vaccination strategy is based on *in vivo* or in *ex vivo* DC function.

It is important to consider the functional plasticity of DC subsets when considering DC-based therapies. For example, it would be advantageous to route antigens directly to the

MHC-I pathway to assure presentation to CD8 T cells [113]. Enhancing cDC1 cross-presentation could be accomplished by specifically recruiting Batf3^{+} DCs to the tumor environment (e.g. by blocking CSF-1 [17]), thereby stimulating endogenous T cell priming in tumors with poor T cell infiltration [21]. Another strategy to specifically target antigens to cross-presenting DCs *in situ* would be to take advantage of receptors such as DEC-205 [114], Clec10A [115], or other endocytic receptors specific for cross-presenting DCs such as XCR1 [13]. One caveat of specifically targeting the MHC-I pathway, however, is that CD4 T cell help could be required for the formation of immunological memory, and therefore stimulating CD8 T cells alone might be insufficient for anti-tumor immunity [113].

Defects in MHC-II-dependent antigen processing and presentation must be remedied to make cDC2 cells efficient stimulators of naïve CD4 T cells. To counteract DC dysfunction in initiating anti-tumor response, DC-based vaccines could be improved by manipulating pathways that are dysregulated in DCs in cancer and potentially include normalization of lipid levels by inhibiting fatty acid synthesis using an acetyl-CoA carboxylase inhibitor [85], by using IL-10R antagonists to restore IL-12 production by DCs [17, 116] or by TLR2 blockade with neutralizing antibodies to reduce the autocrine production of IL-6 and IL-10 by DCs [69].

7. Concluding remarks

Efficient immune-mediated elimination of tumor cells is a multi-dimensional problem. Whereas T cells are major effectors of anti-tumor immune responses, activation of both CD4 and CD8 T cells requires tumor antigen presentation by APCs (primarily DCs). Only by understanding the distinct roles different DC subsets play in anti-tumor immunity, how soluble factors present in the tumor microenvironment affect DC function, and how tumor cells can affect MHC-I and MHC-II antigen processing and presentation will be able to manipulate the tumor microenvironment in a way that will foster anti-tumor immunity.

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HIGHLIGHTS

- DCs are important regulators of CD4 T cell and CD8 T cell function
- Tumor-derived factors suppress the ability of DCs to fully mature
- Tumor-derived factors directly suppress the molecular machinery of antigen processing and presentation

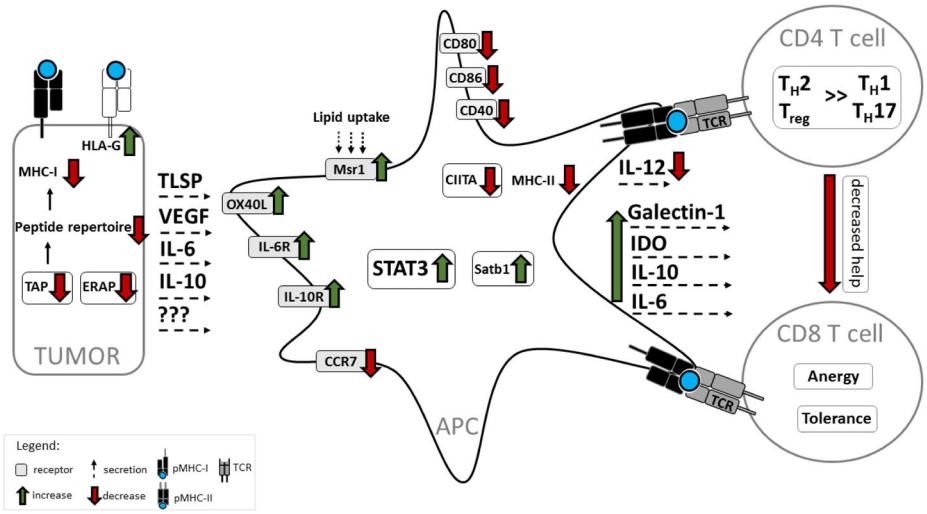

Figure 1. The impact of tumor-derived factors on antigen presentation by DCs

Immune escape by tumors is based on two main mechanisms. One mechanism is to directly become “invisible” to immune cells. Mutations in *MHC-I* and downregulation TAP or ERAP lead to reduced surface expression of peptide-loaded MHC-I. Tumor cells can also express the non-classical MHC molecule HLA-G that can lead to T cell tolerance. Another mechanism is by indirectly escaping immune surveillance by impacting APCs activation and function. Tumor-derived IL-6, IL-10, VEGF and other unidentified factors inhibit production of IL-12 and decrease expression of peptide-MHC-II, costimulatory molecules, and the LN homing receptor CCR7 on the DC surface. Tumor-derived IL-6 and IL-10 activate the transcription factor STAT3, which suppresses DC maturation and promotes DC dysfunction. These cytokines also induce autocrine production of IL-6 and IL-10 in DCs, which further augments STAT3 signaling. Tumor-derived TSLP upregulates OX40L, which, together with reduced expression of IL-12, promotes DC-based skewing of T cell differentiation towards the tumor-supporting T_H2 phenotype instead of the anti-tumor T_H1 or T_H17 phenotype that support CD8 T cell expansion. The tumor environment can also induce regulatory DCs, possibly by enhancing expression of the transcription factor Satb1. Tumors also promote Galectin-1, TGF-β, and IDO production in DCs, thereby leading to Treg generation. Finally, upregulation of the scavenger receptor Msr1 leads to enhanced lipid uptake and results in impaired antigen presentation by DCs. Additional defects in MHC-II expression, including downregulation of CIITA and impaired removal of the MHC-II CLIP peptide, have been observed in malignant B cells, however it remains to be determined if these changes also occur in DCs in the tumor microenvironment.