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Role of Myeloid Derived Hematopoietic Cells in Inflammation and Immune Tolerance to Cancer

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ABSTRACT

Tumor microenvironment is the collection of cells such as neutrophils, monocytes, lymphocytes, stromal fibroblasts, macrophages, smooth muscle cells and endothelial cells, all embedded in an extracellular matrix that fibroblasts produce. Myeloid derived cells in and around tumor help cancer cells survive, grow and spread to new locations where they seed metastasis. Cancer cells from growing tumors hijack mechanisms used by the normal tissues for wound repair such as the productions of growth and angiogenic factors, matrix metalloproteinases, fibroblasts, cells of myeloid lineage and chemokines to promote their survival and growth. Cells of myeloid lineage origin have a crucial role in malignant organ development by protecting the growing tumor mass from immune recognition hampering the immune rejection of cancer cells. Malignant tumors recruit cells of myeloid derivation to promote the growing tumor and its invasive abilities. Survival of patients with adenocarcinoma of the breast, colon, lung and prostate is inversely proportional to the number of infiltrating cells of myeloid derivation of tumors. Such malignancies are associated with shorter survival and detecting molecular signatures typical for macrophage infiltration such as CD68 in tumors herald poor diverse malignancies. There is two way editing of the growing malignancy and immune system of the affected patient: the malignant process shapes the immune system of the patient and at the same time the immune system of the patient shapes the growing tumor by selecting for the cancer cells resistant to immunodetection to survive and multiply.

Keywords: *Immune system, malignancy development, cancer, macrophages, dendritic cells, cancer outcome, T-regulatory cells*

Malignancies are immunoprivileged organs

Amongst the main actors in metastasis are cells of myeloid lineage such as macrophages, dendritic cells, myeloid suppressor cells and neutrophils. A cradle created by a heterogenous group of hematopoietic cells, fibroblast and stromal cells becomes an immuno-privileged site, the metastatic niche, favorable to the growth of cancer cells.

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The immune system employs cells and secreted factors to discriminate between self and non-self antigens allowing for immune mediated destruction of non-self antigens and tolerance to self.

The immune system is made up by cells of hematopoietic derivation and classically was described as having two arms: the innate immunity and the adaptive immunity with distinct cellular components and physiology [1].

The cellular components of the innate immunity include: neutrophils, monocytes, macrophages, dendritic cells (DC) and natural killer (NK) cells. The adaptive immune system consists of lymphocytes B-cells (CD8+ effector, CD4+ helper) and αβ T-cells.

Other cells function both in innate and adaptive immunity such

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as NK-T cells, regulatory T-cells ($CD4^+CD25^+FOXP3^+$), and γδ T-cells [1].

Type 1 Immune Responses are Required for Immune Surveillance, Recognition and Elimination of Tumor Cells

After appropriate activation dendritic cells become antigen presenting cells, potent stimulators of immune responses (type I immunity) recognizing cancer cells as non-self. (Figure 1) They polarize lymphocytes, neutrophils and macrophages to proinflammatory activities. Lymphocytes become effector cells (CD8+-Tcells), capable of recognition and destruction of tumor cells. Macrophages become M1 proinflammatory cells able to recruit other immune cells to the malignant site. Neutrophils acquire an anti-tumor N1 phenotype helping to recognize and kill tumor cells.
(Figure 1)

Type 1 immune responses require antigen presentation to occur in the presence additional signals. First signal is provided by the interaction between antigen specific signal linked to Major Histocompatibility Complex [MHC] and T-cell receptor [TCR] interaction. The second signal is provided by, the linkage of B7-1 (CD 80) or B7-2 (CD86) on the Antigen Presenting cell (dendritic and others APC) coupling with CD28 on the T-cell an antigen-independent signal and the third signal comes from the interaction of CD40L on APC to CD40 interaction. These interactions result in either CD8+ effector (cytotoxic) T-cells or Th1 CD4+ Helper T-cells maturing the immune response to tumor recognition and elimination. (Figure 1) [2].

CD8+ effector T-cells have a central role in active killing and elimination of the tumor cells, they recognize 8-10 amino acid long peptides buried in the antigen-presenting groove of the major histocompatibility complex class I molecules [3]. Activation of a naïve CD8+ T-cell into an effector is rapid occurring and less than 24 hours of antigen presence and less

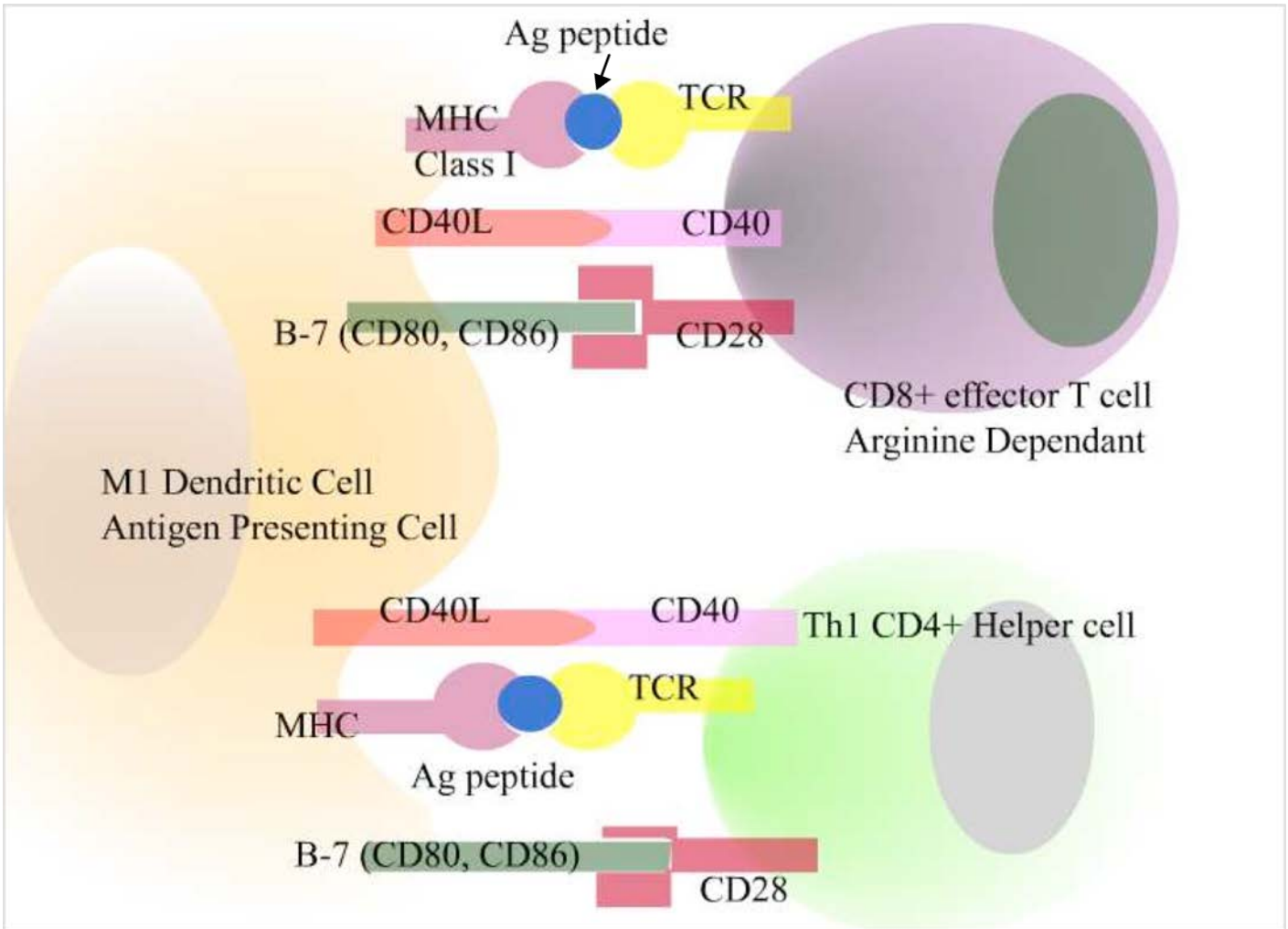

Figure 1: Type 1 immune responses require antigen presentation to occur in the presence additional signals. Ag peptide antigen peptide, TCR T-cell receptor: First signal is provided by the interaction between antigen specific signal linked to Major Histocompatibility Complex [MHC] and T-cell receptor [TCR] interaction. The second signal is provided by, the linkage of B7-1 (CD 80) or B7-2 (CD86) on the Antigen Presenting cell (dendritic and others APC) coupling with CD28 on the T-cell an antigen-independent signal and the third signal comes from the interaction of CD40L on APC to CD40 interaction. These interactions result in either CD8+ effector (cytotoxic) T-cells or Th1 CD4+ Helper T-cells maturing the immune response to tumor recognition and elimination [2].

than 24 hours antigen stimulation induces enough clonal expansion and differentiation of effector cells to elicit protective responses [4].

One key regulator of CD 8+ T-cells is the aminoacid arginine [5] needed for their normal replication and for the production or the zeta chain the principal signal-transduction element of the T-cell receptor (TCR) [6,7]. CD8+ T-cells proliferation and Th-1 responses requires the presence of essential amino acid tryptophan.

Blood monocytes are able to generate human dendritic cells: in the presence of macrophage colony stimulating factor M-CSF they generate macrophages while in the presence of GM-CSF and IL-4 and TNF-they produce DC1 that expresses CD14-CD38+CD68+ and surface major histocompatibility complex (MHC) II.

Microbial products, antigens from specific cancer cells (recognized as non-self) or interferon γ induce antigen presenting cells such as dendritic cells or macrophages to express an M1 phenotype, M1 macrophages promote activity of killer T-cells through their production of interleukin 12 (IL-12), high interleukin 23 (IL-23) and low interleukin 10 (IL-10). M1 macrophages interact with the T-helper 1 cells they produce major histocompatibility complex molecules rendering T-cells capable of killing pathogens and tumor cells [8]. In response to lipopolysaccharides (LPS) M1 macrophages produce reactive oxygen and nitrogen intermediates, interleukin 1 (IL-1), tumor necrosis factor α (TNFα) and thus function as the first line of defense against bacterial invasions [8,9] (Table 1).

Maturation of monocytes into M1 macrophages induces them to release IL-12 that in turn promotes activation of NK cells and optimal production of Interferon γ (INF-γ) [10]. Due to their differential expression of the MHC class I, especially HLA-E, immature dendritic cells are uniquely susceptible to NK-induced cell death, whereas mature dendritic cells are protected [11]. Cancer cells take a risk in trying to evade the immune attack through the loss of HLA molecules, cytotoxicity of natural killer cells is the greatest when target cells have lost their HLA molecules [12] (Table 1).

Type 2 Immune Responses the Immune Tolerance to Self

The immune system has developed several check-points to control for the potential destructive power of autoimmunity. For example newly formed lymphocytes are eliminated either in the bone marrow (B-cells) or in the thymus (T-cells) if they are strongly autoreactive. Antigens placed in the brain, anterior chamber of the eye, testis or fetus to not elicit type 1 immune responses making these immuno-privileged niches. The immuno-privilege arises from a specific interaction between cells, cytokines and other secreted factors of the immune system collectively called type-2 immune response.

Type-2 immune responses require at least 3 signals to occur between the antigen presenting cells (APC) and other cells of the immune system. First signal is provided by antigen specific signal linked to the Major Histocompatibility Complex [MHC] and T-cell receptor [TCR]. The second signal is an antigen-independent signals and involves linking of B7-1 (CD 80) or B7-2 (CD86) on the antigen presenting cells (APC) to Cytotoxic-T-Lymphocytes Associated Antigen (CTLA-4) or interaction with Programmed Death-1 (PD-1) receptor on T-cells. The last signal is provided by the CD40L on APC to CD40 interaction. These interactions result in production of maturation of the immune cells towards a self-tolerant phenotype. CD4 Th2 type T-cells (CD4+FOXP3+ Regulatory T-cells), M2 macrophages and N2 neutrophils [13,14] (Figure 2).

Type 2 immune responses also provide for wound healing and tissue remodeling during growth. Myeloid derived macrophages provide support for developing tissues because of their matrix remodeling abilities, synthesis of growth and angiogenic factors and engulfment of apoptotic cells. In-vivo multiphoton images showed that M2 macrophages aid the invasion of normal epithelial cells during duct development in normal breast and they also help the invasive edge of the mammary tumor [15].

Type 1 or Type 2 Immune Responses Depend on Local Growth Factors Stimulating the Immune Cells

Human monocytes, dendritic cells and other antigen presenting cells (APC) are plastic and their type 1 or Type 2 immune response depends on local conditions and cell stimulations.

During the type 1 immune response these cells produce IL-6 and TNF-a, express TLR-1, -2, -4, -5, -8 responding to microbial ligands, or express TLR-7, -9 and respond to bacterial CpG oligonucleotides. Each mature APC has a short lifespan in the uninfected individual and changes over after interacting with T-cells, B-cells and other cells of the immune system. The responses are not static but change, responding to the local conditions [16].

In the bone marrow common, monocytes progenitors give rise to antigen presenting dendritic cell (DC): either early DC progenitors (c-kit$^+$) with high proliferation potential precursors leading to macrophages or late DC progenitors CD11c$^+$ C-kit$^-$ with low proliferation potential with potential development into plasmacytoid (CD11c$^-$ CD45RA$^+$ CD123$^+$ blood DC antigen 2 [BDCA2]$^+$) and macrophages [17,18]. Macrophages are monocytes recruited from the circulation at the site of injury, inflammation, infection, or malignancy where they differentiate into scavenging cells Gr-1$^+$CD11b+ with inflammatory functions [19].

Polarization of immature dendritic cells to activated dendritic cells depends on the local factors. Dendritic cells may become activated dendritic cells producing IL-12 and helping in

maturation of Th1 cells to help eliminating non-self antigens or quiescent DC helping to induce tolerance to presented self antigens. Repeated stimulation of activated DC leads DC to produce IL-4, which has a type 2 an immunosuppressive effect (Table 1).

Activated dendritic cells are able to produce IL-12 when their CD40 binds CD40L expressed on CD4+ T-cells. IL-12 and the interaction between CD40L and CD40 expressed on B-cells and leads to B-cell proliferation, somatic hypermutation of the immunoglobulin heavy chain and allows for the expression of mature immunoglobulins.

After antigen recognition DC initiate a process, which results in up-regulation of antigen presenting molecules (MHC class I and II) and of co-stimulatory molecules (such as CD40, CD80 and CD86). This stimulates naïve T-cells to become effector cells and eliminate the pathogen or, alternatively in the absence of appropriate signals the DC induces tolerance for that antigen [20] (Figure 1 and 2).

Dendritic cells are derived either from monocyte lineage of from lymphoid lineage and are classified by their differential responses to toll-like receptors (TLR): signaling through TLR3, TLR4 and TLR8 occurs in monocytoid dendritic cells but not in plasmacytoid ones and signaling through TLR9 occurs in plasmacytoid DC exclusively [21].

The immature monocyte-derived and activated myeloid dendritic cells can become either M1 or M2 macrophages showing great plasticity until late in their differentiation [22]. The environment in which they differentiate determines their ultimate fate. IL-6 mediated maturation favors macrophage development [23,24] while tumor necrosis factor α (TNFα) exposure results in dendritic cells [25].

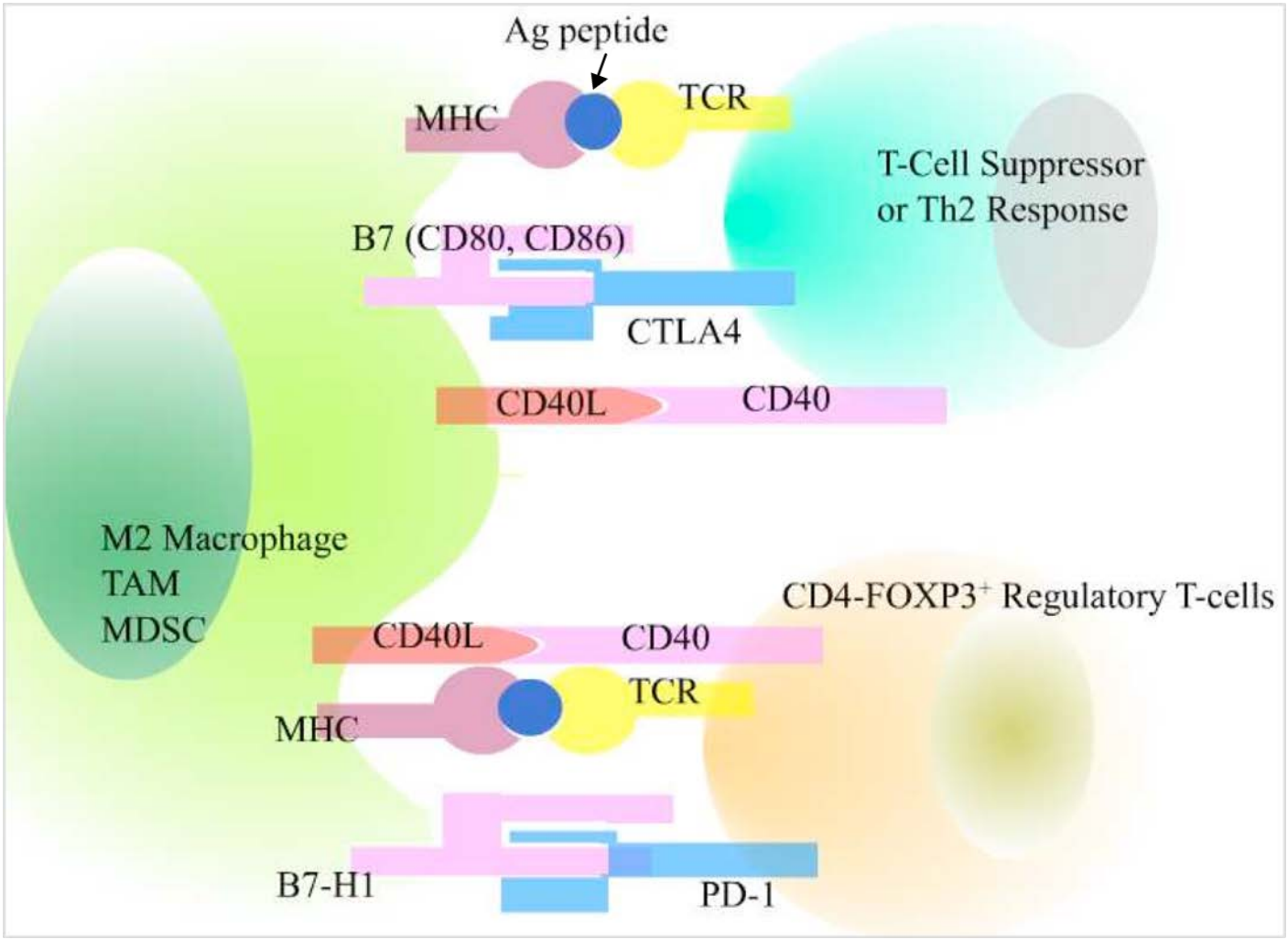

Figure 2: Type 2 immune responses requires at least 3 signals to occur between the antigen presenting cells (APC) and other cells of the immune system. First signal is provided by antigen specific signal linked to the Major Histocompatibility Complex [MHC] and T-cell receptor [TCR]. The second signal is an antigen-independent signals and involves linking of B7-1 (CD 80) or B7-2 (CD86) on the APC to Cytotoxic-T-Lymphocytes Associtated Antigen (CTLA-4) or interaction with Programmed Death-1 (PD-1) receptor on T-cells. The last signal is provided by the CD40L on APC to CD40 interaction. These interactions result in production of maturation of the immune cells towards a self-tolerant phenotype. CD4 Th2 type T-cells (CD4+FOXP3+ Regulatory T-cells), M2 macrophages and N2 neutrophils [13,14]. *Ag peptide- antigen peptide, TCR-T-cell receptor, PD-1-programmed death 1; TAM-tumor associated macrophages, MDSC-myeloid derived suppressor cell; MHC-major histocompatibility complex protein.*

M2 macrophages are called into action for tissue repair, remodeling and angiogenesis that customarily takes place after the bacterial infection resolves. M2 macrophages interact with T-helper 2 cells and stimulate the production of IL-4, IL-10 and IL-13, they moderate the inflammatory response, promote angiogenesis, tissue remodeling and clear cell debris and promote tumor formation as well as invasion [8,26,27].

M2 cells have high amounts of scavenger-type receptors. They are recruited into areas of hypoxic tissues or tumors via the hypoxia dependent up-regulation of the chemokine C-X-C motif receptor 4 (CXCR4) [28] where they promote angiogenesis [29]. After trauma and infection, M2 monocytes originating in spleen travel to affected sites and clean up the debris and foster tissue rebuilding [30].

Tumor Microenvironment and Metastatic Niche Foster Skewed Type 2 Immune Responses Allowing The Tumor To Develop in an "Immuno-Privileged" Niche

The growing malignancy exerts an immunosuppressive state with a shift towards a skewed type 2 immunity, cytokine production (important for antibody production), and away from type 1 immunity (associated with cell mediated immunity and tumor rejection).

Many factors are released from the malignant cells (collectively referred to as the tumor secretome) are shed from the tumor into the circulation can bind to monocytes and lymphocytes to induce cytokine release from these cells. Factors released by hemotopoietic cells associated with type 2 immunity are: IL-4, IL-10 and IL-14 cytokines. (Table 1) as well as indolamine 2,3 deoxygenase (IDO) and arginine (Figure 3).

In pancreatic cancer, the malignant cells secrete not only immunosuppressive factors such as transforming growth factor beta-1 (TGF-B1) but also VEGF, both factors known to attenuate type 1 immune responses [31].

In the tumors, monocytes are "educated" (i.e. polarized) to acquire a distinct phenotype (M2) and activated status becoming myeloid derived suppressor cells (MDSC) or tumor associated macrophages (TAMs) or, tumors therefore are "wounds that do not heal" [32,33]; after receiving such instructions TAMs down-regulated their major histocompatibility complex (MHC) class II and their ability to present antigen, decrease expression of IL-12 and increase their production of vascular endothelial growth factor (VEGF), cyclo-oxygenase-2 (COX-2) derived prostaglandin E2, arginase-1 (Arg-1), 2,3 indolamine deoxygenase IDO and IL-10 [33].

Tumor associated macrophages (TAMs) have been considered as mandatory helper cells for tumor-cell migration, invasion and metastasis. [34] In the macrophage deficient mouse with breast cancer, tumors developed normally but were unable to develop pulmonary metastasis in the absence of macrophages [35]. In this model metastasis occurred by interactions between tumor cells and TAM and paracrine growth factors: macrophage-colony stimulating factor and macrophage epidermal growth factor [35,36].

There are paracrine effects between malignant cells and monocytes. Cancer cells release chemoattractants such as CCL2, vascular endothelial growth factor and CXCL12 (SDF1) into the blood stream luring monocytes from the blood stream into the tumor microenvironment [37].

Myeloid-derived suppressor cells (MDSCs) are a population of immunosuppressive myeloid cellsmark edly increased in patients with head and neck cancer [38], breast [39], hepatocellular carcinoma [40] and renal cancers [41]. MDSCs circulate in higher numbers in patients with higher cancer stages [39]. MDSC share common characteristics: lack or reduced expression of markers of mature myeloid cells, expression of both Gr-1^{high} CD31+ and CD11b+ molecules [42], inability to differentiate into mature myeloid cells in the presence of tumor-derived factors, high levels of reactive oxygen species, and activation of arginase I [43]. Cancer patients especially head and neck, non-small cell lung cancer, pancreatic cancer, colon and breast cancer have three to five times more myeloid derived suppressor cells in circulation than normal controls [44-46].

MDSC from human cancer patients have high levels of arginase I that degrades the arginine, high levels of indolamine 2,3 deoxygenase (IDO) which depletes tumor microenvironment of the essential amino acid tryptophan and produce large amounts of nitric oxide synthase (NOS) another enzyme that degrades arginine impairs normal T-cell function [47] (Figure 3). Efforts to decrease the NOS synthesis retard cancer growth for example in mice with colon or mammary tumors experimental treatment with T-cells and sildenafil decreased production of arginase I and NOS from MDSCs and inhibited tumor growth more than the treatment with T-cells alone [38]. The immunosuppressive abilities of the MDSC translate into the inhibition of CD8 T-cell activity by the expression of NOS2 and Arg1 [48], the triggering of development of $CD4^{+}FOP3^{+}$ T-regulatory cells [49], and the induction of M2 differentiation of macrophages present in the tumor and circulation by releasing high levels of IL-10 [50].

Vascular endothelial growth factor (VEGF) released by the tumor cells promotes the accumulation of MDSCs by blocking signal 3 of antigen presenting cell maturation [51] (Figure 1 and 2).

MDSCs are known to produce VEGF further promoting tumor growth and their own formation. [52] Hypoxia dependent up-regulation of chemokine (C-X-C motif) receptor 4 (CXCR4) induces accumulation of these MDSCs in the hypoxic areas of the tumors promoting angiogenesis. [28,29] CXCR4-CXCL12 signals are implicated in trafficking of myeloid cells into tumors, inducing a skewed type 2 immune responses [53] that

Table 1: Inflammatory Mediators of Malignancy

Interleukins	Source	Function in Malignancy	Cellular Pathway	Reference
IL-1A, 1B	T, B, monocytes	Help carcinogenesis	IL-1R-TLR, NF-KB, STAT3	[80]
IL-2	T cells	Cytotoxic T-cell response	M1 Maturation	[32]
IL-3	CD4+ helper T-cells	Not defined	Stimulates hematopoietic cells	[81]
IL-4	T, Mast Cells	M2 differentiation, helps carcinogenesis	STAT-6	[82]
IL-5	T cells, Mast Cells	Help carcinogenesis in adult T-cell leukemia lymphoma	JAK2-STAT5	[61]
IL-6	Stroma Cancer Cells	Helps carcinogenesis	JAK-2 STAT3	[23]
IL-7	B-cells, intestinal cells, hepatocytes, stroma	Memory T-cells maintenance anti-cancer activities	STAT-5	[83,84]
IL-8	T-cell, B-cell, monocytes	Angiogenic factor, promotes M2 DC and malignancy, tumor neovascularization	NF-KB	[85]
IL-9	Tumor cells, stroma	Promotes tumor cell survival and proliferation	JAK1-STAT3/5	[86]
IL-10	B, T cells and monocytes	Help carcinogenesis, blocks Th1 T-cell cytokines	p38MAPK	[27]
IL-11	monocytes, mast cells, tumor cells	Help development of colitis associated malignancy	gp130 mediated STAT3	[87]
IL-12	M1 DC, TH-1 cells	Cytotoxic T-cell response, anticancer activity	STAT4	[8]
IL-13	NK-cells	Promotes malignant transformation in ulcerative colitis	STAT-6	[88]
IL-15	Hepatocytes, placenta, follicular dendritic cells	Memory T-cells maintenance anti-cancer activities	SMAD-3 TGF-beta	[89]
IL-16	Stroma, fibroblasts, monocytes	Promote TH1 CD4+ T-cell development and survival, anticancer activity	MAP kinase	[90]
IL-17	TH2 T-cells, NK cells	promote tumor cell survival and proliferation	IL-6/STAT3	[91]
IL-18	Monocytes	Cytotoxic T-cell response, anticancer activity	JAK3 p38MAPK	[92]
IL-20	Monocytes, T-cells	Anti-angiogenic, anticancer activity	WNT, PI3 pathway	[93]
IL-21	Activated T-lymphocytes	Anti-tumor activity	STAT3	[94]
IL-22	B, T cells and monocytes	helps carcinogenesis, blocks Th1 T-cell cytokines	STAT 3	[95]
IL-23	M1 DC, TH-1 cells	Promotes TH1 CD4+ T-cell development and survival, anticancer activity	STAT4	[8]

IL interleukin; TLR toll like receptor; STAT signal transduction and activator of translation; JAK Janus activated kinase; NF-KB nuclear factor KB; MAPK mitogen activated protein kinase; DC dendritic cells; NK natural killer cells [96].

increase tumor vascularization [54]and promote metastasis [55]. MDSCs produced VEGF secretion is an important factor the development of a vascular system by the growing tumor and depends on the enzyme matrix metalloproteinase-9 (MMP-9) [56].

A subgroup of bone marrow derived CD11b+ monocytes cells also expressing Carcioembryonic antigen (CEA) related-cell adhesion molecule-1 (CEACAM-1) are involved in resolution of inflammation by promoting the formation of the blood and lymphatic vessels [57]. Mice with a gene knockout for monocytes expression CEACAM-1 have prolonged inflammatory response and edema of the skin when exposed to cutaneous leishmaniasis and decreased angiogenesis and lymphangiogenesis. Transplanting bone marrow cells from normal mice corrected the wound healing process through reintroduction of CD11b+ CEACAM-1+ monocytes [57].

Efforts to manipulate the tumor secreted factors tend to improve immune recognition and elimination of malignant cells. For example, in mice with a homozygous null mutation of the gene that encodes the macrophage growth factor colony stimulating factor -1 (CSF-1) not only reduced the rate of tumor progression in a mouse model of breast cancer (induced by polyoma middle T oncoprotein) but completely ablates the metastasis [35].

The tumor microenvironment skews normal immune responses, the antigen presenting cells (dendritic cells or B-cells) a dysfunctional Th1. Common melanoma epitopes for example show low affinity for MHC-Tcell interaction and low co-stimulatory molecules (Figure 1) resulting in maturation of T-lymphocytes that ignores the common melanoma allowing for progression of metastatic disease [58-60]. The initiation of type 1 immune responses and recognition of abnormal melanoma cells occurs when the melanoma antigen is presented in the context of high affinity MHC-Tcell interaction or when antigen presenting cells express high levels of co-stimulatory molecules.

MDSC (CD11b+Gr1+ monocytes) have been implicated in tumor refractoriness to anti-VEGF therapies (Bevacizumab), [61] used in solid tumors [62]. In experimental mouse tumor models mixing anti-VEGF therapy sensitive tumors with MDSC (CD11b+Gr1+ cells) from refractory tumors resulted 60% greater new vessel formation compared with levels resulting from mixture with CD11b–Gr1–monocytes [62].

The molecular basis for tumor refractoriness to anti-VEGF therapies was elucidated with help from gene array analysis that identified genes differentially expressed in tumor microenvironment such as: G-CSF, and MCP-1, known to be involved in the mobilization of bone marrow–derived myeloid cells to the peripheral blood [63]; the number of circulating MDSC (expressing CD11b+Gr1+ cells) increase after implantation of tumor cells [64,65] and proinflammatory factors such as MIP-2 and IL-1R found to be highly expressed in tumors refractory to anti-VEGF therapies [66].

Support of Metastasis and Tumor Angiogenesis Originates and is Sustained by Cells of Hematopoietic Derivation

Tumor cells spread in the disease process to establish distant micrometastasis [67]. The micrometastatic disease may not always become successful macrometastatic disease unless a vascular supply develops to supply the metastatic niche. New blood vessels formation requires recruitment of circulating endothelial progenitor cells derived from the bone marrow [68-70]. A study of metastatic Lewis lung carcinoma and spontaneous mouse mammary tumor virus (MMTV) breast cancer found that more than 10% of the endothelial cells in the macrometastasis blood vessels were derived from bone marrow monocytes phenotypically CD31+, VGEFR2+ and Id1+ [71]. In the metastasis these cells provide not only structural (vessel incorporation) roles but also paracrine (instructive) roles initiating metastatic colonization [72]. When researchers reduced the Id1 expression on these monocyte progenitor cells their mobilization from the bone marrow decreased 96% and metastatic processed decreased proportionally, animals' survival improved providing direct evidence that minor manipulation in bone marrow monocyte differentiation leads to major impact in tumor progression [71].

The involvement of MDSC metastatic process and aberrant lymphangiogenesis in, development and progression of ascites places CD11b+ M2 and immature dendritic cells at the center of this process [73]. CD11b+ M2 and immature dendritic cells are able to differentiate into lymphatic endothelial cell [73], produce the lymphatic endothelial cell-specific growth factor VEGF-C and its tyrosin kinase receptor VEGFR-3 [74], express podoplanin, a membrane mucoprotein [75], and the CD-44 related hyaluronic acid receptor LYVE-1 [76].

In a mouse model generated by implantation of human ovarian cancer cell lines (MDAH-2774, SKOV-3, and OVCAR3) into athymic nude mice dysfunctional lymphangiogenesis, progressive chylous ascites formation and disseminated carcinomatosis were mediated by the bone marrow derived CD11b+ monocytes migrating to the tumor areas and producing vascular endothelial growth factors (VEGF-C, -D and -A) [77]. When injections of clodronate liposomes at 25 mg/kg every 3 days was used after tumor implantation to decrease the CD11b+ monocytes [78] apoptosis by 90%, the aberrant lymphatic formation in the mesentery was reduced by 80% [77].

In another mouse model generated by implantation of highly metastatic gastric carcinoma (OCUM-2MLN) cell line, Iwata and his colleagues demonstrated that the major source of vascularendothelial growth factor-C (VEGF-C) and VEGF-D were M2 TAM not the carcinoma cells and lymphangiogenesis was driven by bone marrow derived macrophages [79].

Conclusion

Multiple lines of evidence from clinical and translational

research show that the malignant tissue is regarded by the immune system as an immune privileged site. Pathways involved in immune suppression in cancer are intimately related to the cells of hematopoietic derivation such as monocytes (macrophages, dendritic cells and neutrophils), lymphocytes and cytokines made by these cells. Factors secreted in the tumor microenvironment such as arginase or nitric oxide from MDSC, IDO from dendritic cells and immunosuppressive cytokines such as TGF-B, VGEF, IL-4, IL-10, IL-13 induce tolerance of the immune system to the growing microenvironment characteristic or many malignancies.

The question remaining from the studies presented is whether the heterogeneous group of immune cells (MDSC, TAM, T-regulatory cells, immature dendritic cells and neutrophils) are unique entities developing in the presence of certain malignancies and in specific patients or represent a functional status of normal myeloid and lymphoid cells, status elicited by inflammation and skewed immune responses in the tumor microenvironment. Characterization of MDSC showed that tumor conditioning of the immune system is dependent of the time and site of tumor progression with the same secreted factors mediating different activities in the innate tolerance to malignant tumors.

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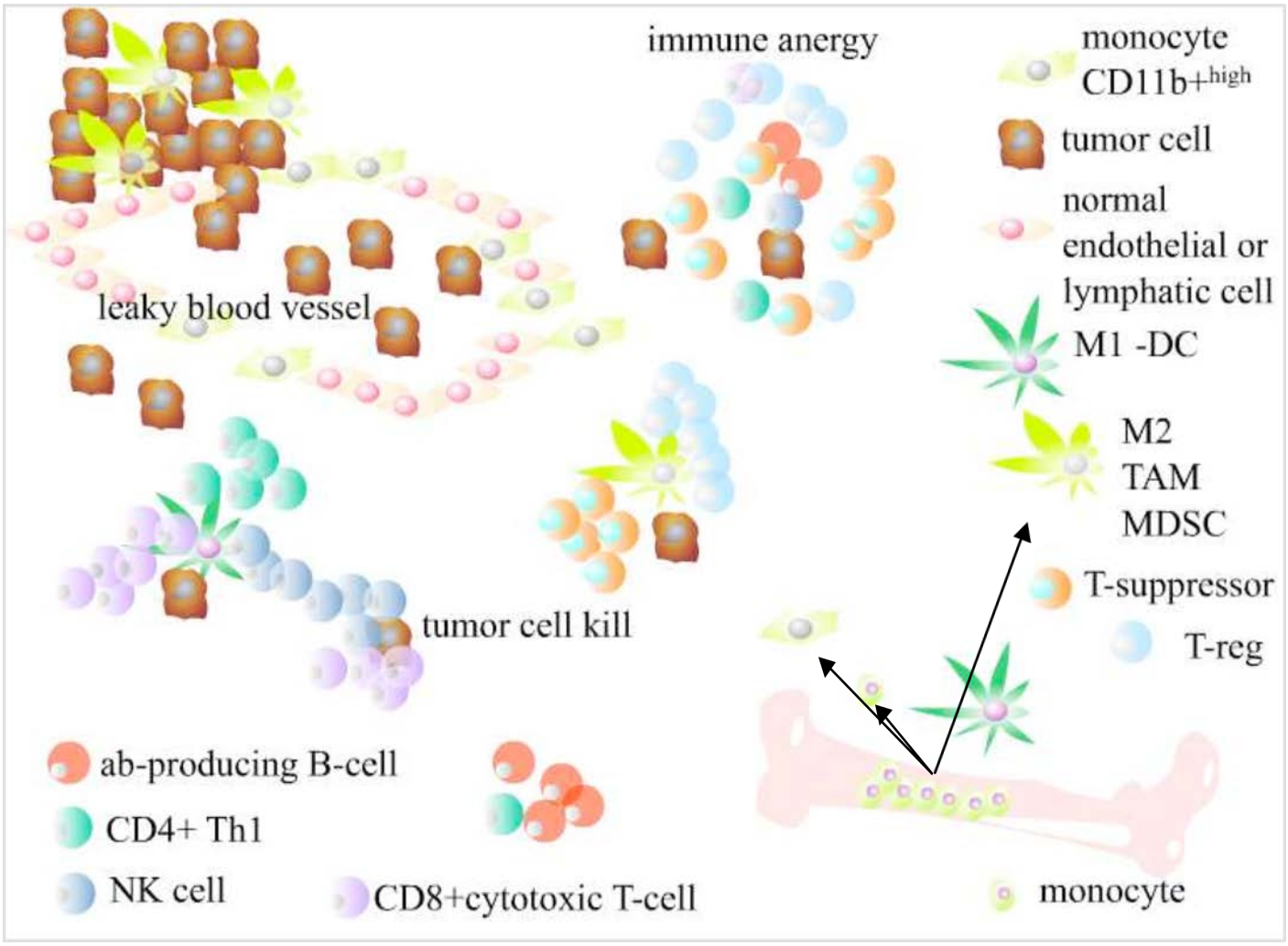

Figure 3: The interactions between tumor cells in brown with cells of hematopoietic derivation. Monocytes originating in the bone marrow are polarized by tumor cells to become M2 macrophages (TAM, MDSC) and travel to the growing malignancy to promote immune anergy. The tumor secretome recruits myeloid and stromal cells from the bone marrow and polarizes them towards an immunosuppressive phenotype. The immunosuppressive phenotype leads to immune anergy in the tumors. Polarized macrophages (M2), dendritic cells (DC) and neutrophils (monocytes), function as antigen presenting cells to lymphocytes transforming them into T-suppressor (T-regulatory cells) T-reg; In addition cells of myeloid derivation use arginase, indolamine 2,3 deoxygenase (IDO), nitric oxide (NO) and interleukins IL-4, IL-10 and IL-13 and transforming growth factor beta (TGF-beta) leading to immune anergy in the tumor and converting the growing tumor and metastatic sites into an immuno-privileged organ. Ab-(producing B-cell) antibody; M1-dendritic (type 1 immune response polarized dendritic or macrophage cell), NK-cell natural killer cell; TAM tumor associated macrophages, MDSC myeloid derived suppressor cell [97].

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