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REVIEW

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Immature myeloid cells and cancer-associated immune suppression

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Abstract Impaired balance between mature and immature myeloid cells is one of the hallmarks of cancer. In cancer patients as well as in mouse models there is increasing evidence that progressive tumor growth is associated with an accumulation of immature myeloid cells, monocytes/macrophages, and with a decreased number and function of dendritic cells (DC). This review examines recent findings on the contribution of immature myeloid cells (ImC) to cancer-induced immune suppression.

Keywords Cancer · Immature myeloid cell · Immune suppression · Immune tolerance · T-cell response

Introduction

Failure of T cells from tumor-bearing hosts to effectively recognize and eliminate tumor cells is one of the major factors of tumor escape from immune system control [18, 35, 46]. An effective antitumor immune response requires participation of the host bone marrow antigen-presenting cells (APC) responsible for the presentation of tumor-specific antigens [24]. Dendritic cells (DC) and macrophages are the two most potent groups of APC. These cells are capable of inducing primary immune responses including the cytotoxic T-lymphocyte response. Recent studies have clearly demonstrated that the immunostimulatory characteristics of DC are dependent on their maturation state [14, 27]. Increasing evidence supports the notion that both immune activation and immune suppression depend on antigen presentation by APC [35]. DC as well as macrophages and granulocytes arise from a common myeloid progenitor that has the ability to capture antigen but lacks the expression of major histocompatibility complex (MHC) class II and co-stimulatory molecules [25]. Mature DC loaded with antigen are highly effective in eliciting a protective immune response against tumors [37, 38, 42, 48], whereas immature DC [14] may induce the antigen-specific inhibition of $CD8^+$ T cell effector function.

It appears that impaired balance between mature and immature myeloid cells is one of the hallmarks of cancer. There is increasing evidence that progressive tumor growth is associated with an accumulation of immature myeloid cells, monocytes/macrophages, and with a decreased number and function of DC in cancer patients as well as in tumor-bearing mice [2, 3, 9, 20, 22, 28, 51, 56, 57]. The increased presence of immature myeloid cells (ImC) capable of inhibiting T cell responses could be the major factor responsible for immune suppression in cancer patients. In this review, we examine the recently published reports that address the contribution of ImC to immune suppression in cancer. Molecular events and signaling defects in T cells from tumor-bearing hosts have been reviewed recently elsewhere [18, 53].

Tumor-derived factors affect myelopoiesis

A number of experimental tumor models have been shown to induce myelopoiesis that manifests as splenomegaly, extramedullary hematopoiesis, neutrophilia, and increased presence of immature macrophage/monocytes in the spleen and bone marrow. The growth of many murine carcinomas, such as Lewis lung carcinoma [54]; colon carcinomas CT-26 [4, 26], MCA-26 [28], and MCA-38 (S.K; unpublished observations); mammary adenocarcinomas such as Ehrlich [36], TS/A [9], D1-DMBA-3 [51, 52]; and to a lesser extent sarcomas such as MethA, C3 [23] or CMS5 [41] is associated with the early development of splenomegaly and the marked accumulation of ImC in the lymphoid organs. Similar findings

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have been recently reported in cancer patients. Decreased presence of DC in the peripheral blood of patients with breast, lung, head and neck cancer was associated with the accumulation of cells lacking markers specific for mature myeloid and lymphoid lineages [2]. About one-third of these cells were immature macrophages and DC, and the remaining cells were ImC at earlier stages of differentiation [3]. The presence of these cells was dramatically increased in patients with advanced stage cancer, but dropped considerably within three to four weeks after surgical resection of the tumor. This finding is consistent with the hypothesis that the generation of ImC is due to the production of soluble factors by tumors. Resection of experimental tumors also results in a decrease in the number of immature Gr-1^+/Mac-1^+ cells and an increase in the number and function of $CD3^+$ T cells in the spleen [41].

Several cytokines produced by tumors such as vascular endothelial growth factor (VEGF), GM–CSF, M–CSF, IL-6 and IL-10 have been implicated in defective DC maturation and impairment of myelopoiesis in tumor-bearing hosts.

VEGF is produced by most tumors, and its production is closely associated with poor prognosis [49]. VEGF stimulates the proliferation of endothelial cells and thus plays an important role in the formation of tumor neovasculature (reviewed in [17]). Neutralizing anti-VEGF antibody blocked the negative effects of tumor cell supernatants on DC maturation in vitro [21]. Furthermore, an inverse correlation between the density of DC and the expression of VEGF has been demonstrated within tumor tissue [40] and peripheral blood [29] of cancer patients. The elevated level of circulating VEGF in cancer patients was also closely correlated with the increased number of ImC [2]. VEGF inhibited the activation of transcription factor NF-κB in hematopoietic progenitor cells, which was accompanied by alterations in the development of multiple lineages of hematopoietic cells [15, 34]. Chronic administration of recombinant VEGF in naive mice resulted in an inhibition of DC development and an increased production of B cells and immature Gr-1^+ myeloid cells [34].

GM–CSF is another factor that has been shown to be responsible for the stimulation of myelopoiesis in tumor-bearing hosts. About 30% of 75 tested human tumor cell lines spontaneously secrete this cytokine [9]. Early studies demonstrated that several experimental tumors could produce colony-stimulating factors that induced expansion of ImC capable of inhibiting T-cell mediated immune response in vitro [19, 33, 50]. Administration of anti-GM–CSF and anti-IL-3 antibodies in vivo abrogated the accumulation of tumor-induced immune suppressive granulocyte/macrophage progenitor cells in mice bearing Lewis lung carcinoma [55]. Production of GM–CSF correlated with the ability of tumor cells to spontaneously metastasize [50]. More recently it was shown that chronic administration of GM–CSF to mice resulted in the generation of a cell population that morphologically resembled granulocyte–monocyte progenitors that expressed the granulocyte–monocyte markers Mac-1 and Gr-1 [9]. These Gr-1^+/Mac-1^+ cells could be differentiated in vitro in the presence of IL-4 and GM–CSF to genuine mature, fully functional APC.

It is likely that in combination GM–CSF and VEGF may have a much stronger immune suppressive effect than individually. GM–CSF stimulates myelopoiesis, whereas VEGF blocks maturation of multiple lineages of hematopoietic cells, so together they can severely depress the differentiation of myeloid cells and increase the accumulation of immature cells, which may promote the escape of tumor cells from immune surveillance.

Other tumor-derived factors such as M-CSF, IL-6, and IL-10, or gangliosides have also been involved in defective DC differentiation in vitro [1, 10, 16, 31, 45]. However, it appears that these factors do not stimulate myelopoiesis and mostly affect relatively mature cells. For instance, incubation of $CD34^+$ progenitor cells with IL-6 and M-CSF shifted cell differentiation from DC to monocytes [31]. IL-10 prevented the differentiation of monocytes to DC, but promoted their maturation to macrophages [1]. Professional APC derived from IL-10 transgenic mice were found to have suppressed capacity to induce MHC alloreactivity, CTL response and IL-12 production [45].

Immature myeloid cells are involved in suppression of both $CD8^+$ and $CD4^+$ T cell responses

Inhibition of $CD8^+$ T cell response

The marked accumulation of ImC in tumor-bearing hosts raises the question about their role in cancer. Several groups have recently studied the functional significance of these cells. Bronte et al. [9] demonstrated that Gr-1^+ myeloid cells in tumor-bearing mice were responsible for the loss of the cytotoxic T-lymphocyte (CTL) response to recall antigens. Depletion of Gr-1^+ cells with specific antibody resulted in the restoration of CTL activity. The similar inhibitory effect of Gr-1^+/Mac-1^+ on the secondary immune response was described after immunization of mice with recombinant vaccinia virus encoding IL-2 [8].

Recently, we have found that Gr-1^+ ImC accumulating in tumor-bearing mice inhibited interferon-γ (IFN-γ) production by $CD8^+$ T cells in response to the specific peptide presented by MHC class I in vitro and in vivo [23]. This effect was not mediated by soluble factors, and blockade of the MHC class I molecules on the surface of Gr-1^+ cells completely abrogated the observed inhibitory effect. These tumor-induced Gr-1^+ cells were not able to inhibit the proliferative response of T cells to concanavalin A (Con A) or specific peptide presented by MHC class II molecules. This could be explained by the fact that these Gr-1^+ cells expressed MHC class I but lacked expression of MHC class II and co-stimulatory molecules. Stimulation of T cells in the absence of co-stimulation might result in T-cell anergy.

Consistent with these findings, in humans injection of immature DC (derived from normal volunteers and pulsed with peptides) resulted in the specific inhibition of $CD8^+$ T cell effector function and in the appearance of antigen-specific IL-10-producing cells [14]. When T cells were derived from immunized donors and boosted in vitro, they showed lack of killer activity and reduced IFN-γ production. To investigate whether ImC obtained from cancer patients might affect a specific MHC class I-restricted response, a CTL cell line specific for an influenza virus-derived peptide was generated from a HLA-A2-positive healthy volunteer [3]. Addition of Lin^- $HLA\text{-}DR^-$ immature cells isolated from the peripheral blood of HLA-A2-positive cancer patients specifically inhibited production of IFN-γ by $CD8^+$ T cells re-stimulated with DC pulsed with the specific peptide.

Thus, immature myeloid cells and immature DC isolated from humans [3, 14] or immature myeloid cells from mice [9, 23] were able to inhibit $CD8^+$ T cell responses in an antigen-specific manner. Since cancer progression is associated with increased production of ImC as well as immature DC, this could be one of the mechanisms by which growing tumor may induce antigen specific $CD8^+$ T-cell unresponsiveness in their host.

Inhibition of $CD4^+$ T-cell response

Induction of optimal antitumor immunity involves the priming of both $CD4^+$ and $CD8^+$ T cells with tumor-associated antigens. In some experimental models, $CD4^+$ T lymphocytes may play a central role in the induction of effective antitumor immunity. However, tumor growth induced antigen-specific anergy of $CD4^+$ T cells at an early stage of tumor growth [46]. Isolated transgenic $CD4^+$ T cells from A20HA tumor-bearing hosts were not able to secrete IFN-γ or IL-2, and did not proliferate in response to cognate peptide-pulsed APC. This non-responsiveness developed early in the course of tumor progression, and occurred when other elements of the T-cell repertoire functioned normally.

Several findings reinforce the hypothesis of ImC involvement in the development of $CD4^+$ T cell unresponsiveness. As discussed above, $Gr\text{-}1^+/Mac\text{-}1^+$ myeloid cells expressed MHC class I molecules but lacked expression of MHC class II and co-stimulatory molecules [9, 23]. However, culture of $Gr\text{-}1^+$ cells in the presence of GM–CSF for five to six days induced the surface expression of MHC class II molecules on 20% to 25% of surviving cells [23]. Almost all of the MHC class II- positive cells were also positive for F4/80 antigen, a marker of mature macrophages (unpublished data). Taken together, these results indicate that GM–CSF may differentiate some of the immature $Gr\text{-}1^+$ cells into MHC class II-positive macrophages.

The involvement of $Gr\text{-}1^+/F4/80^+$ myeloid cells in the suppression of the $CD4^+$ T cell response has recently been demonstrated in several experimental models of infection [5, 11, 13]. Repeated injections of staphylococcal enterotoxin A (SEA) into TCR-transgenic mice caused tolerance of $CD4^+$ T cells to subsequent restimulation ex vivo [11]. $Gr\text{-}1^+$ cells were found to be responsible for suppression of the $CD4^+$ T cell response. Addition of $Gr\text{-}1^+$ cells isolated from SEA-treated mice to purified and re-stimulated in vitro $CD4^+$ cells resulted in apoptosis of the responding T cells. Inhibition of the T-cell response required IFN-γ-dependent secretion of nitric oxide and oxygen-reactive intermediates by $Gr\text{-}1^+$ cells. Atochina et al. [5] have demonstrated that intraperitoneal administration of antigen derived from helminth parasite *Schistosoma mansoni* induced the rapid expansion of the $Gr\text{-}1^+/Mac\text{-}1^+/F4/80^+$ cell population. $Gr\text{-}1^+$ cells that co-expressed macrophage marker F4/80 suppressed proliferation of naive $CD4^+$ T cells via an NO-dependent mechanism.

Recently we have demonstrated that $Gr\text{-}1^+/Mac\text{-}1^+$ ImC inhibits the activation of T cells in vitro by immobilized anti-CD3/C28 mAb. Reversal of these inhibitory effects could be achieved by depletion of Gr-1-positive cells, neutralization of IFN-γ, or by the addition to cultures of a combination of inhibitors of reactive nitrogen and oxygen intermediates [32]. Interestingly, incubation of $Gr\text{-}1^+$ cells for three days in the presence of cell supernatant obtained from CD3/CD28-stimulated T cells induced the expression of F4/80 on 29% of cells (unpublished data).

Heterogeneity of $Gr\text{-}1^+/Mac\text{-}1^+$ myeloid cell populations

In animal tumor models, it appears that the increased population of $Gr\text{-}1^+/Mac\text{-}1^+$ immature myeloid cells is heterogeneous and consists of at least two immunoregulatory subpopulations. The first subpopulation represents myeloid cells committed to the granulocyte lineage. These myeloid cells readily block antigen-specific IFN-γ production by $CD8^+$ T cells via direct cell–cell contact. The second subpopulation contains the monocyte/macrophage precursors that may control expansion of $CD4^+$ and probably $CD8^+$ cells via IFN-γ and NO-dependent mechanisms. The reactive nitrogen and oxygen species secreted by $Gr\text{-}1^+Mac\text{-}1^+F4/8^+$ cells display a strong anti-proliferative effect on activated T cells, and may induce their apoptosis. The level of T-cell suppression depends on the intensity of the antigenic stimuli, the amount of secreted IFN-γ, and the number of $Gr\text{-}1^+Mac\text{-}1^+$ myeloid cells present at the site of T-cell activation.

There is a difference between tumor-bearing and immunized/infected hosts in one critical aspect (see Fig. 1). Accumulation of immature myeloid cells in peripheral lymphoid organs of infected or immunized mice is a temporary event, and after several days the number of these cells gradually decreases [38]. In contrast, the number of ImC in tumor-bearing hosts gradually increases during tumor progression. The difference in kinetics of ImC may be explained by the effects of tumor-derived factors that block differentiation/maturation of

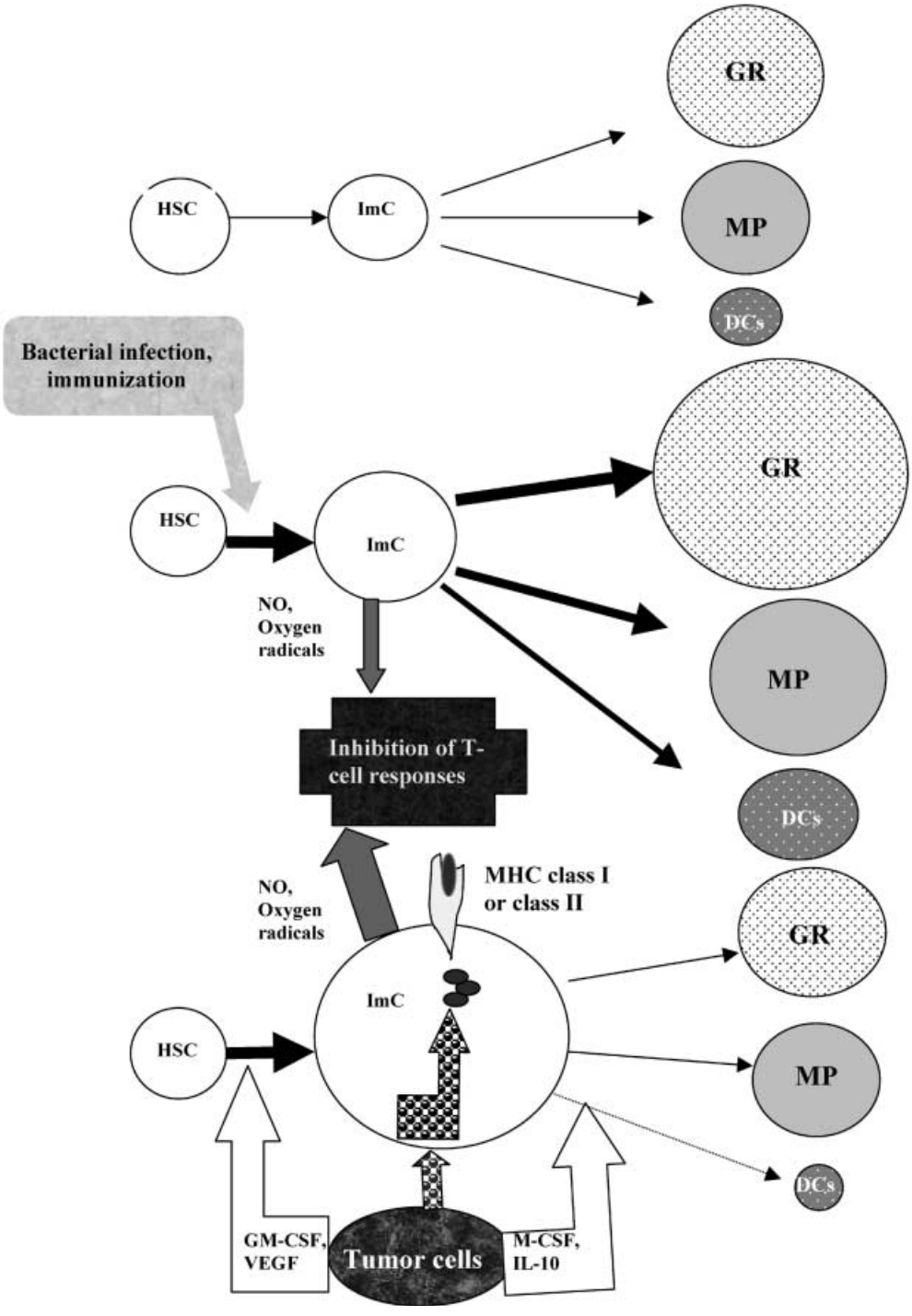

Fig. 1. Impaired myeloid cell differentiation in tumor-bearing but not infected or immunized hosts leads to a profound dysfunction in the immune response. Under physiological conditions (weak conventional antigenic stimuli) differentiation of myeloid progenitor cells results in the generation of granulocytes, macrophages and DC. Just as it is needed for maintaining homeostasis. In infected or immunized organisms, the intensity of myelopoiesis and the size of the pool of ImC is increased. However, cell differentiation is not affected and immature myeloid cells quickly progress to mature granulocytes, macrophages, or DC. A growing tumor stimulates myelopoiesis and affects cell differentiation through the production of growth factors and cytokines. This results in the accumulation of a large number of ImC. These cells produce NO and oxygen radicals, and have the ability to pick up the tumor antigen and present it to T cells in association with MHC class I. Lack of co-stimulatory molecules leads to the induction of T-cell anergy. *HSC* Hemopoietic stem cells, *Imc* immature myeloid cells, *GR* granulocytes, *MP* macrophages, *DC* dendritic cells

myeloid cells as described above, resulting in a progressive accumulation of these myeloid cells in tumor-bearing hosts.

Concluding remarks

Taken together, these recent studies indicate that ImC accumulated in tumor-bearing hosts may control both $CD4^+$ and $CD8^+$ T cell response via different mechanisms. We suggest that physiologically, ImC may serve as a defense mechanism that limits the expansion of activated T cells and prevents the development of autoimmune diseases. However, in the case of cancer, factors such as VEGF, GM–CSF, M–CSF, IL-6, IL-10, etc. secreted by growing tumors cause abnormal myelopoiesis that ultimately leads to the profound suppression of immune responses. This process is closely associated with IFN-γ production. Expansion of activated T cells that are able to secrete IFN-γ can be

prevented via a feedback mechanism involving IFN-γ-dependent production of reactive oxygen intermediates by immature myeloid cells. This leads to a deficit in IFN-γ-producing $CD4^+$ and $CD8^+$ T cells in tumor-bearing hosts. IFN-γ has been previously shown to play a critical role in the regulation of the antitumor immune response, primarily because of its ability to shape tumor immunogenicity in co-operation with T lymphocytes [43]. The downregulation of IFN-γ production, which is mediated by ImC, may also contribute to immune unresponsiveness in a tumor-bearing host. This mechanism suggests an approach to improve the immune response in cancer via the elimination of ImC. The most effective way to achieve this goal would be to differentiate immature myeloid cells using various growth factors and differentiation agents.

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