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Effect of tumor-derived cytokines and growth factors on differentiation and immune suppressive features of myeloid cells in cancer

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Abstract

It is well established that cancers affect differentiation of dendritic cells and promote systemic expansion of immune suppressive immature myeloid cells. This phenomenon may represent a mechanism of tumor escape from immune attack and could have significant impact on tumor progression. In this review we discuss the role of different tumor-derived factors, which were implicated in abnormal myeloid cell differentiation. The role of reactive oxygen species as well as JAK/STAT signaling in mechanisms of the effects of tumor-derived factors on myeloid cells is also discussed.

Keywords

tumor immunology; immune suppression; cytokines; growth factors; myeloid cells

I. Introduction

It has been repeatedly shown that tumor growth in mice manifests in splenomegaly, extramedullary hematopoiesis, neutrophilia, and increased presence of immature myeloid cells in the spleen, peripheral blood and bone marrow (1–7). These observations were made in a large number of different tumor models including colon carcinomas, lung carcinoma, mammary carcinomas, lymphoma and to a lesser extent fibrosarcomas (1–7). Most of these studies were performed in mice using a model of subcutaneous inoculation of tumor cells, however, orthotopic intrahepatic inoculation of metastatic colon carcinoma tumor cells also results in a systemic increase of immature myeloid cells (iMC) population in tumor host (1, 8). Importantly, spontaneous tumor development in transgenic mice with tissue-restricted expression of oncogene also promotes an expansion of iMC (2). iMC, which accumulate in tumor-bearing mice, are double positive for Gr-1 and CD11b myeloid cell markers. This is a heterogeneous population of myeloid cells that comprises of immature macrophages, granulocytes, DCs and myeloid cells at early stages of differentiation. iMC have immune suppressive features and are able to inhibit T cell immune responses. Several groups have demonstrated that this phenomenon is associated with T cell dysfunction including: i) loss or significant decrease of the expression of the T cell receptor ζ chain (CD3 ζ), which is the principal part of TCR complex (9); (ii) inhibition of CD3/CD28-induced T cell activation/proliferation by production of reactive nitrogen and oxygen intermediates (1); (iii) inhibition of interferon- γ (IFN- γ) production by CD8⁺ T cells in response to the specific peptide presented by MHC class I molecules (10); (iv) prevention of the development of CTL *in vitro* (11). Since

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cancer progression is associated with an increased production of immature myeloid cells and APC precursors, this could be one of the potential mechanisms by which growing tumors in their host may induce an antigen specific immune unresponsiveness.

Similar findings have been recently reported in cancer patients. Decreased presence of DCs in the peripheral blood of patients with breast, lung, head and neck cancer was associated with accumulation of cells lacking markers specific for mature myeloid and lymphoid lineage (12). About one-third of these cells were immature macrophages and DCs, and the remaining cells were immature myeloid cells at earlier stages of differentiation (13). The presence of these cells was dramatically increased in the patients with advanced stage cancers, but dropped considerably within 3–4 weeks after surgical resection of the tumor. These findings are consistent with the hypothesis that the generation of iMC is due to the production of soluble factors by tumors. Resection of experimental tumors also resulted in decrease in the number of immature Gr-1⁺/CD11b⁺ cells and increase in the number and function of CD3⁺ T cells in the spleen (4).

II. Tumors affect differentiation of iMC into dendritic cells but drive its differentiation into tumor-associated macrophages

iMC derived from peripheral blood of cancer patients (12) or from spleen of tumor-bearing mice (14) can be differentiate *in vitro* in the presence of GM-CSF and IL-4 toward mature MHC class II-positive dendritic cells or macrophages. Addition of tumor cell supernatants significantly delays APC differentiation and increases proportion of immature myeloid cells (15). This is consistent with the idea that tumors block or significantly delay APC differentiation and simultaneously induce accumulation of its myeloid precursors. Interestingly, freshly derived iMC could not survive *in vitro* in the absence of growth factors and most of them die within 24 hours after culture initiation (SK and DG, unpublished observation). This observation also underlines the undifferentiated immature status of these myeloid cells, which require the presence of cytokines or growth factors in order to survive and differentiate into mature myeloid cell. To evaluate the ability of iMCs to differentiate *in vivo*, we adoptively transferred Gr-1⁺ cells derived from tumor-bearing or naïve control mice into *congenic* naïve mice. We found that Gr-1⁺ cells derived from naïve and tumor-bearing mice significantly differ in their ability to differentiate in a tumor-free environment. Almost all iMC isolated obtained from tumor-free mice differentiated into mature DC and macrophage within 5 days after the transfer into congenic mice. In contrast, a substantial proportion of iMC derived from tumor-bearing mice retained the phenotype of immature cells (16). In order to investigate fate of iMC *in vivo* in tumor host, we have transferred freshly purified Gr-1⁺ cell into congenic mice with pre-established syngeneic tumor. Obtained results indicate that growing tumors severely affect differentiation of immature myeloid cells (16). Thus, when Gr-1⁺ cells from tumor-bearing mice were transferred into tumor-bearing recipients very few DCs of the donor's origin were found in spleens of recipients. These data were consistent with previously published observations that tumor-derived factors inhibit differentiation of DC from hematopoietic progenitor cells (17). Interestingly, many of Gr-1⁺ cells after adoptive transfer into congenic tumor-bearing mice could be recruited in tumor-site (18). Most of these cells become F4/80⁺ tumor-associated macrophages. In fact, more than 70 % of transferred cells isolated from the tumor site were positive for F4/80 marker. At the same time, a significant portion of those cells also retained an immature phenotype (Gr-1⁺CD11b⁺). These results suggest that splenic Gr-1⁺ iMC could be precursors of F4/80 tumor-associated macrophages.

III. Tumor-secreted factors are responsible for abnormal DC differentiation and the expansion of immature myeloid cells in tumor host

Accumulation of Gr-1⁺ iMC cells in tumor-bearing mice is gradual time-dependent process, which directly correlates with time and tumor mass (DG and SK, unpublished observation). This phenomenon is systemic. Alternatively, surgical resection of tumor results in a gradual decrease of iMC's numbers and normalization of the cellular phenotype of the spleen (4). These observations suggest a *direct* role of tumor-derived factors in dysregulation of myelopoiesis in tumor host, inhibition of DC differentiation and expansion of iMC in peripheral organs. Indeed, several different tumor-derived factors including VEGF, GM-CSF, IL-10, IL-6, TGF-beta, prostaglandins and gangliosides have been implicated in this phenomenon. Importantly, these different tumor-derived factors affect myeloid cells on various stages of differentiation. The list of tumor-derived factors that affect myeloid cell differentiation is not complete and is constantly growing.

I.A. VEGF

Vascular endothelial growth factor (VEGF) is produced by most tumors and has a crucial role in the development of tumor neovasculature. Increased levels of VEGF in the plasma of patients with cancer have been shown to correlate with an adverse prognosis (19). It has also been established that VEGF is involved in tumor-induced abnormalities of DC differentiation (17) and *an* inverse correlation between the density of DCs and the expression of VEGF has been demonstrated within tumor tissue and peripheral blood of cancer patients (20). The elevated level of circulating VEGF in cancer patients also closely correlated with increased number of iMC. The involvement of VEGF in tumor-induced defects in DC differentiation was demonstrated initially by *in vitro* experiments in which neutralizing VEGF-specific antibody abrogated the negative effect of tumor-cell-conditioned medium on the differentiation of DCs from HPCs (17). This observation has been confirmed in studies performed *in vivo* (21). Thus, continuous VEGF infusion in naïve animals resulted in a dramatic inhibition of dendritic cell development, associated with increase in the production of B cells and immature Gr-1⁺ myeloid cells (21). Chronic administration of VEGF was associated with inhibition of the activity of the transcription factor NF-kappaB in hematopoietic progenitor cells, which was accompanied by alterations in the development of multiple lineages of hematopoietic cells. *In vivo* administration of VEGF also abrogated the stimulatory effect of FLT3L on DC production (22). Consistent with this, administration of neutralizing VEGF-specific antibody to tumor-bearing mice improved DC differentiation and increased the number of mature DCs (23,24). More recent studies indicate that VEGFR1 is a primary mediator of the VEGF inhibition of DC maturation (25), whereas VEGFR2 tyrosine kinase signaling is essential for early hematopoietic differentiation, but only marginally affects final DC maturation. VEGFR1 signaling was sufficient to block NF-kappaB activation in bone marrow. Recently, an inhibitory effect of VEGF on DC differentiation has been shown in patients with gastric cancer or non-small-cell lung cancer (26). These data suggest that targeting of VEGFR1 could be effective strategy to reverse immune suppressive effects in cancer patients.

III. B. GM-CSF

Physiologic concentrations of GM-CSF are required for normal myelopoiesis and DC differentiation. However, excessive amounts of this growth factor could exert immune suppressive effects and could be responsible for induction of iMC. Thus, chronic administration of GM-CSF to mice results in generation of immune suppressive Gr-1⁺CD11b⁺ cell population that morphologically resembled granulocyte-monocyte progenitors (14). These Gr-1⁺CD11b⁺ cells could be differentiated *in vitro* in the presence of IL-4 and GM-CSF to genuine mature, fully functional antigen-presenting cells.

Some types of tumors express and produce GM-CSF constitutively. It has been reported that about 30% of 75 tested human tumor cell lines spontaneously secrete this cytokine (14). Experimental tumors that release GM-CSF have shown to induce systemic increase of immature myeloid cells tumor host, which is associated with suppression of T cell immune response (14,27–29). Administration of anti-GM-CSF and anti-IL-3 antibodies in vivo abrogated accumulation of tumor-induced immune suppressive granulocyte/macrophage progenitor cells in mice bearing Lewis lung carcinoma (30). Production of GM-CSF correlated with the ability of tumor cells to spontaneously metastasize (30). It is important to note that GM-CSF has shown therapeutic potential as a component of cancer vaccines. When irradiated and administered intradermally as vaccines, cancer cells that are genetically engineered to secrete GM-CSF elicit potent anti-tumour immune responses in various animal tumor models (31). However, as we mentioned above, it seems that production of large amounts of GM-CSF by some tumors is detrimental to the host immune system. This hypothesis was recently confirmed by Serafini et al., who showed that vaccination of mice with tumor cells producing large amounts of GM-CSF generated a large number of GR1⁺ immunosuppressive iMCs (27); consequently, this had a negative impact on the effect of vaccination.

III.C. IL-10

Various tumor cells express and release IL-10. This cytokine is also produced by tumor-infiltrating lymphocytes and tumor-associated macrophages (32). It appears that IL-10 does not affect relatively immature myeloid cells, however this cytokine is potent modulator of differentiation and antigen-presenting function of more mature myeloid cells such as macrophages and dendritic cells. In tumor-bearing mice, tumor-induced IL-10 was found to be specifically responsible for DC dysfunction in response to antigen-driven maturation in vivo. This was shown by the improvement of DC function in tumor-bearing IL-10-deficient mice (33). IL-10 is able to convert immature DC into tolerogenic APC through decreased expression of co-stimulatory molecules (34). Subsequently, DCs derived from transgenic mice that over-express IL-10 markedly suppressed allogeneic T-cell responses, CTL responses and IL-12 production (35). IL-10-treated human DCs have been found to induce CD4⁺ and CD8⁺ T cells that suppress the antigen-specific proliferation of other T cells through cell–cell contacts (36). It has also been reported to block the differentiation of monocytes into DCs, and to promote their maturation into macrophages (37). Tumors through production of IL-10 may inhibit broad range of macrophage functions including tumor cytotoxicity, production of IL-12 and nitric oxide (38). It is important to note that IL-10 could also function as a mediator of PGE2, which is also secreted by many types of tumors. Thus, suppressive effect of PGE2 on IL-12 production by DCs and its immune stimulatory potential could be completely reversed by specific anti-IL-10 neutralizing antibody (39). IL-10 itself inhibits function of Langerhans cells (40–42) and DCs derived from CD14⁺ monocyte precursors or CD34⁺ progenitors (34, 43). However, co-administration of IL-10 and the DC growth factor FLT3L to mice did not alter the yield of generated DCs (44). Taken together, these observations indicate that tumor-derived IL-10 might directly affect the generation of antigen-presenting cells at relatively late stages of myeloid cell differentiation.

III. D. M-CSF and IL-6

Both M-CSF and IL-6 are potent modulators of myeloid cell differentiation. It has been found that human renal cell carcinoma cells release large amounts of M-CSF and IL-6, which inhibit the differentiation of myeloid progenitor cells into DCs and promote their commitment toward monocytic lineage (45). These monocytic cells were found to have characteristic features of macrophages in terms of morphology and function, with high phagocytic capacity and poor APC function. Combination of neutralizing IL-6- and M-CSF-specific antibodies abrogated the negative effect of renal-cell-carcinoma-conditioned medium on DC differentiation from CD34⁺ myeloid progenitor cells (45,46), whereas addition of exogenous IL-6 and M-CSF had

an inhibitory effect on DC differentiation (46). The inhibition of DC differentiation by RCC CM was preceded by an induction of M-CSF receptor (M-CSFR) and a loss of granulocyte-macrophage colony-stimulating factor receptor α (GM-CSFR α) expression at the surface of CD34⁺ cells, two phenomenon reversed by anti-IL-6/IL-6R and anti-M-CSF antibodies, respectively. Interestingly, that using the combination of other cytokines such as IL-4 and IL-13 could reverse the inhibitory effects of either renal-cell-carcinoma-conditioned medium or IL-6 and M-CSF on the phenotypic and functional differentiation of CD34⁺ cells into DCs (46). The protecting effect of IL-4 on DC differentiation involved a down-modulation of the expression of M-CSF receptor at the surface of DC progenitors early during the differentiation process, a decrease in M-CSF production, and also the maintenance of GM-CSFR α expression. In recent study, IL-6 was found to suppress DC maturation *in vivo* (47). Involvement of IL-6 in inhibition of DC differentiation has also been shown in patients with multiple myeloma (48). It has been demonstrated that sera from the bone marrow of patients with multiple myeloma inhibited the generation of DCs. Anti-VEGF and/or IL-6-specific antibodies neutralized this inhibitory effect (49). Taken together, it suggests that IL-6 and M-CSF are involved in the inhibition of DC development in certain types of cancer.

III. E. Gangliosides

Gangliosides are ubiquitous membrane-associated sialic-acid-containing glycosphingolipid, which are involved in the regulation of cellular proliferation and differentiation (50). Most tumor cells synthesize and shed large amounts of gangliosides into their microenvironment and, eventually into circulation. Neuroblastomas and other tumors, such as medulloblastomas, melanomas, leukaemias, lymphomas and breast tumors, express abnormal patterns of gangliosides compared with the corresponding normal tissues (51). Approximately 100 different gangliosides have been detected in different tissues; these include GD2, GD3 and GM3, which have an important role in tumor progression. Tumor-derived gangliosides are potent modulators of myeloid cell proliferation and its differentiation into antigen-presenting cells (52). The neuroblastoma tumor cell supernatants, which contained high amounts of gangliosides have been shown to profoundly (up to 90%) inhibit generation of DCs from mouse bone-marrow progenitors or from human CD34⁺ precursors (52). When purified from human neuroblastoma gangliosides were added to DC cultures, they caused similar effect on *in vitro* DC generation. GM3 and GD3 gangliosides purified from melanoma also inhibited phenotypic and functional differentiation of DC from blood-derived monocytes in dose-dependent manner (53). Furthermore, these gangliosides induced DC apoptosis.

III. F. Prostaglandines

Prostaglandines (PGE) are strong immune modulators, which normally secreted in course of immune response by many types of cells including APCs i.e. macrophages and dendritic cells. Autocrine production of PGEs is indirectly involved in regulation of IL-12 production through stimulation of IL-10 production (54) and also it has been implicated in regulation of APC differentiation/maturation from myeloid cell precursors. Frequently, prostaglandins, mainly PGE₂, have been implicated in this tumor-associated subversion of immune function, with immune reactivities to tumor typically being enhanced by prostaglandin synthesis inhibitor. In fact, it has been demonstrated that cyclooxygenase-2 (COX-2) overexpression is a widely recognized feature of human lung, colon, breast cancer and prostate cancers. Interestingly, freshly excised solid human tumor cells produce substantially more PGE than established tumor cell lines (55). Subsequently, while primary tumor cell conditioned media profoundly hampered the *in vitro* DC differentiation from CD14⁺ monocytes or CD34⁺ myeloid precursors, the effects of tested tumor cell line-derived supernatants were minor (55). COX-1- and COX-2-regulated prostanoids were found to be solely responsible for the observed reduced differentiation of monocyte-derived DC. In contrast, both PGE and IL-6 were found to contribute to the tumor-induced inhibition of DC differentiation from CD34 + myeloid

precursor cells. Recent study shows that tumor-induced dendritic cell abnormalities at least partially mediated by the prostaglandin EP2 receptor (56).

III. G. TGF-beta

Transforming growth factor-beta (TGF-beta) is a potent regulator of numerous processes including hematopoiesis, cell proliferation, differentiation and activation. TGF-beta is also known as the most potent immunosuppressive cytokine described to date. Evidence exists that the immunosuppressive potential of TGF-beta is an important promoter of malignant cell growth. Many tumors secrete this cytokine. It has been reported that tumor-derived TGF-beta is involved in regulation of immune suppressive activity of iMC. In early studies of Young and colleagues (57) tumor-derived TGF-beta was found to be responsible for increase of immune suppressive activity of immature myeloid cells cultured with Lewis lung carcinoma (LLC) tumor cell supernatant. When anti-TGF beta antibodies were added to the LLC supernatants, the suppressive activity of bone myeloid cell was diminished. These results suggest that the tumor-induced immune suppressive activity of immature myeloid cells is mediated at least partially through production of TGF beta. Murine fibrosarcoma has been shown to induce immune suppressive macrophages in tumor host through the production of increased amounts of TGF-beta (58). There is evidence that tumor-derived TGF-beta may induce overproduction of IL-10, which in turn stimulate immune suppressive features of myeloid cells and/ or macrophages (59).

IV. Role of reactive oxygen species in tumor-induced abnormal differentiation and function of myeloid cells

Until recent years, the role of ROS in immunity was limited to innate immune responses and mainly to anti-microbial defense. Indeed, huge amounts of ROS are generated by phagocytic cells, which utilize oxidative burst to kill invading microorganisms (60). There is ample evidence now that iMC in both cancer patients and tumor-bearing mice produce increased amounts of reactive oxygen species (ROS) (9,16,61,62). Recent studies have shown that peripheral blood of patients with metastatic adenocarcinomas of the pancreas, colon and breast, contains unusually large numbers of activated CD15⁺ granulocyte-type myeloid cells with the accompanying markers of oxidative stress. Decreased IFN- γ production by patient's T cells and reduced T-cell receptor zeta-chain expression correlated with the presence of activated granulocytes in their PBMCs (61).

Gr-1⁺CD11b⁺ iMCs have been found to be a major source of ROS in tumor-bearing mice (16). Myeloid cells from tumor-bearing mice had significantly higher levels of ROS than their counterparts from tumor-free mice. Hydrogen peroxide, but not superoxide radical anions was found to be the major component of this increased ROS production in splenic iMCs derived from mice with tumors. Importantly, this tumor-induced production of ROS by iMCs was found as one of the major mechanisms, by which tumors stimulate proliferation of iMC and prevent its differentiation into mature of antigen-presenting cells (16). It was demonstrated that the high levels of hydrogen peroxide production by myeloid cells maintains its highly proliferative and undifferentiated status, whereas scavenging of ROS could diminish proliferation and stimulate differentiation of iMC.

ROS produced by myeloid has been implicated for inhibition of antigen-specific T cell response through down-regulation of the CD3 ζ chain of the TCR complex in tumor-bearing mice (9). Inhibition of ROS in iMC completely abrogated the negative effect of iMC (62). Interaction of iMC with antigen-specific T cells in the presence of specific, but not control antigen, resulted in a significant increase of ROS production. This effect depends on MHC class I expression by iMCs, is not mediated by soluble factors and requires direct cell-cell contact (62). Taken

together, these findings suggest that ROS produced by iMC are involved: 1) in inhibition of T cell responses in both cancer patients and tumor-bearing animals; 2) in mechanisms of abnormal differentiation of myeloid cells which is observed in cancers.

How can tumor activate ROS in myeloid cells? Is there a link between tumor-secreted factors and increased ROS production? A number of cytokines and growth factors may induce ROS production. ROS have been shown to be involved in the mitogenic cascade initiated by the receptors of several growth factors such as GM-CSF, TGF-beta, EGF, PDGF. Hyperproduction of some of these factors by tumor cells may result in constant stimulation of ROS in myeloid cells, which may prevent their effective differentiation. ROS regulate transcription of many genes via their effect on several transcription factors including NF- κ B, AP-1, c-myc, SP-1 and others (63). Tumor-stimulated ROS production may alter the balance of expression of different genes, which may affect differentiation of myeloid cells.

V. JAK/STAT signaling pathway and tumor-associated dysregulation of myeloid cell differentiation

The tumor-derived factors that have been implicated in abnormal DC differentiation bind different receptors on hematopoietic cells. This indicates that, to exert similar functional effects on DC differentiation, the cellular response to these factors needs to converge at the level of signal transduction. Recent studies have identified one possible pathway involving JAK2 and STAT3. The Janus activated kinase (JAK) family of tyrosine kinases and signal transducer and activator of transcription (STAT) proteins are crucial components of diverse signal-transduction pathways that are actively involved in cellular survival, proliferation, differentiation and apoptosis. Four members of the JAK family have been identified in mammals (JAK1, JAK2, JAK3 and TYK2) (64). JAKs are constitutively associated with many cytokine and growth factor receptors, including those implicated in defective DC differentiation. The binding of a cytokine to its receptor induces receptor oligomerization, which triggers JAK activation by either auto- or transphosphorylation. Although JAK activation might contribute to the specificity of the receptors, the JAKs are not absolute determinants of the specificity of cytokine-mediated signalling, because different cytokines can activate the same JAKs (65). Following ligand binding, the activated JAKs phosphorylate receptors on target tyrosine residues, generating docking sites for STATs through the STAT src homology 2 (SH2) domain. STATs are subsequently recruited and phosphorylated by activated JAKs. After that they are dimerized and translocated to the nucleus, where they modulate the expression of target genes. The STAT family of transcription factors consists of seven members (STAT1, -2, -3, -4, -5A, -5B and -6). Aberrant activation of JAKs has been observed in several hematological malignancies (66),(67). In addition, constitutive activation of STAT3 has been shown in most tumors and is crucial for tumor-cell proliferation and survival. STAT3 signaling is important for normal process of DC differentiation (68). However, hyperactivation of JAK2/STAT3 signaling pathway may negatively affect differentiation of these cells. When HPCs were cultured in the presence of tumor-cell-conditioned medium myeloid cells maintained high levels of STAT3 activity (15). This resulted in the accumulation of iMCs with a high proliferative potential. These cells could not differentiate into mature DCs, even in the presence of appropriate growth factors (15). However, DC differentiation was restored after removal of tumor-derived factors. Inhibition of STAT3 activity using a dominant-negative STAT3 or a STAT3-selective inhibitor abrogated the negative effects of these factors on myeloid-cell differentiation (15,69), whereas expression of constitutively active STAT3 reproduced the effects of tumor-derived factors. These data indicate that Jak2/STAT3 pathway may be important mediator of signaling from soluble tumor-derived factors.

VI. Conclusions

Various tumor-derived factors may alter myeloid cell differentiation and maturation *via* different surface receptors and different signaling pathways. However, common feature of various tumor-derived factors is that its action results in inhibition of DC differentiation/maturation and subsequent increase of undifferentiated myeloid cells in tumor host. iMC have certain biochemical features, which allow them to inhibit T cell responses and prevent development of adaptive anti-tumor immune attack. This phenomenon may represent a frequent mechanism by which tumor cells escape immune recognition and could have significant impact on tumor progression. Initially, it was thought that one factor could be responsible for the observed phenomenon. However, almost a decade of intensive research failed to define such a factor, and it is now clear that the abnormal differentiation of DCs in cancer is the result of the combined effect of many different factors. It appears that the combinations of tumor-derived factors varies from cancer to cancer, and depends mostly on tumor type. It is possible that signaling from various receptors converge on common signal transduction pathway, for instance Jak2/STAT3 (Fig. 1). Tumor-derived factors can activate production of ROS and inhibit transcription factors NF- κ B (Fig. 1). In addition, these pathways may interact with each other. For instance, ROS may activate STAT3 and NF- κ B, STAT3 can inhibit NF- κ B, activation of STAT3 may result in increased synthesis of the members of NADPH complex, which in turn may result in increased production of ROS (Fig. 1). More studies are needed to clarify these complex interactions. In addition, it is likely that not all tumor-derived factors able to affect myeloid cell differentiation are identified. We can expect new exciting findings in this area. In order to improve cancer vaccination strategies and enhance immune response against tumors, it is critically important to identify molecular targets and signaling pathways utilized by tumor-derived factors to affect process of differentiation and/or function of antigen-presenting cells. This probably will be the main focus of research in near future.

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Figure 1.
Possible effect of tumor-derived cytokines on signaling in iMC