Myeloid-Derived Suppressor Cells in the Development of Lung Cancer

Myrna L. Ortiz¹, Lily Lu¹, Indu Ramachandran¹,², and Dmitry I. Gabrilovich¹,²

Abstract

Myeloid-derived suppressor cells (MDSC) are widely implicated in immune suppression associated with tumor progression and chronic inflammation. However, very little is known about their possible role in tumor development. Here, we evaluated the role of MDSC in two experimental models of lung cancer: inflammation-associated lung cancer caused by chemical carcinogen urethane in combination with exposure to cigarette smoke; and a transgenic CC10Tg model not associated with inflammation. Exposure of mice to cigarette smoke alone resulted in significant accumulation in various organs of cells with typical MDSC phenotype (Gr-1⁺CD11b⁺). However, these cells lacked immunosuppressive activity and could not be defined as MDSC. When cigarette smoke was combined with a single dose of urethane, it led to the development of tumor lesions in lungs within 4 months. By that time, Gr-1⁺CD11b⁺ cells accumulated in the spleen and lung and had potent immunosuppressive activity, and thus could be defined as MDSC. In the CC10Tg model, accumulation of immunosuppressive MDSC was observed only at 4 months of age, after the appearance of tumor lesions in the lungs. Accumulation of MDSC in both models was abrogated in S100A9 knockout mice. This resulted in a dramatic improvement in survival of mice in both models. Thus, cigarette smoke results in the expansion of immature myeloid cells lacking suppressive activity. Accumulation of bona fide MDSC in both models was observed only after the development of tumor lesions. However, MDSC played a major role in tumor progression and survival, which suggests that their targeting may provide clinical benefits in lung cancer.

Introduction

Myeloid-derived suppressor cells (MDSC) are one of the major factors that negatively regulate immune responses in cancer (1, 2). In mice, these cells are defined as Gr-1⁺CD11b⁺ cells comprising pathologically activated CD11b⁺Ly6C⁺Ly6G⁻ immature granulocytes, CD11b⁺Ly6C⁻Ly6G⁺ monocytes, and a small proportion of myeloid precursors. The main characteristic of these cells is their potent ability to suppress T-cell function. In addition, MDSC promote tumor progression through a number of different other mechanisms (3). The role of MDSC in tumor progression is well established. In contrast, the contribution of these cells to tumor development is not clear. Some cells with a typical MDSC phenotype are present in healthy individuals and control mice. However, these cells lack immunosuppressive activity and largely represent immature myeloid cells (IMC). Therefore, the term IMC was coined to distinguish these cells from MDSC. In tumor-bearing mice, the accumulation of MDSC is usually observed after the tumor has become palpable (4). In patients with cancer, a strong association between stage of cancer and presence of MDSC has been established in various types of cancer (5–9). Proinflammatory factors were always considered a critical element of MDSC accumulation in cancer (10). In recent years, ample reports have described the appearance of cells with an MDSC phenotype and function in mice and human patients with various chronic infections and inflammation (11). These observations raised the possibility that MDSC can contribute directly to the development of tumors, as it is known that inflammation plays an important role in cancer development (12).

In this study, we tested possible contributions of MDSC to the development of lung cancer using two experimental models: a lung cancer model in CC10 transgenic mice (CC10Tg) and a lung cancer model caused by the injection of carcinogen urethane in combination with cigarette smoke. The mCC10TAg transgene was created by fusing the coding sequences of the SV40 TAg gene with the mCC10 promoter (13). This promoter targets transgene expression specifically to the proximal pulmonary lung epithelial Clara cells. The Clara cells are the nonciliated secretory cells of the pulmonary epithelium characterized by a large apical dome shape and abundant endoplasmic reticulum. At 2 months of age, CC10Tg mice display areas of hyperplasia of the bronchiolar epithelium. At 3 months of age, a number of tumor foci are observed, and after 4 months, the majority of the lung is composed of transformed cells (13).
Smoking is the leading cause of lung cancer. Each cigarette contains a complex mixture of polycyclic aromatic hydrocarbons along with other lung carcinogens, tumor promoters, and cocarcinogens (14). Tobacco-associated carcinogens by themselves may not recapitulate the exact nature of tobacco’s effect on tumor development. In addition to carcinogens, smoking causes chronic inflammation. The local lung inflammation initiated by cigarette smoke persists after patients have stopped smoking, generating smoking-independent oxidant stress, thus explaining the persistence and progression of the disease after smoking has been discontinued (15). The most appropriate model to recapitulate the complexity of the effect of cigarette smoke on mice is a smoking chamber in which mice are exposed to tobacco smoke for prolonged periods of time. This approach, however, requires a very long exposure of mice to smoke and results in the development of lung cancer only in a proportion of mice (16). Therefore, cigarette smoke is combined with the use of chemical carcinogens. In this study, we used urethane, a tobacco-related carcinogen known to induce lung cancer (17, 18).

To clarify the role of MDSC in the development of lung cancer, we used S100A9 knockout mice. S100A9 was implicated in the abnormal differentiation of myeloid cells in cancer and the accumulation of MDSC (5, 19–22). The expansion of MDSC was significantly reduced in S100A9-deficient tumor-bearing mice and mice treated with complete Freund’s adjuvant (CFA; refs. 21, 22). Consistent with these findings, dendritic cells derived from S100A9-deficient mice induced stronger response of allogeneic T cells (23). Using these experimental models, we tested the hypothesis that MDSC are directly involved in the development of experimental lung cancer. Our results demonstrated that although immunosuppressive bona fide MDSC are critically important for tumor progression, and their presence negatively affects the survival of mice, the initial phase of tumor development is not associated with immunosuppressive MDSC. In our smoking model, cigarette smoke caused strong accumulation of IMC lacking immunosuppressive activity. MDSC accumulated in these mice only after tumor lesions became detectable. In the transgenic model of lung cancer, MDSC accumulation was also evident after tumor development.

Materials and Methods
Mice
All animal experiments were approved by the University of South Florida (Tampa, FL) Institutional Animal Care and Use Committee (IACUC). Mice were housed in pathogen-free facilities. FVB/N and C57BL/6 mice were obtained from the National Cancer Institute (Frederick, MD). S100A9KO mice on C57BL/6 background were described previously (24). These mice were backcrossed to FVB/N background for 10 generations. CC10Tg mice were obtained from Dr. F. DeMayo (Baylor College of Medicine, Houston, TX) and described previously (13). These mice were on C57BL/6 background. CC10Tg mice were crossed with C57BL/6 S100A9KO mice for six generations with subsequent backcross to S100A9KO mice. CC10Tg+/- S100A9+/- mice were used in the experiments. The control group comprised CC10Tg+/- S100A9+/- mice from the same generation of backcross.

Lung carcinogenesis model
Exposure of mice to cigarette smoke was performed using a whole-body smoke inhalation system (Teague TE-10C; Teague Enterprises). Mice were exposed to an average of 250 mg/m³ total suspended particulate (TSP) of cigarette smoke for 2 hours/day, 5 days/week during 2 to 4 months using the standard Federal Trade Commission (FTC) method: a 2-second 35 cm³ puff once per minute for a total of nine puffs. TSP concentration was characterized daily by collecting particles on 25-mm Pallflex membrane filters. Standard reference cigarettes 3R4F were purchased from the Tobacco Research Institute (University of Kentucky, Lexington, KY) and used in this study. At the end of week 3 of smoke exposure, some mice received a single intraperitoneal injection of urethane (1.5 g/kg). Cigarette smoke continued for 3 to 4 more months. After 3 or 4 months of exposure to smoke, mice were euthanized and the presence of myeloid cells and the size and number of tumor lesions were evaluated.

Preparation of single-cell suspensions and antibody staining
Lungs were thoroughly minced and digested in RPMI-1640 medium containing collagenase XI (2 mg/mL; Sigma-Aldrich) at 37°C for 15 minutes. Samples were resuspended in calcium- and magnesium-free PBS-EDTA at room temperature. Red blood cells were lysed with ammonium–chloride–potassium buffer, washed in PBS-EDTA, and passed through a 50-μm cell strainer. After single-cell preparation, cells were counted and stained with the following antibodies: Gr1-APC, CD11b-PEy7, F480-PE, CD11c-FITC, Ly6C-FITC, and Ly6C-PE. All antibodies were from BD Biosciences. To obtain single-cell suspension from lymph nodes and spleens, tissues were smashed through a 70-μm strainer without the use of collagenase digestion. Peripheral blood was collected from the submandibular vein.

T-cell–suppressive activity of MDSC
In experiments with CC10Tg mice on C57BL/6 background, the effect of MDSC on antigen nonspecific (CD3/CD28 antibodies inducible) and antigen-specific (OVA-derived peptide-specific OT-1 CD8+ T cells) proliferation were measured. Briefly, T cells obtained either from wild-type (WT) C57BL/6 mice or from C57BL/6 OT-1 mice were labeled with carboxy-fluorescein diacetate succinimidyl ester (CFSE) and mixed with irradiated (20 Gy) syngeneic splenocytes at a 1:4 ratio. MDSC were added at different ratios and cells were stimulated with either 1 μg/mL CD3 and 0.5 μg/mL CD28 antibodies or 0.5 μg/mL OT-1–specific peptide SIINFEKL. Proliferation of T cells was assessed 72 hours later by flow cytometry. Experiments were performed in triplicate.

In experiments with urethane/cigarette smoke models on FVB/N background, antigen-specific T-cell proliferation was assessed using allogeneic mixed leukocyte reaction. Briefly, 10⁵ splenocytes from BALB/c mice (responders) were mixed with 10⁵ T cell–depleted and irradiated (20 Gy) splenocytes from FVB/N mice (stimulators) in U-bottom 96-well plates.
Fluorescence-activated cell sorting (FACS)–purified Gr-1+ cells were added into wells at different ratios. On day 4, cells were pulsed with 3H-thymidine (1 μCi/well; GE Healthcare) for 18 hrs. 3H-thymidine uptake was counted using a liquid scintillation counter and expressed as counts per minute (cpm).

**Evaluation of lung tumors**
Whole lungs were flushed with PBS and fixed in 4% paraformaldehyde for at least 24 hours and paraffin embedded. Paraffin-embedded lungs were serially sectioned transversally at 4 μm and histologically examined with hematoxylin and eosin (H&E) stain.

**Evaluation of myeloid cells by flow cytometry**
Several populations of myeloid cells were evaluated in this study: (i) IMC/MDSC defined as Gr-1+CD11b+ cells, including subset of CD11b+Ly6CloLy6G+ granulocytic and CD11b+Ly6ChiLy6G/CD0 monocytic cells; (ii) macrophages (MΦ), which were defined as Gr-1−CD11b−F4/80− cells; and (iii) dendritic cells, defined as Gr-1−F4/80+CD11c+ cells.

**Statistical analysis**
Statistical analysis was performed using unpaired two-tailed Student t test with significance determined at P < 0.05. For the analysis of survival, log-rank Mantel–Cox analysis was used.

**Results**
**Myeloid cells in spontaneous model of lung cancer**
To assess the potential role of MDSC/IMC in the development of lung cancer in oncogene-driven transgenic model, we used CC10Tg C57BL/6 mice. Consistent with a previous report (13), these mice develop multiple tumor lesions in the lungs by 4 months of age (Fig. 1A). CC10Tg mice had a significantly higher proportion of Gr-1+CD11b+ cells in the peripheral blood at 2.5 to 3 months of age (Fig. 1B), and higher presence of these cells in the spleens and lymph nodes at 3 to 4 months of age (Fig. 1C and D). No differences in the proportion of Gr-1−CD11b− cells among CD45+ hematopoietic cells in the lung were found at that time between WT and CC10Tg mice (Fig. 1E). In contrast, the proportion of MΦ in the lungs increased significantly in CC10Tg mice at 3 months of age (Fig. 1F).

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![Figure 1](image.png)

**Figure 1.** The accumulation of myeloid cells in a spontaneous lung cancer model. A, lung tissues from CC10Tg mice at 4 months of age were harvested and stained with H&E. Images (magnification, ×20) are representative of lung tissues from 5 mice. B–D, percentages of Gr-1+CD11b+ cells in peripheral blood (B), spleen (C), and lymph nodes (LN; D) from CC10Tg mice and WT mice at indicated ages. Representative FACS data are shown in top. E and F, the proportions of MDSC (E) and macrophages (F) among CD45+ hematopoietic cells isolated from lungs. In all panels mean and SEM from 3 to 6 mice per group are shown. *, P < 0.05 between CC10Tg and WT mice.
Thus, Gr-1<sup>+</sup>CD11b<sup>+</sup> cells increased in peripheral blood, spleens, and lymph nodes of CC10Tg mice around the time of the appearances of the first tumor lesions (3 months) and expanded further by 4 months. We previously found that lung Gr-1<sup>+</sup>CD11b<sup>+</sup> cells from 4-month-old CC10Tg mice had potent immunosuppressive activity (25). We asked whether the spleen Gr-1<sup>+</sup>CD11b<sup>+</sup> cells from 3-month-old mice had immunosuppressive activity. The cells were tested on their ability to inhibit CD3/CD28<sup>+</sup>-inducible T-cell proliferation (Fig. 2A) and the proliferation of OT-1 T cells in response to the specific OVA-derived peptide—SIINFEKL (Fig. 2B). In both cases, no inhibition of T-cell proliferation was observed (Fig. 2A and B).

To establish a possible role of MDSC in the natural progression of lung tumors in CC10Tg mice, we crossed CC10Tg mice with S100A9KO mice. In contrast with CC10Tg mice, double-transgenic S100A9KO/C2 CC10Tg mice had no upregulation of Gr-1<sup>+</sup>CD11b<sup>+</sup> cells in the peripheral blood (Fig. 3A). Survival of S100A9KO/C2 CC10Tg mice was significantly enhanced compared with CC10Tg mice (Fig. 3B). Analyses were performed at the indicated time points. Each group included 3 mice.
$P = 0.0001$) higher than that of the single-transgenic CC10Tg mice (Fig. 3B). These results indicate that MDSC accumulation in the transgenic model of lung cancer did not precede the formation of lung tumors, but was rather the result of tumor development. However, MDSC significantly affect tumor progression, which was manifested in better survival of S100A9KO mice.

Exposure of mice to cigarette smoke induces expansion of myeloid cells in mice

To better clarify the role of MDSC in lung cancer directly associated with inflammation, we used the cigarette smoke model in FVB/N mice. First, we asked whether cigarette smoke alone affected the presence of different populations of myeloid cells. Cigarette smoke did not change the total number of Gr1+CD11b+ cells. However, the proportion of Gr1–F4/80+ cells was significantly increased in the lung of smoking mice compared to controls (Fig. 4A). Similarly, the proportion of CD11c+ cells was increased in the spleen and lung of smoking mice (Fig. 4B). In contrast, the proportion of Ly6G/Ly6C ratio was not significantly affected by smoking (Fig. 4B).

Figure 4. The proportion of myeloid cells in the peripheral blood of mice exposed to cigarette smoke. FVB/N mice were exposed to cigarette smoke for 1 month (A) and 3 months (B). The proportions of the indicated population of myeloid cells were evaluated. Each group included 3 mice. $P$ values were calculated in two-tailed Student t test. ns, $P > 0.05$.

Figure 5. The proportion of myeloid cells in different organs of mice exposed to cigarette smoke. Mice were exposed to cigarette smoke for 4 months, and the proportions of the indicated populations of myeloid cells were evaluated in different organs. Each group included 3 to 6 mice. The proportions of cells isolated from the lungs were calculated among CD45+ hematopoietic cells. $P$ values were calculated in two-tailed Student t test. ns, $P > 0.05$.
leukocytes (data not shown). However, 1-month exposure to cigarette smoke caused a significant \( P = 0.01 \) increase in the presence of Gr-1\(^+\)CD11b\(^+\) cells in peripheral blood. Granulocytic and mononuclear subsets were equally increased and their ratio remained unchanged (Fig. 4A). Three-month exposure of mice to cigarette smoke did not further increase the presence of Gr-1\(^+\)CD11b\(^+\) cells in peripheral blood. It remained 2-fold \( (P = 0.003) \) higher than in control. However, the dramatic redistribution of myeloid cells toward granulocytic cells was evident (Fig. 4B). Despite some trend to an increase in mice exposed to cigarette smoke, the presence of M\( \Phi \) and dendritic cells was not significantly different from that in nontreated mice (Fig. 4B).

Myeloid populations in the bone marrow, spleens, and lungs were evaluated after 4 months of cigarette smoke exposure, which caused a significant \( P < 0.05 \) increase in the presence of Gr-1\(^+\)CD11b\(^+\) cells in all tested organs. In the spleens, this increase was associated with a preferential accumulation of granulocytic cells (Fig. 5). The population of M\( \Phi \) did not change in any tested organ, whereas the proportion of dendritic cells was significantly decreased in the lungs (Fig. 5).

Thus, cigarette smoke caused a substantial increase in the presence of Gr-1\(^+\)CD11b\(^+\) cells, which could be represented by MDSC. We evaluated the immunosuppressive activity of these cells. Gr-1\(^+\)CD11b\(^+\) cells were isolated from the spleens, lungs, or bone marrow and tested in different assays. These cells did not affect the CD3/CD28\(-\)inducible T-cell proliferation (Fig. 6A) or T-cell proliferation in allogeneic mixed leukocyte reaction (Fig. 6B). These results indicate that cigarette smoke by itself caused a substantial accumulation of IMC with granulocytic phenotype. However, these cells lacked immunosuppressive activity and thus were not bona fide MDSC.

**MDSC are critically important for tumor progression**

To assess the possible roles of MDSC in the development and progression of lung tumors, WT and S100A9KO FVB/N mice were treated with a single injection of urethane and 4-month exposure to cigarette smoke. This treatment resulted in the appearance of a small number of tumor lesions (Fig. 7A). No significant differences in the number of lesions were found between WT and S100A9KO mice at that time (Fig. 7B). However, in contrast with Gr-1\(^+\)CD11b\(^+\) cells isolated from spleens of mice exposed to cigarette smoke alone, cells with the same phenotype isolated from mice treated with urethane and cigarette smoke and bearing lung tumors had potent immunosuppressive activity (Fig. 7C). After 4 months of treatment, WT mice had a significant increase in the presence of MDSC, but not M\( \Phi \), in their spleens and lungs (Fig. 7D). The number of MDSC in S100A9KO mice was significantly lower, similar to the level seen in untreated mice (Fig. 7D). The number of M\( \Phi \) in S100A9KO mice was lower in the spleens but not in the lungs (Fig. 7D). MDSC isolated from the spleens of S100A9KO mice had significantly lower T-cell suppressive activity than MDSC from the spleens of WT mice (Fig. 7C).

In a separate set of experiments, we evaluated whether the lack of S100A9 had an effect on the survival of mice treated with urethane and cigarette smoke. The fate of the mice was drastically different. All WT mice succumbed to the disease within 5 months after the start of the treatment. In contrast, all S100A9KO mice were still alive at that time point \( (P = 0.005) \; \text{Fig. 7E} \). Thus, cigarette smoke, by itself, caused the expansion of IMC lacking immunosuppressive activity. Bona fide MDSC accumulated only after the appearance of tumor lesions in the lung. These cells, however, played a major role in tumor progression and survival of the mice.

![Figure 6](http://cancerimmunolres.aacrjournals.org/data/images/figure6.png)

**Figure 6.** Gr-1\(^+\)CD11b\(^+\) myeloid cells from mice exposed to cigarette smoke do not suppress T-cell proliferation. A, splenocytes from naïve FVB/N mice were stimulated with CD3- and CD28-specific antibodies in the presence of Gr-1\(^+\)CD11b\(^+\) IMC purified from control mice and mice exposed to cigarette smoke at the indicated IMC:splenocyte ratios. T-cell proliferation was measured in triplicate by \(^{3}H\)-thymidine incorporation. Each group included 3 mice. B, purified IMC from the spleens or lungs of smoking or control FVB/N mice were added at the indicated ratios to a mixed lymphocyte reaction, which was set up using splenocytes from BALB/C mice as responders and irradiated splenocytes from FVB/N mice as stimulators mixed at 1:1 ratio. T-cell proliferation was measured in triplicate by \(^{3}H\)-thymidine incorporation. Mean and SEM from three experiments are shown.
Discussion

In this study, we investigated the possible contribution of MDSC to the development of lung cancer. Although ample evidence has linked inflammation and cancer, the nature of the immune cells directly involved in the process of tumor development remained unclear. This is especially true for lung cancer. Cigarette smoke is the major cause of lung cancer, and inflammation is closely associated with smoking. Because MDSC are shown to be an inherent part of chronic inflammation, it was tempting to speculate that MDSC may be directly involved in the early stages of the development of lung tumor associated with chronic inflammation. To address this question, we used two contrasting models of lung cancer. Lung cancer in

CC10Tg mice is driven by the SV40Tag oncogene and is not associated with inflammation (refs. 13, 26; data not shown). Lung tumor lesions started as focal hyperplasia and advanced rapidly until a considerable portion of the lung parenchyma was represented by tumor masses. In this model, we observed the accumulation of cells with a typical MDSC phenotype and suppressive activity only in mice at 4 months of age when the lungs were already full of tumor lesions. Gr-1\(^+\)CD11b\(^+\) cells isolated from the spleens of mice at 3 months of age did not have T-cell suppressive activity. The appearance of lung tumor lesions was associated with the accumulation of Gr-1\(^-\)F4/80\(^-\)CD11b\(^+\) macrophages in the lungs. This observation is consistent with a previous report describing the differentiation of MDSC to
macrophages in tumor tissues (25). These data indicate that in CC10Tg mice MDSC were likely the consequence of tumor development. These results were predictable. We expected that the situation would be different in the model of lung cancer associated with the inflammation–cigarette smoke model. Indeed, even a 1-month exposure of mice to cigarette smoke led to an increase in the presence of Gr-1+CD11b+ cells in the peripheral blood, and 4 months of cigarette smoke caused a significant increase of these cells in the lungs and spleens. These cells were largely represented by the granulocytic subset. However, contrary to our expectation, these cells lacked immunosuppressive activity, indicating that they were not bona fide MDSC. Immunosuppressive MDSC accumulated in these mice only after the development of tumor lesions. These data suggest that in this model, MDSC accumulation was also the result of tumor formation. Our results are largely consistent with those of previous reports demonstrating the association of lung tumor formation caused by urethane injection with the accumulation of Gr-1+CD11b+ cells. However, whether those cells had immunosuppressive activity was not determined (27).

These data indicate that cigarette smoke, despite causing the expansion of IMC, was not sufficient to convert them into MDSC. These results are consistent with the two-signal concept of MDSC accumulation in cancer (28), suggesting that the expansion of IMC cells and their conversion to MDSC phenotype is governed by different factors and signaling pathways. Some factors involved in the expansion of IMC are well characterized [i.e., granulocyte macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF)]. However, the mechanism responsible for MDSC conversion is largely unclear and needs to be determined. Although bona fide MDSC are not present in mice until the appearance of tumor lesions, these cells are critically important for the survival of the mice. We addressed the role of MDSC in the natural history of lung tumor progression by using S100A9KO mice. The S100A9/S100A8 heterodimers (S100A8/A9) are expressed predominantly in myeloid cells. The differentiation of myelocytes and granulocytes is associated with an increase of S100A8/A9 expression, whereas the differentiation of MF and dendritic cells is associated with the loss of these proteins (29–32). We, and others, have shown that the accumulation of MDSC and the inhibition of dendritic cell differentiation in cancer were closely correlated with the upregulation of S100A8/A9 (19–21). The expansion of MDSC was significantly reduced in S100A9-deficient tumor-bearing mice and mice treated with CFA (21). The S100A8/A9 proteins were implicated in lung cancer progression. In an early study, S100A8 and S100A9 were shown to be important in attracting CD11b+ cells to premetastatic lung. Neutralizing anti-S100A8 and -S100A9 antibodies blocked the morphologic changes and migration of tumor cells and CD11b+ myeloid cells (33). In a more recent report, upregulation of S100A8/A9 in the lung adenocarcinoma was found to correlate with the stage of the disease (34). Patients with lung cancer overexpressing S100A9 had a significantly lower 5-year overall survival rate than patients with low or no expression of S100A9. Overexpression of S100A9 was an independent factor predictive of poor disease outcome (35). Consistent with these data, another study also found an association of the expression of S100A8/A9 in stromal cells with negative outcome in patients with lung cancer (36). Another recent report described a direct link of S100A9 and MDSC by demonstrating an accumulation of immunosuppressive CD14+ S100A9+ monocytic MDSC in patients with non–small lung cancer. The amount of these inflammatory monocytes was associated with poor response to chemotherapy (37). An upregulation of the S100A8 and S100A9 genes in the bronchial airway epithelial cell brushings was found to be associated with smoking (38).

These results suggested that a lack of S100A9 could decrease the accumulation of MDSC and thus open the opportunity to directly test the role of these cells in tumor progression. In our experiments, mice lacking S100A9 had reduced presence of MDSC in both experimental models. In the urethane/cigarette smoke model, it did not significantly reduce the number of initial tumor lesions. However, in both lung cancer models, the S100A9KO mice had much better survival than their WT counterparts. In a recent study on multiple myeloma, improved survival of S100A9KO tumor-bearing mice was associated with an enhanced tumor-specific response of CD8+ T cells, which could be reversed by the administration of MDSC (22).

Taken together, these data suggest that early stages of tumor development in cigarette smoke–related lung cancer are associated with the accumulation of nonsuppressive IMC. Bona fide MDSC appear only after the development of tumors and contribute greatly to tumor progression regardless of whether tumor development was associated with inflammation or not. This necessitates the search for a better way to therapeutically target these cells in patients with cancer. IMC, for their part, may play an important role in tumor development via mechanisms not involving immune suppression. We recently have found that IMC could promote the development of skin cancer by recruiting proinflammatory CD4+ T cells (data not shown). These results indicate that IMC and MDSC may be major factors in the regulation of various stages of tumor development and progression and their precise role needs to be further elucidated.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: M.L. Ortiz, L. Lu, D.I. Gabrilovich
Development of methodology: M.L. Ortiz, L. Lu, D.I. Gabrilovich
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Lu, I. Ramachandran
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.L. Ortiz, L. Lu
Writing, review, and/or revision of the manuscript: L. Lu, I. Ramachandran, D.I. Gabrilovich
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.L. Ortiz, L. Lu
Study supervision: M.L. Ortiz, L. Lu, D.I. Gabrilovich

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