Transforming Growth Factor-Beta₁ and Myeloid-Derived Suppressor Cells Interplay in Cancer

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Received: May 31, 2017 Revised: August 08, 2017 Accepted: August 18, 2017

Abstract:

Background:
Transforming growth factor-beta₁ (TGF-β₁) is a pleiotropic cytokine with a double role in cancer through its capacity to inhibit early stages of tumors while enhancing tumor progression at late stages of tumor progression. Moreover, TGF-β₁ is a potent immunosuppressive cytokine within the tumor microenvironment that allows cancer cells to escape from immune surveillance, which largely contributes to the tumor progression.

Method:
It has been established that the cancer progression is commonly associated with increased number of Myeloid-derived suppressor cells (MDSC) that are a hallmark of cancer and a key mechanism of immune evasion.

Result:
MDSC represent a population of heterogeneous myeloid cells comprised of macrophages, granulocytes and dendritic cells at immature stages of development. MDSC promote tumor progression by regulating immune responses as well as tumor angiogenesis and cancer metastasis.

Conclusion:
In this review, we present an overview of the main key functions of both TGF-β₁ and MDSC in cancer and in the immune system. Furthermore, the mutual contribution between TGF-β₁ and MDSC in the regulation of immune system and cancer development will be analyzed.

Keywords: Transforming growth factor-beta₁, TGF-β₁, Myeloid-derived suppressor cells, MDSC, Immunosuppression, Cancer.

1. INTRODUCTION

TGF-β₁ is a pleiotropic cytokine implicated in almost all aspects of cell biology including cell proliferation, survival and migration, and cell differentiation. TGF-β₁, depending on the cell context, can modulate either negatively or positively the transcription of target genes [1]. In cancer, TGF-β₁ can act either as a tumor suppressor in the early stages of tumorigenesis or as a tumor promoter in the late stages of tumor progression. TGF-β₁ plays a key role in promoting cancer progression at multiple stages of the metastatic process, including epithelial to mesenchymal transition (EMT) [2, 3]. TGF-β₁ expression is increased within the tumor compared with the normal surrounding tissue and elevated.

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expression of TGF-β1 is a poor prognosis marker. Actually, TGF-β1 is implicated in the increased malignancy features of cancer cells due to its capacities to induce cell motility, extracellular matrix degradation and angiogenesis [4, 5]. Within the tumor microenvironment (TM), TGF-β1 is considered to be one of the main factors regulating the inflammatory response by modulating the activity of the innate and adaptive immune systems. Furthermore, TGF-β1 is produced and it acts on the different types of immune cells such as T and B cells, natural killer (NK) cells and macrophages among others [6].

In tumors, Myeloid-derived suppressor cells (MDSC) are considered as one of the main orchestrators of cancer-related inflammation. Within TM, MDSC can express different polarized features that contribute to the inflammatory milieu and cancer cell out-growth promotion. Moreover, MDSC in both human cancer and cancer mouse models are implicated in the subversion of the immune surveillance by downregulating T cell immunity. Furthermore, MDSC can be recruited and expanded by cancer cells-expressed factors, while the pathological increase of MDSC frequency into TM establishes an immune permissive microenvironment that contributes to the tumor progression [7, 8]. In this review, we attempt to describe the main aspects in the interplay of TGF-β1 and MDSC in cancer, and the positive pernicious loop between TGF-β1 and MDSC that contributes to the escape of cancer cells from immune surveillance, which finally increases tumor malignancy.

2. TRANSFORMING GROWTH FACTOR BETA-1, MICROENVIRONMENT AND IMMUNE SYSTEM IN CANCER

2.1. Transforming Growth Factor Beta-1

Transforming growth factors (TGF-βs) were described according to their capacity to “transform” fibroblast rat cells in vitro [9]. Three isoforms [TGF-β1, -β2, -β3] were found to be expressed in mammals sharing a degree of homology from 64 to 82% [10]. To date, more than 40 secreted ligands have been described that comprise the TGF-β superfamily. These include several subfamilies, such as TGF-βs per se, BMPs (bone morphogenetic proteins), GDFs (growth and differentiation factors), MIF (Müllerian inhibitory factor), activins and inhibins. Regardless of their structural similarities, TGF-β superfamily factors function as regulators of a variety of processes during embryogenesis and later on in adult tissue homeostasis [11, 12].

Namely, TGF-β1 has been involved in a plethora of distinct biological process, which includes cell growth, differentiation and development, angiogenesis, suppression of immune response and promotion of tumorigenesis [11, 13]. TGF-β1 is synthesized as precursor of 75kDa that comprises two main domains: The latency associated peptide (LAP) and TGF-β1. Later on, this precursor is subjected to cleavage by the furin-type convertase, this produces an inactive small latent complex (SLC) via a non covalent bond between mature TGF-β1 and LAP [14]. Moreover, a large latent complex (LCC) can be produced by the binding of SLC with the latent TGF-β1, binding protein (LTBP). This complex is secreted and remains covalently associated to the extracellular matrix (ECM) for further activation. Several TGF-β1 activation mechanisms have been described, which include acidic microenvironments, proteolytic cleavage by plasmin and metalloproteinases and oxidative stress [14, 15]. Bioavailable and active TGF-β1 binds first to cell-surface serine/threonine kinase type II receptors (TβRII) which activate and form heteromeric complex with the TGF-β1 type 1 receptor (TβRI) Fig. (1). Then, TβRI phosphorylates Smad2 and Smad3, which induces their release from the inner face of plasma membrane to form a heteromeric complex with the common Smad4. Next, this complex is translocated into the nucleus to regulate genes target expression [14, 16, 17]. In turn, TGF-β1 signaling is regulated by the expression of other components of Smads, the inhibitory Smads proteins (Smad6 and Smad7 or I-Smads) [18].

Beyond the canonical Smad2,3 pathway, TGF-β1 activates several non-canonical intracellular signal pathways Fig. (1), named also non-Smads pathways, which include: mitogen-activated protein kinases (MAPK) ERK1,2, JNK and p38; PI3K (phosphoinositide 3-kinase)/ AKT1,2 and mTOR; NF-κB (nuclear factor κB), Cyclooxygenase-2 and prostaglandins; the small GTPase proteins Ras, Rho family of GTPases, among others [19]. The plethora of the TGF-β1 signal transduction pathways in part explains the capacity of TGF-β1 to regulate many cellular functions at both molecular and biological levels.

2.2. Tumor Microenvironment Overview

The tumor microenvironment or tumor stroma consists mainly of the cellular components, the surrounding extracellular matrix, and interstitial fluid. These factors interact with each other, contributing to the hallmarks of cancer
having significant influence on immune responses against the tumor [20]. In this sense, cancer cells avoid recognition by the immune surveillance and simultaneously secrete inflammatory mediators to establish and maintain a constant state of inflammation [21]. In turn, the cellular components in the tumor include tumor cells themselves, associated stromal cells such as fibroblasts and mesenchymal stromal cells, endothelial cells, and infiltrating immune cells. In this aspect, it is important to note that TM infiltrating immune cells play essential and paradoxical roles in immune responses against cancer. For instance, particular subsets of immune cells, such as cytotoxic T lymphocytes, NK, mature dendritic cells (DC) or M1 tumor-associated macrophages (TAM), participate in tumor growth and progression restrain. Conversely, other infiltrating immune cells, such as M2 TAM, neutrophils, mast cells, regulatory T cells (Treg), immature DC or MDSC, tumor growth and progression [22 - 24].

**Fig. (1).** TGF-β\(_1\) intracellular signaling. TGF-β\(_1\) signals through interaction with TGF-β\(_1\) receptor-type II (TβRII) and subsequently with TGF-β\(_1\) receptor-type I (TβRI). The activated ligand and receptors complex proceeds to the activation by phosphorylation of the canonical effectors Smad2 and Smad3 that then forms a heteromeric complex to translocate into the nucleus and mediate the regulation of the genes target expression. Furthermore, TGF-β\(_1\), is able to activate several non-canonical intracellular signaling including MAP kinases (ERK1,2, p38 and JNK), NF-κB, PI3 kinase pathways, and small Rho GTPases, among others. The canonical and non-canonical signal transductions together regulate many of the cellular and molecular functions of TGF-β\(_1\).

Importantly, the TM is predominantly infiltrated with immunosuppressive factors that cripple T cell responses against the tumor. These factors are not present in normal tissues, but are components of tumor regulatory pathways in response to inflammatory or infectious etiologies [25]. Thus, a balance between pro- and anti-malignancy factors in the microenvironment regulates the growth of the tumor [26].

**2.3. TGF-β\(_1\) and Immune System**

The immune system is a complex and well developed organized structure whose strict balance is required for a normal homeostasis along the human life. The immune system regulation requires a complex crosstalk between the innate and adaptive system by secretion of cytokines, growth factors and cell-cell interactions. Dysregulation of the immune system responses results in autoimmune diseases, inflammatory diseases and cancer [27].
In cancer, TGF-β₁ is the most potent immune-suppressive cytokine; it can act on cancer cells, on “non-transformed cells” associated to tumor stroma and on distal cells in the host. TGF-β₁ suppresses antitumor immune responses and creates an immune-tolerant microenvironment allowing cancer cells to escape from immune surveillance, which contributes to the tumor progression Fig. (2) [28 - 31]. TGF-β₁ importance as master regulator of mammalian immune system function and homeostasis was not highlighted until observing that tgfβ₁-knockout mice exhibit a lethal multi-organ inflammation, primarily as consequence of deregulation in T cells responses [28, 32]. This observation was further supported by Smad3-deficient mice, which exhibited multi-organ inflammatory injuries, as well as severe defects in the responsiveness and chemotaxis of neutrophils, T and B cells, and this primary defect in immune function results to be lethal [33]. In addition, the transgenic targeting of T cells with a truncated TβRII expression results in a severe autoimmune reaction characterized by multi-organ inflammation similar to that seen in TGF-β₁ deficient mice, concomitantly to the autoantibody production [28, 34].

Fig. (2). Overview of TGF-β₁ regulation of immune system. TGF-β₁ as a potent immune-suppressive cytokine regulates many cellular components of the immune system. TGF-β₁ inhibits the activation and function of T lymphocytes (T cell) and induces them to differentiate to Tregulatory (Treg) and Th17 phenotypes. Also, it inhibits B lymphocytes (B cell) proliferation, classical dendritic cells (cDC) maturation and natural killer (NK) functions. Furthermore, TGF-β₁ promotes the switch of tumor-associated macrophages M₁ and neutrophils N₁ towards M₂ and N₂ respectively. Also, TGF-β₁ functions as chemotactic factor for mast cells, as well as it contributes to the generation of γδ T cells and regulatory DC (regDC). By these regulations, TGF-β₁ induces an immune-permissive tumor stroma that contributes to the tumor progression. Dotted line arrows indicate inhibition and solid line arrows indicate induction.
Although cancer cells may express tumor specific antigens, potentially recognized by immune system, tumor immunotherapy is frequently unsuccessful as a result of cancer cells capacity to evade the immune surveillance by diverse strategies [29]. For instance, in malignant cells TGF-β, downregulates the MHC Class I molecules making them invisible to the immune system. Moreover, TGF-β, profoundly regulates the innate immune cells compartment. In tumors, TGF-β, promotes both monocyte recruitment and macrophage differentiation [35]. Moreover, TGF-β, suppresses mouse macrophage expression of TNF-α, MIP-1α, MIP-2 and it contributes to the resolution phase of inflammation [36]. Furthermore, TGF-β, induces the polarization of TAMs M1 toward a protumorigenic M2 phenotype. Additionally, TAMs contribute to a tolerant tumor immunity microenvironment by producing TGF-β, and supporting tumor growth [37, 38]. In neutrophils, TGF-β, may inhibit the ability of these cells to eliminate cancer cells-expressing Fas-Ligand, and similarly to macrophages TGF-β, promotes tumor-associated neutrophils switch from N1 to a protumorigenic N2 phenotype, thus further fomenting a permissive tumor microenvironment [39]. Besides, in tumor associated classical (c)DC, TGF-β, represses the expression of MHC class II, CD40, CD80, and CD86, and TNF-α, IL-12, and CCL5/Rantes, and these DC become functionally defective because of their immature phenotype. Whereas, TGF-β is able to induce DC to adopt a tolerogenic phenotype, defined as regulatory (reg)DC [40 - 42]. Finally, TGF-β is a potent chemo attractant for mast cells, which depending of milieu can produce pro-tumorigenic or anti-tumorigenic factors [43, 44].

Furthermore, TGF-β, regulates also lymphoid compartment, this factor largely inhibits both T cells B cells responses, and hinders the effector cytokines production (including IL-2, IL-4 and IFN-γ); reduces NK cell proliferation and cytotoxicity; meanwhile, it induces the conversion of naive T-cells toward Tregs, and Th17 differentiation that increases the production and secretion of pro-inflammatory cytokine IL-17, which contributes to the immune tolerance as well as to tumor progression and metastasis [42, 45 - 48]. Furthermore, TGF-β, contributes to the generation of γδ T cells, which are the major IL-17-producing cells in naïve animals, and tumor-infiltrating γδ T cells may promote tumorigenesis via IL-17 and PD-L1 upregulation [49, 50]. Accordingly, TGF-β, affects the initiation and stimulation of both primary and secondary immune responses and it also suppresses antitumor effectors cells [51, 52].

Therefore, active TGF-β, produced by the tumor and local stroma cells contributes to the cancer progression and metastatic potential through autocrine and paracrine effects [53]. Importantly, elevated TGF-β, plasma levels have been associated with the advanced stage and poorer clinical outcome. For instance, in breast, prostate, pancreatic and renal cancer the increase in plasma TGF-β, levels are associated with the advanced stage of metastases [54]. Moreover, elevated serum levels of TGF-β, have been observed in patients with myeloma, being both malignant cells and bone marrow stromal cells the source of TGF-β, TGF-β, levels also are elevated in non–Hodgkin’s lymphoma and are markedly elevated in high-grade lymphomas, cutaneous T cell lymphomas with a T-regulatory phenotype, and in splenic marginal zone lymphomas presented as myelofibrosis [30 and references therein].

3. MYELOID-DERIVED SUPPRESSORS CELLS IN CANCER AND TRANSFORMING GROWTH FACTOR-B1 INTERPLAY

3.1. Myeloid-Derived Suppressor Cells

It has been established that the cancer progression is commonly associated with increased number of immature myeloid cells, at various stages of differentiation, in spleen, peripheral blood and within TM. Currently these cells are recognized as MDSC, and they are a hallmark of cancer and a central mechanism of immune evasion [55, 56]. MDSC were described first in mouse models bearing human tumor cells and later on they were described in the patients with head and neck squamous cancer [57].

MDSC primarily include immature myeloid cells (IMC), which in steady-state conditions, leave the bone marrow as myeloid precursor cells and migrate to peripheral tissues, such as the spleen, where they differentiate into mature myeloid cells in response to the specific tissue molecules. Whereas, under pathologic conditions associated with chronic inflammation IMC become to differentiate into functional immunosuppressive MDSC. Nevertheless, immunosuppressive MDSC do not expand under healthy conditions [58, 59].

In general, MDSC include a small group of myeloid progenitors as well as immature mononuclear cells, that in humans can be identified as CD11b+,CD33+, CD15- or CD66b-, CD14 for polymorphonuclear (PMN)-MSC, while monocytic(M)-MDSC are CD11b+ or CD33+,CD14+, HLA-DRlow which distinguish from HLA-DRhi monococytes. Moreover, the Lin− (including CD3, CD14, CD15, CD19, and CD56) and HLA-DR CD33+ cells contain mixed groups
of MDSC, which comprise more immature progenitors [60]. Meanwhile, in mice MDSC are characterized by the expression of Gr-1 (that share common epitope to Ly6C and Ly6G) and CD11b. Two categories can be defined in mice, the PMN-MDSC as CD11b+Ly6G- Ly6Cs− and M-MDSC as CD11b+ Ly6G Ly6Cs+ [1, 60].

Currently, it is accepted that MDSC expansion and accumulation is regulated by two sequential set of factors: first the factors that are implicated in the expansion of MDSC such as GM-CSF, M-CSF and G-CSF, and also by factors produced by cancer cells and tumor stroma including TGF-β1; the second set of factors, such as IFN-γ, TNF-α, IL-4/13, IL-1β and COX2 significantly upregulate MDSC immunosuppressive functions [61, 62].

Several studies reported the immunosuppressive effects of MDSC in HCC, melanoma, prostate cancer, bladder cancer, non–small cell lung cancer and head and neck squamous cell carcinoma, breast cancer, gastric cancer, colorectal cancer and others, which evidences their clinical significance [60]. The capacity of MDSC to support tumor growth and metastases can be defined according to the next functions: (i) protection of tumor cells from immune-surveillance; (ii) remodeling of the tumor microenvironment; (iii) participating in the formation of a pre-metastatic niche; and (iv) by their interaction with cancer cells facilitating the EMT [61].

3.2. Immunomodulatory Role of MDSC

The ability to suppress immune cells is one of the main characteristic of MDSC. Although MDSC are implicated in the suppression of different cells of the immune system such as NK and B cells the inhibition of T cells is the key for evaluation of MDSC function. Moreover, T-cell inhibition appears to be sufficient functional criteria for designation of cells as MDSC [58, 60].

MDSC express enzymes and metabolic by-products contributing to their immune-regulatory functions, such as arginase-1 (Arg-1) inducible nitric oxide synthase (iNOS)/ nitric oxide (NO), reactive nitrogen species (RNS), reactive oxygen species (ROS), Indoleamine 2, 3-dioxygenase (IDO) and programmed death-ligand 1 (PD-L1), among others. Furthermore, they produce high levels of anti-inflammatory cytokines, such as IL-10 and TGF-β, [60, 61]. Namely, T-cell expansion is highly susceptible and linked to the catabolism of L-arginine (Arg). In this sense, iNOS uses Arg as precursor for NO production; meanwhile Arg-1 catabolizes Arg to urea and ornithine. Therefore, the depletion of the T-cell essential nutrient Arg by elevated expression of iNOS and Arg-1 in tumor microenvironment inhibits T-cell proliferation. The main mechanisms of Arg depletion-induced T-cell inhibition are the downregulation of ζ-chains on T-cell receptors and the inhibition of cyclin D3 and cdk4 expression [26, 63]. In turn, the increase of iNOS expression in MDSC and therefore higher levels of NO contributes to T-cell proliferation arrest by blocking IL-2 production [64]. In a similar way, IDO expression, which is a critical rate-limiting enzyme of tryptophan catabolism through the kynurenine pathway, produces tryptophan depletion and halts the effector T cell proliferation [65]

Furthermore, the production of RNS, such as peroxynitrites, drives T-cells apoptosis by nitrotyrosylating key proteins involved in the signaling of T-cell activation. For instance, the nitration of T-cell receptor (TCR) induces conformational changes in TCR-CD3 complex that diminishes the interaction between CD8 and TCR that results in the loss of antigen-specific stimulation [66]. Whereas, the CD3 theta chain expression is reduced by MDSC through ROS (H2O2) dependant mechanisms [67]. Moreover, by cell-cell contact MDSC may suppress T-cell activation via induction of T-cell apoptosis through interaction of programmed death-1 (PD-1) molecules with its cognate ligands PD-L1 and PD-L2 [68].

Additionally to direct T-cell inhibition, MDSC cells are able to induce and recruit Tregs by TGF-β1, and IL-10 expression [63]. Moreover, M-MDSC-derived TGF-β1, and retinoic acid participates in the transdifferentiation of TH17 cell towards Tregs [69]. Furthermore, MDSC inhibit cytotoxicity of NK Cells towards autologous activated T cells in an in vitro model [70]. Finally, MDSC inhibit DC function via IL-10 by reducing the DC-mediated T-cells activation [71].

Thus, MDSC possesses several mechanisms to counteract T-cell activation and response that contributes to produce a supportive TM for cancer cell development.

3.3. MDSC Contribution to Cancer Progression

One of the main aspects, beyond immunomodulatory functions, that support tumor growth is the MDSC contribution to the remodeling of tumor microenvironment by producing VEGF, bFGF and Matrix metalloproteinases (MMPs), which contribute to tumor neoangiogenesis and to the increase of cancer cell motility and invasion [58, 61]. Intriguingly, MDSC can also contribute to the tumor endothelium by transdifferentiation toward endothelial cells as is
demonstrated by VEGFR2 expression [72]. Moreover, MDSC may contribute to the cancer-associated EMT by the expression of TGF-β1, HGF, EGF, and IL-6. In in vitro studies it has been demonstrated that co-culture of cancer cells with MDSC produces a stem-like phenotype of cancer cells, whereas in vivo depletion of PMN-MDSC decreases the frequency of cancer cell displaying EMT phenotype in the primary tumor [73].

Due to the increasing evidences that support the relation between MDSC frequency and clinical outcome in cancer, these cells have been postulated as cellular biomarkers for monitoring tumor progression and cancer patients response to chemotherapy [74]. Circulating MDSC number is elevated in cancer patients and can be inversely correlated with clinical response. For instance, in renal cell carcinoma the resistance to the TK inhibitor sunitinib is associated with elevated peripheral blood MDSC levels [75], while in small cell lung cancer they predict a poorer response to cisplatin chemotherapy, the level of M-MDSC is associated with poor response to bevacizumab and disease progression [76, 77]. Similarly, in breast cancer patients M-MDSC levels may represent biomarker for monitoring disease progression [78]. Meanwhile, in B cell acute lymphoblastic leukemia (B-ALL), PMN-MDSC levels correlated positively with therapeutic responses and B-ALL prognostic markers, including minimal residual disease, and the frequencies of CD20+ and blast cells [79]. Furthermore, MDSC also seems to impact the clinical course and prognosis of adult acute myeloid leukemia [80].

### 3.4. TGF-β1, and MDSC

Clinical data demonstrated that TGF-β1 levels correlate with poor prognosis in cancer patients. Beyond cancer cell production of TGF-β1, several stromal cells are also able to increase the level of TGF-β1, the tumor, which include cancer associated fibroblast, mesenchymal stromal cells, and also the innate immune system cooperates to the augment of TGF-β1 tumor levels [31, 81].

Tumor production of TGF-β1 can contribute to the increment of MDSC frequency and function Fig. (3). In vitro TGF-β1 is able to induce functional M-MDSC from purified human monocytes [82]. One interesting mechanism implicated tumor exosomes (TEXs) in the induction and accumulation of MDSC. Generally, exosomes are described as 30 to 100 nm size vesicles originated from the endosome organelles carrying different genes, lipids, proteins, and microRNAs (miRs). Many cells, including tumor cells, have the capacity to release exosomes. Recently, increased evidence has suggested that TEXs might act as a vehicle for transmitting signals for suppression thus having negative effects on antitumor immune responses [83]. Furthermore, TEXs-associated TGF-β1 also contributes to MDSC expansion. Namely, in breast cancer mouse model, TEXs-associated TGF-β1, in addition to PGE2, contributes to in vivo MDSC induction and tumor growth [84].

One of the mechanisms involved in TGF-β1-induced MDSC is its capacity to regulate miRs expression. MiRs are noncoding single-stranded RNAs with an average of 22 nucleotides long, which post-transcriptionally regulate gene expression through its capacity to interfere RNAs by binding either to the 3′UTR or 5′UTR or the coding sequence of mRNAs [85]. Specifically, TGF-β1 induces both M-MDSC and PMN-MDSC from mouse bone marrow mononuclear cells by up-regulating the expression of miR-21 and miR-155 [86]. In addition, TGF-β1 is able to regulate mouse MDSC proliferation by induction of miR-494 in a Smad3 dependent way [87].

The capacity of TGF-β to contribute to MDSC immunosuppressive properties is also pictured by the capacity of B regulatory cells (Breg) to educate the MDSC. Cancer associated Breg can educate both M-MDSC and PMN-MDSC subpopulations to suppress T cell proliferation. This relays in part to the presence and activation of TGF-β1 receptors in MDSC, since the use of TβRI inhibitor or mice with TβRII deficient myeloid cells reduces the capacity of Bregs to fully activate the regulatory capacity of MDSC concomitantly to the inhibition of metastasis [88].

TGF-β1, beyond its capacity to induce MDSC, also contributes to the immune suppressive capacity of MDSC, as well as to their contribution to tumor malignancy. For instance, mouse mammary carcinomas with Tgfb1 deletion provoke increased infiltration of Gr-1+CD11b+ MDSC to the invasive front, moreover these MDSC were the main source of TGF-β1 within the tumors. The increment in TGF-β1 levels within the tumor contribute to the enhancement of invasive capacities of mammary cancer cells [89]. Human peripheral blood CD14+HLA-DR+ MDSC subset in squamous cell carcinoma of the head and neck are high producers of TGF-β1 and by blocking this factor with anti-TGF-β1 monoclonal antibody the T-cell immunosuppression is reduced [90]. Also, IL-13 activation of CD11b+Gr-1+ MDSC induces TGF-β1 production, and the inhibition of IL-13 receptor alpha restores in vivo tumor immunosurveillance in a murine syngeneic model of colon carcinoma [91]. Interestingly, the exposition of C57BL6/J mice to an acute dose of
single-walled carbon nanotubes (CNT) provokes the recruitment and accumulation of MDSC into the lung. These CNT-induced MDSC produce TGF-β, resulting in an immunosuppressive microenvironment and increased lung tumor burden. However, in TGF-β-deficient mice the CNT do not enhance the tumor growth. In this model, TGF-β was not involved in the initial recruitment of MDSC to exposed lungs to CNT, while it was critical to the MDSC-dependant stimulation of tumor growth [92].

**Fig. (3).** TGF-β and MDSC collaboration in the regulation of tumor associated immune responses. Tumor production of TGF-β contributes to the induction and accumulation of MDSC frequency and function within stroma. Moreover, MDSC and TGF-β strongly contribute to an immunosuppressive microenvironment by regulation of many components of immune system. One of the hallmarks of MDSC is their suppressor function of T lymphocytes (T cell) responses. MDSC induce T regulatory (Treg) cells, whereas they inhibit NK functions via cell-associated TGF-β. Furthermore, MDSC are educated by B regulatory (Breg) lymphocytes by TGF-β signaling. Also MDSC contribute to cancer cells increase of the levels of tumor TGF-β, whose increase participates in the enhancement of cancer cell malignancy by inducing tumor progression. Dotted line arrows indicate inhibition and solid line arrows indicate induction.
Although the immunosuppressive capacity of the MDSC is in part due to its capacity to produce TGF-β₁, they can also use TGF-β₁ to regulate other immunoregulatory cells. As aforementioned, TGF-β₁ induces the potent immunosuppressive cells Treg cells [93]. In this aspect, mouse MDSC, in an IL-10 and TGF-β₁ dependant manner, induce Tregs cells in tumor-bearing host model, which contributes to the downregulation of T-cell mediated immunity [94]. Conversely, PMN-MDSC obtained from tumor bearing mice have been shown to inhibit the in vitro capacity of TGF-β₁ to induce Tregs cells in ROS/IDO-dependant pathways. These data point out that PMN-MDSC plays fundamental roles in the generation of Tregs cells during tumorigenesis [95]. In addition, MDSC are able to regulate NK cells activity in mouse model of liver cancer. Furthermore, MDSC by membrane bounded TGF-β₁ impair NK function in orthotopic liver cancer-bearing mice, therefore MDSC induce an immune-tolerant tumor microenvironment by also inhibiting NK cytotoxic activity [96, 97].

CONCLUSION

In tumor microenvironment TGF−β₁ plays an important role by contributing to the reduction of immunosurveillance, either by direct induction of MDSC, or by contributing to MDSC regulation of T-cell mediate immune-responses as well as indirectly by mediating the capacity of MDSC to modulate Tregs and cytotoxic NK cells. However, the capacity of MDSC to produce TGF-β₁ suggests a positive feedback that amplifies the role of MDSC in establishing an immune-tolerant microenvironment to promote tumor progression.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors are grateful to Ms. Marija Bozic for her excellent and valuable editorial assistance. We apologize to those colleagues whose work, although relevant to the issues dealt within this review, has not been included due to space limitations. This work was supported by Ministry of education, Science and Technological Development of the Republic of Serbia (grants 175053 and 175024). We also thank to the support of visiting professor program of UBO to J.F.S.

This article is based upon work from the COST Action BM1404 Mye-EUNITER (www.mye-euniter.eu), supported by COST (European Cooperation in Science and Technology) to JFS.

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