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Lung Tumor Microenvironment and Myelomonocytic Cells

Minu K. Srivastava, Åsa Andersson, Li Zhu, Marni Harris-White, Jay M. Lee, Steven Dubinett and Sherven Sharma
University of California Los Angeles and Veterans Affairs Greater Los Angeles, USA

1. Introduction

The lung tumor microenvironment consists of tumor cells, stroma, blood vessels, immune infiltrates and the extracellular matrix. Genetic alterations in oncogenes and tumor suppressor genes or epigenetic changes in the tumor that modulate tumor growth and invasion into the surrounding tissue orchestrate the persistence of inflammatory infiltrates. These cellular infiltrates modulate tumor development and progression. The infiltrates vary by size and composition in diverse tumor types and at different stages of tumor development. The lung tumor programs the cellular infiltrates and dysregulates inflammation to sustain tumor growth, progression and hypo responsiveness of the tumor. Characterization of the complex interactions among the infiltrates and lung cancer will aid in defining their role in tumor progression. This understanding will be important for the development of novel anticancer therapies. Although this is not a trivial undertaking, the information garnered will take us a step closer to personalized medicine. If we know an individual's lung tumor inflammatory infiltrates, we will be able to predict the risk of tumor progression and then give specific treatment to reprogram the tumor microenvironment to control the disease.

Contributing to the inflammatory infiltrates are members of the innate system including natural killer cells (NK) and the cells of the myelomonocytic lineage consisting of immature macrophages, granulocytes, dendritic cells (DC) as well as myeloid cells at earlier stages of differentiation (Sica and Bronte 2007; Talmadge 2007; Gabrilovich and Nagaraj 2009; Peranzoni et al. 2010). The down regulation of MHC expression by tumors enables them to evade T cell immune responses. The presence of NK cells in the infiltrates can contribute to antitumor activity because NK effectors recognize tumor targets independent of MHC expression (Moretta et al. 2001). However, there is usually a paucity of NK cells in the tumor microenvironment suggesting evasion mechanisms preventing their recruitment. Macrophages in the tumor microenvironment play an important modulatory role in the generation of anti tumor responses. The production of chemotactic factors such as CCL2, VEGF and M-CSF (Condeelis and Pollard 2006; Sica et al. 2008) in the tumor microenvironment recruits macrophages. The type of macrophages infiltrating the tumor correlates with favorable or unfavorable prognoses (Lewis and Pollard 2006). The M1

macrophages have potent antigen presentation function and stimulate Type 1 immune responses that lead to tumor rejection, tissue destruction, and host defense. M1 macrophage density in the tumor islets is positively associated with extended survival of non-small cell lung cancer (NSCLC) patients (Ma et al. 2010). The M1 macrophages produce high levels of IL-12, CXCL10 and inducible nitric oxide synthase (iNOS) (Mantovani et al. 2007). In contrast, M2 macrophages are thought to promote tumor formation by enhancing wound healing and tissue remodeling via inhibition of Type1 immune responses by IL-10 and TGFβ secretion. The M2 macrophages express high levels of IL-10 and arginase that suppress antitumor immune responses (Mantovani et al. 2002; Mantovani et al. 2005; Mantovani et al. 2007; Sinha et al. 2007). These macrophages increase metastatic potential by increasing tumor cell migration, invasion and angiogenesis. The tumor microenvironment also consists of T and B lymphocytes of the adaptive immunity. The phenotypes of the T and B subsets evoked in chronic inflammatory state of the tumor microenvironment are regulatory in nature and dampen immune responses against the tumor. B cells and antibodies have a key role in orchestrating macrophage-driven, tumor-promoting inflammation (Andreu et al. 2011), suggesting that modulating the pathways involved might be of therapeutic benefit in cancers driven by chronic inflammation.

Lung cancers contain a significant population of tumor infiltrating myeloid cells that promote tumor growth by suppressing the immune system. In this review we will focus on the interaction between lung cancer and myeloid derived suppressor cells (MDSC) that suppress antitumor immune responses and contribute to tumor progression.

2. Immune modulation in the lung tumor microenvironment by myeloid derived suppressor cells

2.1 Myeloid mediated downregulation of immune responses in the tumor microenvironment

MDSC are a heterogeneous population of immature myeloid cells (IMC) that consists of myeloid progenitors and precursors of macrophages, granulocytes and DC. In tumors immature myeloid cells are partially blocked at the immature state and do not differentiate into mature myeloid cells that results in an expansion of this population. The activation of these cells in cancer results in the upregulated expression of immune suppressive factors such as arginase and iNOS and an increase in the production of nitric oxide (NO) and reactive oxygen species (ROS). These expanded IMC populations with immune suppressive activity; are collectively known as MDSC. Investigations on diverse tumor types have demonstrated that MDSC accrual in the tumor microenvironment is dependent on tumor derived soluble factors including growth factors, cytokines and chemokines. Granulocyte macrophage colony stimulating factor (GM-CSF) supports the survival and expansion of MDSC in the tumor microenvironment (Serafini et al. 2004). The sources of GM-CSF are tumors or activated immune effectors such as T, NK and DC. IL-1β has been demonstrated to accumulate MDSC in tumors of mice (Lu et al. 2011). Tumor derived PGE2 has also been shown to cause an accumulation of MDSC in lung cancer (Zhang et al. 2009). MDSC accumulation and immune suppression, provides one of the mechanisms through which inflammation can contribute to lung cancer development and progression.

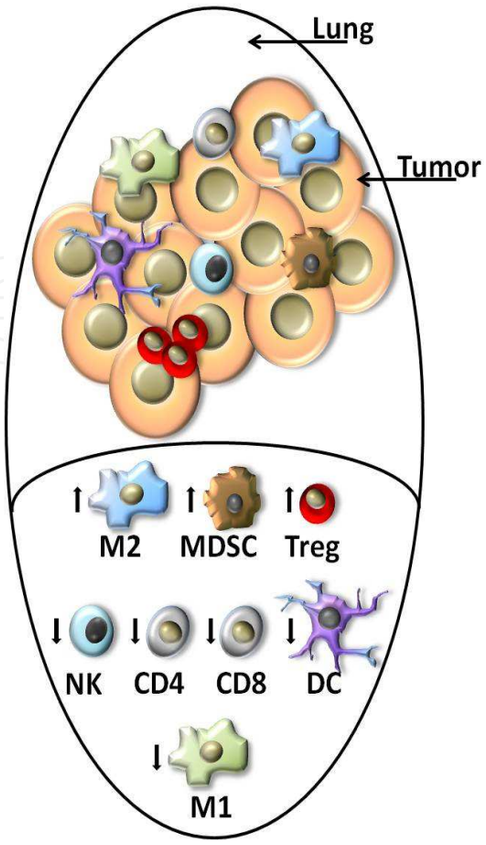

Fig. 1. Modulation in the balance of immune effectors and suppressors in the lung tumor microenvironment. The lung tumor microenvironment has increased myelomonocytic and T regulatory immune suppressors and decreased immune effectors (NK, DC, CD4T, CD8T and M1) that promote tumor growth kinetics and progression.

2.2 Molecular mechanisms of myeloid derived suppressor cell mediated T cell inactivation

MDSC suppress immune responses to newly displayed tumor antigens and promote tumor progression and the metastatic potential of the tumor. MDSC suppress T cell activation in tumor tissues and draining lymph nodes through several mechanisms. MDSC use two enzymes involved in L-arginine metabolism to control T-cell responses: Arginase which depletes the milieu of L-arginine and iNOS which generates NO. L-arginine is essential for T-cell function, including the optimal use of IL-2 and the development of a T-cell memory phenotype. MDSC arginase 1 gene (ARG1) is induced by cytokines such as TGFβ and IL-10 within the tumor microenvironment. The MDSC mediated depletion of arginine suppresses CD4 and CD8 T cell activation. IFNγ and TNFα in the tumor microenvironment induce iNOS in MDSC releasing NO which blocks the phosphorylation and activation of several targets in the IL-2 receptor signaling pathway and induces T-cell apoptosis (Mazzoni et al. 2002).

Cysteine another essential amino acid for T cell activation is depleted by MDSC. T cells lack the enzyme to convert methionine to cysteine and the membrane transporter to import cystine for intracellular reduction to cysteine. T cells obtain their cysteine from extracellular

sources. During normal antigen processing and presentation activity, DC and macrophages synthesize cysteine from methionine and import extracellular cystine for cysteine conversion. Cysteine is then exported by antigen presenting cells (APC) during antigen presentation, and imported by T cells. Like T cells, MDSC are unable to convert methionine to cysteine and are dependent on importing cystine for conversion to cysteine. In the tumor microenvironment MDSC are present in high concentration and import most of the available cystine that deprive DC and macrophages. Since MDSC do not export cysteine, they deprive T cells of cysteine that is necessary for synthesizing proteins required for T cell activation (Srivastava et al. 2010).

MDSC mediated down regulation of T cell L-selectin (CD62L) further impairs T cell activity. CD62L is a plasma membrane molecule necessary for homing of naive T cells to lymph nodes for activation by tumor antigens. MDSC down-regulate CD62L on naive T cell that reduces T cell capacity to migrate to lymph nodes (Hanson et al. 2009).

MDSC-produced ROS and peroxynitrite in the tumor microenvironment inhibit CD8+ T cells by catalyzing the nitration of the T cell receptor and thereby preventing T cell-peptide-MHC interactions. MDSC also down-regulate the T cell receptor-associated ζ chain, a phenomenon common in cancer patients (Nagaraj et al. 2009). In the absence of the zeta chain, T cells are unable to transmit the required signals for activation.

2.3 Cellular mechanisms of myeloid derived suppressor cell mediated immune suppression

MDSC impair T cell activation by directly inducing T regulatory cells (Treg) through the production of IL-10 and TGFβ, or arginase that is independent of TGFβ. The Treg cells actively down regulate the activation and expansion of antitumor reactive T cells (Boon et al. 1994; Sakaguchi 2000; Li et al. 2007) and NK cells (Smyth et al. 2006). MDSC affect tumor immunity by polarizing T cells towards a tumor-promoting type 2 phenotype by producing IL-10 and down-regulating macrophage production of IL-12 (Sinha et al. 2007). The suppressive activity of MDSC on T cells can be antigen-specific or non-specific and can vary depending on the MDSC subpopulation. MDSC impair NK cells by inhibiting their cytotoxicity ability and IFNγ production (Liu et al. 2007; Li et al. 2009).

2.4 Lung cancer genetic signatures as drivers of immune suppression

Our laboratory has been evaluating tumor signatures that maintain tumor growth kinetics through the modulation of immune activity (Huang et al. 1996; Huang et al. 1998). Many tumors, including lung cancer, have the capacity to promote immune tolerance and escape host immune surveillance (Chouaib et al. 1997; Smyth and Trapani 2001). Tumors utilize numerous pathways to inhibit immune responses including the elaboration of immune inhibitory cytokines. In addition to directly secreting immunosuppressive cytokines, lung cancer cells may induce host cells to release immune inhibitors (Huang et al. 1996; Huang et al. 1998; Alleva et al. 1994; Maeda et al. 1996; Halak et al. 1999). In previous studies, we found an immune suppressive network in non-small cell lung cancer (NSCLC) that is due to over expression of tumor cyclooxygenase 2 (COX-2) (Huang et al. 1998; Stolina et al. 2000), which is constitutively expressed in a variety of malignancies. We and others have reported that COX-2 is constitutively elevated in human NSCLC frequently (Hida et al. 1998; Huang

et al. 1998; Hida et al. 2000; Hosomi et al. 2000). Although multiple genetic alterations are necessary for lung cancer invasion and metastasis, COX-2 may be a central element in orchestrating this process (Hida et al. 1998; Huang et al. 1998; Wolff et al. 1998; Achiwa et al. 1999; Hosomi et al. 2000; Riedl et al. 2004). Over expression of COX-2 is associated with apoptosis resistance (Tsujii and Dubois 1995; Lin et al. 2001), angiogenesis promotion (Tsujii et al. 1998; Masferrer et al. 2000), enhanced tumor invasion and metastasis (Tsujii et al. 1998; Dohadwala et al. 2001; Dohadwala et al. 2002) and decreased host immunity (Huang et al. 1998; Stolina et al. 2000; Sharma et al. 2003). In murine lung cancer models, we found that specific genetic or pharmacological inhibition of COX-2 reduced tumor growth (Stolina et al. 2000). In other related studies, we documented that COX-2 inhibition prevented tumor-induced suppression of DC activities (Sharma et al. 2003). In recent studies, we have demonstrated that treatment of mice with a COX-2 inhibitor, promoted a Type 1 cytokine response, inducing IFNγ, IL-12 and CXCL10 and augmented the vaccination response to tumor challenge (Sharma et al. 2005).

Tumor COX-2 can also modulate MDSC activity through ARG1 in lung carcinoma. MDSC producing high levels of arginase block T cell function by depleting arginine. Until recently, the mechanism that induces ARG1 in MDSC in cancer was unknown. Rodriguez PC et al, utilizing the mouse Lewis lung carcinoma (3LL, that spontaneously arose in the C57BL/6 mice), showed that ARG1 expression was independent of T cell-produced cytokines but rather tumor derived PGE2 maintained ARG1 expression in MDSC. 3LL tumor cells constitutively express COX-1 and COX-2 and produce high levels of PGE2. Genetic or pharmacological inhibition of COX-2 but not COX-1 blocked ARG1 induction *in vitro* and *in vivo*. Signaling through the PGE2 receptor E-prostanoid 4 expressed in MDSC induced ARG1. Furthermore, blocking ARG1 expression using COX-2 inhibitors elicited a lymphocyte-mediated antitumor response. These results demonstrate a new pathway of prostaglandin-induced immune dysfunction and provide a novel mechanism that can help explain the antitumor benefits of COX-2 inhibitors (Rodriguez et al. 2005) that targets the major immune suppressive pathways mediated by MDSC.

The complex nature of interactions between MDSC and Treg cells are yet to be fully defined however it is evident that MDSC promote T reg development *in vivo.* Tumor-reactive T cells have been shown to accumulate in lung cancer tissues but fail to respond because of suppressive tumor cell-derived factors (Yoshino et al. 1992; Batra et al. 2003) and because high proportions of NSCLC tumor infiltrating lymphocytes are CD4+CD25+ T reg cells (Woo et al. 2001). CD4+CD25+ T regulatory (Sakaguchi et al. 2001) cells play an important role in maintenance of immunological self-tolerance. T regulatory cell activities increase in lung cancer, and appear to play a role in suppressing antitumor immune responses. Treg cells actively down regulate the activation and expansion of self-reactive lymphocytes (Sakaguchi 2000). Given that many tumor–associated antigens recognized by autologous T cells are antigenically normal self-constituents, Treg cells engaged in the maintenance of self tolerance may impede the generation and activity of antitumor reactive T cells (Boon et al. 1994; Sakaguchi 2000). Thus, reducing the number of Treg cells or abrogating their activity within the tumor environment may induce effective tumor immunity in otherwise non-responding hosts by activating tumor-specific as well as nonspecific effector cells (Shimizu et al. 1989; Onizuka et al. 1999; Sutmuller et al. 2001). In recent studies we have demonstrated that tumor COX-2 expression contributes to decreased host antitumor

immune responses by impacting the frequency and activity of CD4+CD25+FOXP3+ T reg cells (Baratelli et al. 2005; Sharma et al. 2005). Definition of the pathways controlling Treg cell activities will enhance our understanding of limitation of the host antitumor immune responses. We demonstrated that lung tumor-derived COX-2/PGE2 induced expression of the Treg cell-specific transcription factor, Foxp3, and increased Treg cell activity. Assessment of E-prostanoid (EP) receptor requirements revealed that PGE2-mediated induction of Treg cell *Foxp3* gene expression was significantly reduced in the absence of the EP4 receptor and ablated in the absence of the EP2 receptor expression. *In vivo*, COX-2 inhibition reduced Treg cell frequency and activity, attenuated Foxp3 expression in tumor-infiltrating lymphocytes, and decreased tumor burden. Transfer of Treg cells or administration of PGE2 to mice receiving COX-2 inhibitors reversed these effects. Our studies were the first documentation that COX-2 inhibition down regulated tumor induced T regulatory cell activity leading to the restoration of antitumor responses.

2.5 Lung cancer snail knockdown reduces MDSC and increases CD107a activated effector T cells in the tumor microenvironment

We are defining genetic programs in lung cancer that modulate tumor growth and metastases. Cancer cells acquire the ability to progress, invade and metastasize by undergoing the process of epithelial-mesenchymal transition (EMT), by activating transcription factors (for example, Snail, Twist, Zeb, Slug) that repress E-Cadherin, a transmembrane glycoprotein essential for epithelial cell-cell adhesion (Bussemakers et al. 1993; Cano et al. 2000). These transcriptional repressors are normally active during embryogenesis where they program EMT to enable various morphogenetic steps. EMT is involved in tumor progression (Thiery 2002; Jeanes et al. 2008). Snail expression in primary NSCLC has been associated with a shorter overall survival (Yanagawa et al. 2009). Tumor Snail expression has recently been demonstrated to be important in EMT induced metastases in melanoma (Kudo-Saito et al. 2009). We are evaluating the mechanistic role of tumor snail expression that modulates tumor growth and metastases in immune competent mice. Our data (AACR Abstract: Frontiers in Basic Cancer Research, September 14-18 2011., San Francisco) demonstrates that tumor snail expression alters tumor growth and metastasis by impacting MDSC in the tumor microenvironment. 3LL, 3LL Snail knockdown and 3LL control vector cells were implanted in C57BL/6 mice. Compared to controls, 3LL Snail knockdown mice had (i) decreased MDSC, (ii) reduced MDSC as well as the non MDSC populations intracellular expression of ARG1 in the tumors, (iii) increased expression of the CD107a cytolytic marker in tumor infiltrating CD8 T cells and (iv) increased tumor infiltrates of CD4 and CD8 T lymphocytes that elaborated enhanced IFNγ but reduced levels of IL-10 and (v) augmented the frequencies of innate NK effectors and DC. Accompanying the inflammatory signature, Snail knockdown cells demonstrated reduced subcutaneous tumor growth and lung metastases. Current experiments are mechanistically delineating the genetic program(s) induced by tumor Snail knockdown that alter the balance and activity of immune effectors and suppressors in the tumor and the impact of adoptive transfer of MDSC on tumor growth kinetics of Snail knockdown cells. An adequate understanding of the genetic signatures in the tumor and tumor-host interactions that induce immune evasion and promote tumor growth, invasion and metastases will be crucial for the development of effective therapies for lung cancer.

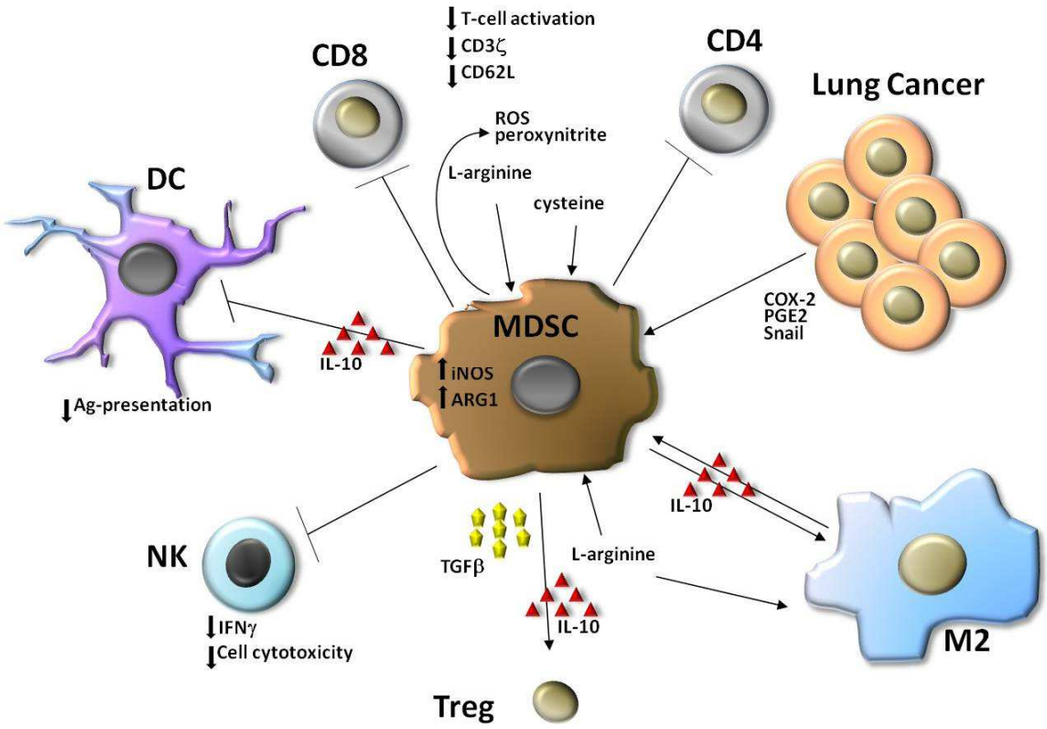

Fig. 2. MDSC accumulation in Lung cancer suppresses antitumor activity MDSC are recruited to and expanded in the tumor through the induction/production of COX-2, PGE2, and Snail in lung cancer. T cell activation is suppressed by MDSC mediated: (i) deprivation of L-arginine and cysteine from the environment, (ii) production of ROS and peroxynitrite, (iii) down regulation of CD62L and the T cell receptor-associated ζ chain and (iv) the induction of Tregs through MDSC IL-10 and TGFβ production. MDSC suppresses NK cell cytotoxicity, NK IFNγ production and induces tumor associated macrophages with a type 2 phenotype. MDSC expansion and IL-10 production inhibits DC antigen presentation.

2.6 Impact of depleting Gr1 or Ly6G myelomonocytic cells on lung cancer growth kinetics

Increases in MDSC evoke strong natural suppressive activity in cancer patients (Young et al. 1997; Kusmartsev et al. 1998) or tumor-bearing mice (Kusmartsev and Ogreba 1989; Subiza et al. 1989; Young et al. 1997). It has been demonstrated that Gr1+CD11b+ immune suppressive cells are capable of inhibiting the T cell proliferative response induced by alloantigens (Schmidt-Wolf et al. 1992), CD3 ligation (Young et al. 1996), or various mitogens (Sugiura et al. 1988; Angulo et al. 1995), and can also inhibit IL-2 utilization (Brooks and Hoskin 1994) as well as NK cell activity (Kusmartsev et al. 1998). These studies indicate that progressive tumor growth is associated with the down-regulation of T cell responses and that the Gr1+CD11b+ myeloid cells are involved in negative immunoregulatory mechanisms in the tumor bearing host. In murine tumor models there is an increase in the MDSC populations in the tumors, spleens, bone marrow and blood as the tumor progresses. In the 3LL lung cancer model as the tumors progress the frequency and activity of immune suppressive cells are enhanced in the tumor microenvironment. We have

found that tumors have as much as 45% infiltrates that are predominantly of the Gr1+ CD11b+ immature myeloid phenotype. As has been recently reported for glioblastoma (Fujita et al. 2011) and colon (Mundy-Bosse et al. 2011) murine cancer models, we evaluated the contribution of the Gr1 and Ly6G expressing myelomonocytic cells on 3LL tumor growth kinetics in C57BL/6 mice, by depleting cells expressing these markers with anti-Gr1 (RB6-8C5) or anti-Ly6G (1A8) administered every other day via *i.p* route starting on day 5 post tumor inoculation. Compared to isotype matched control antibody, the anti-Gr1 antibody or anti-Ly6G led to a significant decrease in the $Gr1^{hi}CD11b$ expressing myeloid subset and a subsequent increase in the CD107a expressing CD3T lymphocytes and NK cells in the tumors respectively. Accompanying the decrease in the $Gr1^{hi}CD11b$ expressing myeloid subset was a 8 fold decrease in tumor weight. While the anti-Gr1 antibody reduced both $Gr1^{hi}$ and $Gr1^{lo}$, the anti-Ly6G antibody reduced the $Gr1^{hi}$ subset only. Both these antibodies depleted the Ly6G expressing cells. Although these depletion antibodies impact other Gr1 or Ly6G expressing monocytes, our data suggests that the broad targeting of MDSC along with other myeloid cell types is beneficial in eliciting anticancer effects. This data is consistent with studies by several groups (Fujita et al. 2011; Mundy-Bosse et al. 2011). It would be interesting to evaluate the impact of MDSC depletion on DC and tumor associated macrophages (TAM) functional activity. This may resolve further compensatory pathways of immune suppression. Currently we are evaluating strategies that target the myeloid suppressor subsets in combination with various immune potentiating strategies to increase the antitumor benefit.

2.7 Critical role of antigen presentation in lung cancer: T-cell tolerance versus T-cell priming

Effective antitumor responses require antigen processing cells (APCs), lymphocyte and NK effectors, as well as the elaboration of effector molecules that promote antitumor activity. Although lung cancer cells express tumor antigens, the limited expression of MHC antigens, defective transporter associated with antigen processing (TAP) and lack of costimulatory molecules, make them ineffective APCs (Restifo et al. 1993). Many tumors, including lung cancer, have the capacity to promote immune tolerance and escape host immune surveillance (Chouaib et al. 1997; Smyth and Trapani 2001). Tumors utilize numerous pathways to inhibit immune responses, including reduction in APC activity. The accumulation of MDSC in the tumor microenvironment negatively impacts DC and their APC activity.

The central importance of functional APCs in the immune response against cancer has been well defined (Huang et al. 1994). The study revealed that even highly immunogenic tumors require host APCs for antigen presentation. Thus, host APCs, rather than tumor cells, present tumor antigen. This is consistent with a study indicating that $CD8^+$ T-cell responses can be induced *in vivo* by professional APCs that present exogenous antigens in a MHC I-restricted manner (Albert et al. 1998). This has been referred to as cross-priming or representation and may be critical for effective antitumor responses (Bevan 1995). DCs have been demonstrated to be the host APC responsible for cross-priming by presenting epitopes obtained from apoptotic cells (Castellino and Germain 2006).

However, in tumor-bearing hosts, there is a state of T-cell unresponsiveness (Staveley-O'Carroll et al. 1998; Cuenca et al. 2003; Willimsky and Blankenstein 2005). The dominant

mechanism underlying the development of antigen-specific T-cell unresponsiveness is thought to be through tumor-antigen processing and presentation by APCs (Sotomayor et al. 2001). The intrinsic APC capacity of tumor cells has little influence over T-cell priming versus tolerance, an important decision that is regulated by bone marrow-derived APCs. DCs, macrophages and B cells are all bone marrow-derived cells that express both MHC and the costimulatory molecules CD80 and CD86 and present tumor antigens to antigen-specific T cells.

Several studies have shown that DCs play a critical role leading to T-cell tolerance versus T-cell priming (Fuchs and Matzinger 1996; Belz et al. 2002; Munn et al. 2002; Steinman et al. 2003), which is dictated by the environmental context in which the DCs encounter the antigen. Antigen capture by DCs in an inflammatory context triggers their maturation to a phenotype capable of generating strong immune responses, whereas antigen capture in a noninflammatory environment leads instead to the development of T-cell tolerance. The tumor microenvironment not only fails to provide the inflammatory signals needed for efficient DC activation, but also inhibits DC differentiation and maturation through IL-10 (Gerlini et al. 2004) and VEGF (Gabrilovich et al. 1996). DCs, which are pivotal for T-cell priming, remain immature and become dysfunctional in hosts bearing growing tumors, acquiring tolerogenic properties that induce T-cell tolerance to tumor antigens. Immature DCs (iDCs) have little or no expression of costimulatory molecules such as CD80, CD86 and CD40 on their surface and produce little or no IL-12, which is required to support T-cell proliferation. iDCs are unable to induce antitumor immune response but can induce T-cell tolerance. If APCs fail to provide an appropriate costimulatory signal for T cells, tolerance or anergy can develop. The importance of restoring APCs with immune-stimulating activity in the tumor microenvironment is crucial. In a recent study ectopic lymph node or tertiary lymphoid structures were retrospectively identified within human non-small-cell lung cancer specimens and demonstrated that there is a correlation of cellular content with clinical outcome (Dieu-Nosjean et al. 2008). The density of DC-Lamp, indicating mature DCs within these structures, is a predictor of long-term survival within their selected lung cancer patient population. The authors observed that a low density of tumor-infiltrating CD4+ and T-bet+ T lymphocytes present in tumors poorly infiltrated by DC-Lamp+ mature DCs appears to provide additional supporting evidence for the prognostic importance of an adaptive immune reaction to a solid tumor.

We have previously demonstrated that elements from the tumor microenvironment can suppress DC function. We found that bone marrow derived DCs stimulated with GM-CSF and IL-4 in the presence of tumor supernatants (TSNs) failed to generate antitumor responses and caused immunosuppressive effects that correlated with enhanced tumor growth. Functional analyses indicated that TSNs cause a decrement in DC capacity to process and present antigens, induce alloreactivity and secrete IL-12. The TSNs caused a reduction in cell surface expression of CD11c, DEC205, MHC I antigen, MHC II antigen, CD80 and CD86, as well as a reduction in TAP 1 and 2 proteins (Sharma et al. 2003).

2.8 IL-7/IL-7Rα-Fc promotes the M1 macrophage phenotype in lung cancer

Although tumor growth and invasion leads to inflammatory responses, the immune system generally develops tolerance to cancer. One way to induce potent immune responses against tumors is to activate key innate and immune effector mechanisms. Toward this end, we are

evaluating the utility of chimeric γc homeostatic cytokine, IL-7/IL-7Rα-Fc, to restore host APC and T cell activities dysregulated in cancer patients (Almand et al. 2000; Zou 2005). It is evident from previous studies that intratumoral infiltration by relatively high numbers of activated T lymphocytes (Johnson et al. 2000; Hiraoka et al. 2006) and APC (Dieu-Nosjean et al. 2008) leads to better prognosis in lung cancer patients.

We evaluated the utility of chimeric γc homeostatic cytokine, IL-7/IL-7Rα-Fc, to restore host APC and T cell activities in lung cancer (Andersson et al. 2011). Utilizing murine lung cancer models we determined the antitumor efficacy of IL-7/IL-7Rα-Fc. IL-7/IL-7Rα-Fc administration inhibited tumor growth and increased survival in lung cancer. Accompanying the tumor growth inhibition were increases in APC and T cell activities. In comparison to controls, IL-7/IL-7Rα-Fc treatment of tumor bearing mice led to increased: i) tumor macrophage infiltrates characteristic of M1 phenotype with increased IL-12, iNOS but reduced IL-10 and arginase, ii) frequencies of T and NK cells, iii) T cell activation markers CXCR3, CD69 and CD127,^{low} and iv) effector memory T cells. IL-7/IL-7Rα-Fc treatment abrogated the tumor induced reduction in splenic functional APC activity to T responder cells. Our findings demonstrate that IL-7/IL-7Rα-Fc promotes the afferent M1 macrophage phenotype and the efferent (CXCR3/CXCR3 ligand biological axis) limbs of the immune response for sustained antitumor activity in lung cancer. IL-7/IL-7Rα-Fc provides the cues that address the deficits in the lung tumor microenvironment to achieve the requirements for the inhibition of tumor growth kinetics by: (i) generating sufficient numbers of T cells systemically (ii) increasing the activated T cell infiltrates in the tumor and (iii) activating the innate and immune cells in the tumor to manifest antitumor benefit. Although IL-7/IL-7Rα-Fc is potent at reducing tumor growth kinetics, it does not lead to complete tumor eradication. This may in part be due to the presence of MDSC in the tumor microenvironment that dampens the antitumor activity of IL-7/IL7Rα-Fc and remains to be resolved.

2.9 Drug targets impacting myeloid derived suppressor cells

Several pharmacological approaches that target MDSC are currently being explored in a variety of tumor models. The drugs can be divided into classes based on their ability to control: (i) MDSC differentiation into mature DC and macrophages capable of APC activity (ATRA and Vitamin D3); (ii) MDSC maturation from precursors [(STAT 3 inhibitors, Tyrosine Kinase inhibitors (TKI) (Sunitinib and Sorefnib), Bevacizumab, Anti-BV8 mAb, Amino-Biphosphonates and MMP9 inhibitors]; (iii) MDSC accumulation (Gemcitabine, 5-Fluorouracil (5-FU), CXCR2 and CXCR4 antagonists) and (iv) MDSC function [(ROS scavengers and ARG and NOX inhibitors (Nitroaspirin, PDE-5, COX-2 inhibitors and Cytokines)] (Ugel et al. 2009).

Gabrilovich et al demonstrated that differentiating MDSC to DC and macrophages by using all-trans retinoic acid (ATRA) reduced MDSC numbers and augmented the responses to cancer vaccines. ATRA induced differentiation of MDSC primarily via neutralization of high ROS production in these cells. The mechanism involves specific up-regulation of glutathione synthase and accumulation of glutathione in the MDSC and could be used in developing and monitoring therapeutic application of ATRA (Nefedova et al. 2007).

Recent advances in targeted therapy for cancer have provided small-molecule kinase inhibitors that recognize specific targets on the surface or inside cancer cells. These

inhibitors have shown efficacy against several hematopoietic malignancies and solid tumors. Most drugs generally have inhibitory effects on several kinases, including tyrosine kinases (TK) that are critical for the survival, proliferation, migration and invasion of tumor cells. With regards to the effects of TKI on tumor immunity, some studies have demonstrated the immune stimulatory effects of the TKI (eg imatinib) (Wang et al. 2005) whereas others report the immune suppressive effects of the same inhibitor (Seggewiss et al. 2005).

Administration of sunitinib, a receptor TKI, has been shown to reduce the frequency of MDSC and reversing T cell immune suppression in the peripheral blood of patients with metastatic renal cell carcinoma (RCC) and in several murine tumor models. However sunitinib has variable impact at reducing MDSC and restoring T cell activity in the tumor microenvironment that seems to be tumor dependent. The authors suggest that the persistence of MDSC in the tumor following sunitinib treatment in RCC may in part be due to increased GM-CSF expression by the tumors that prolong the survival of MDSC and protect from sunitinib through pSTAT5 pathway. The authors contend that GM-CSF mediated MDSC survival in patient tumors is supported by the observation that GM-CSF produced by RCC cultures protect MDSC from sunitinib induced cell death. However, tumors transduced with GM-CSF in several tumor models have been shown to lead to strong immune dependent rejection. It would be interesting to see in these models the activity of MDSC in the tumor microenvironment of the GM-CSF secreting tumors. Additionally, an alternate explanation for the persistence of MDSC may be associated with increased expression of proangiogenic proteins, such as MMP9, MMP8 and IL-8 produced by tumor stromal cells or infiltrating MDSC (Ko et al. 2010; Finke et al. 2011). More studies are required to evaluate the role of TKI (sunitinib, sorafenib, imatinib and dasatinib) on MDSC activity in the tumor microenvironment and tumor immunity in several tumor models and in clinical samples.

GW2580, a selective molecule kinase inhibitor of colony stimulating factor 1 receptor (CSF1R), blocks the recruitment of CSF1R expressing TAMs as well as MDSC in different tumor models without having an impact on tumor burden (Priceman et al. 2010). PLX3397, another TKI of CSF1R, has also been used to efficiently deplete CD11b+Ly6G-LY6ClowF4/80+ TAMs (70%) without altering the presence of granulocytic MDSC. The treatment of mammary tumor bearing mice with PLX3397 led to a decrease in tumor burden (DeNardo et al. 2011).

Studies by Ping Ying Pan et al have demonstrated that the expression of c-kit ligand [(stem cell factor, (SCF)] by tumor cells may be important for MDSC accumulation in tumor-bearing mice, and that blocking the c-kit ligand/c-kit receptor interaction can reverse MDSC mediated immune suppression. Mice bearing tumor cells with SCF siRNA knockdown exhibited significantly reduced MDSC expansion and restored proliferative responses of tumor-infiltrating T cells. The blockade of SCF receptor (ckit)–SCF interaction by anti-ckit prevented tumor-specific T-cell anergy, Treg development, and tumor angiogenesis. The authors found that the prevention of MDSC accumulation in conjunction with immune activation therapy showed synergistic therapeutic effect when treating mice bearing large tumors. Their data suggests that modulation of MDSC development may be essential to enhance immune therapy against advanced tumors (Pan et al. 2008).

N-acetyl cysteine (NAC) has been proposed as an anti-tumorigenic agent because of its ability to reduce the oxidative stress that promotes genetic instability. NAC treatment of mice with progressively growing tumors have demonstrated therapeutic efficacy (Gao et al. 2007). NAC may have the additional benefit of facilitating T cell activation by increasing extracellular pools of cysteine in the presence of high levels of MDSC in cancer patients. Although NAC targets the cysteine pathway of MDSC mediated T cell suppression, MDSC production of arginase and nitric oxide, can still maintain the suppressive effects of MDSC. However, administration of NAC, an already FDA-approved drug, in combination with other agents that block other MDSC suppressive pathways (ARG1 and NO), maybe more effective at inhibiting MDSC and facilitate the treatment of cancers.

COX-2 is required for PGE2 synthesis; drugs that specifically block COX-2 and reduce PGE2 delay tumor growth by reducing MDSC accumulation. Therefore, inhibition of PGE2 biosynthesis in tumor-bearing mice blocks MDSC generation and subsequently retards tumor progression (Rodriguez et al. 2005; Sinha et al. 2007).

Studies have demonstrated that the chemotherapeutic agent, gemcitabine, enhances T cell responsiveness by reducing the number of MDSC levels in the spleens of murine lung cancer models. In this study, gemcitabine, was administered at a dose similar to the equivalent dose used in patients, was able to specifically reduce the number of MDSC found in the spleens of animals bearing large tumors without significant reductions in CD4+ T cells, CD8+ T cells, NK cells, macrophages, or B cells. The loss of MDSC was accompanied by an increase in the antitumor activity of CD8+ T cells and activated NK cells. Since all measurements on MDSC frequency and activity in this study was performed from the spleens of tumor bearing animals it is not clear from this work as to the extent of depletion of MDSC from the lung tumor microenvironment following gemcitabine treatment and restoration of immune responses in the tumor microenvironment. The authors did observe however, that combining gemcitabine with cytokine immunogene therapy using IFN-β markedly enhanced antitumor efficacy leading to a greater reduction in tumor burden than when either therapy was administered singly (Suzuki et al. 2005).

3. Conclusion and future perspectives

Lung cancer is the most common cause of cancer mortality worldwide for both men and women, causing approximately 1.2 million deaths per year (Jemal et al. 2009). With the existing therapeutic efforts, the long-term survival for lung cancer patients remains low with only 15% surviving for 5 years following diagnosis. Therefore, new therapeutic strategies are needed. One such approach is the development of immune therapy for lung cancer. Immune approaches for lung cancer remain attractive because although surgery, chemotherapy and radiotherapy alone or in combination produce response rates in all histological types of lung cancer, relapse is frequent. Immunologic targeting of lung cancer has the potential for nontoxic and specific therapy. Strategies that harness the immune system to react against tumors can be integrated with existing forms of therapy for optimal responses toward this devastating disease. Immune therapy for lung cancer has potential; however, there have not been improvements in survival with previous regimens. Tumor-induced immune suppression may have contributed to the limited efficacy of the approaches.

Lung cancer growth and invasion into surrounding tissue promotes an inflammatory response that is important for tumor development and progression. Dysregulated inflammation in cancer leads to hypo responsiveness of the tumor. MDSC play a major role of suppressing T cell activation in the lung tumor microenvironment and sustain overall tumor growth, proliferation and metastases. Regulating MDSC recruitment, differentiation/expansion and inhibiting MDSC suppressive function will serve as a multifaceted approach to control lung cancer. Although the broad targeting of MDSC along with other myeloid cell types with anti-Gr1 or anti Ly6G mAbs alone is beneficial in eliciting anticancer effects, the benefit of chemotherapeutic agents that regulate MDSC are evident only when combined with immune therapy and not when administered alone. Cancer immune therapy offers an attractive therapeutic addition, delivering treatment of high specificity, low toxicity and prolonged activity. Despite the identification of a repertoire of tumor antigens, hurdles persist for immune-based therapies. Tumor-induced immune suppression may be contributing to the limited efficacy of the current approaches. Effective immunotherapeutic strategies for lung cancer will result from a basic understanding of the mechanisms that sustain tumor growth kinetics. Strategies that reprogram the tumor niche could alter the inflammatory infiltrate in the lung tumor microenvironment making it permissive for immune destruction of tumors. It is likely that combination therapies that focus on methods to address the immune deficits in the lung cancer microenvironment will be required to develop effective therapies for this disease. Targeting MDSC induced immune suppression is at the forefront of these therapeutic approaches. The future of immune therapy for lung cancer holds promise with novel combined approaches that simultaneously downregulate MDSC suppressor pathways, restore APC immune-stimulating activity, and expand tumor-reactive T cells with γc homeostatic cytokines such as IL-7, IL-15 and IL-21 to generate effective therapy. The optimal way to integrate novel immune targeted combinations will be the major focus of future studies and will require a coordinated and cooperative multidisciplinary effort by the international scientific community. Objective lung cancer regressions and extensions in survival should be correlated with multiple predictive and prognostic molecular and cellular biomarkers of response. This information will prove useful in improving therapy.

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Tumor Microenvironment and Myelomonocytic Cells
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Tumor microenvironment represents an extremely dynamic niche shaped by the interplay of different cell types (e.g. tumor cells, stromal cells), their soluble products (e.g.cytokines, chemokines and growth factors) and varied physico-chemical conditions (e.g low oxygen concentration or hypoxia). Recent studies have identified myelomonocytic cells as key players in regulating the tumor microenvironment and hence, tumor progression in a variety of cancers. In view of these findings, the present book attemps to provide a comprehensive account of the diversity of tumor microenvironment across different cancers and how myelomonocytic cells have taken the center-stage in regulating this niche to direct cancer progression. A better understanding of the myelomonocytic cells and the mechanisms by which they regulate cancer progression will open new vistas in cancer therapeutics.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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