



# Myeloid-derived suppressor cell-dependent inhibition of B cell responses in non-small cell lung cancer

Rui Li, Steven M. Dubinett

David Geffen School of Medicine at UCLA, Los Angeles, California, USA

Correspondence to: Steven M. Dubinett. Division of Pulmonary and Critical Care, David Geffen School of Medicine at UCLA, Los Angeles, California, 90095, USA. Email: sdubinett@mednet.ucla.edu.

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Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of cells with potent immune suppression activities. These cells are derived from the bone marrow (BM) and consist of two populations: polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs), morphologically similar to neutrophils and monocytes, respectively. In mice, PMN-MDSCs are recognized as CD11b<sup>+</sup>Ly6C<sup>low</sup>Ly6G<sup>+</sup>, whereas M-MDSCs are CD11b<sup>+</sup>Ly6C<sup>high</sup>Ly6G<sup>-</sup>. In contrast, in humans, CD11b<sup>+</sup>CD14<sup>-</sup>CD15<sup>+</sup>CD33<sup>+</sup> cells with low density are defined as PMN-MDSCs, while CD11b<sup>+</sup>CD14<sup>+</sup>CD15<sup>-</sup>CD33<sup>+</sup>HLA<sup>-</sup>DR<sup>-low</sup> are markers for M-MDSCs (1). Accumulation of MDSCs is often dependent on persistent inflammation in the tumor microenvironment (TME) which provides signals for their expansion and pathological activation. Upon activation, MDSCs gain increased capacity to generate reactive oxygen species (ROS) and nitric oxide (NO), express high levels of arginase and PD-L1, and secrete a variety of tumor-promoting inflammatory factors, including IL-10, TGF- $\beta$  and PGE2 (1). Under the influence of the TME, MDSCs fail to differentiate into mature myeloid cells, such as mature neutrophils, macrophages and dendritic cells (DCs) that could promote antitumor immune activities. Instead, MDSCs function as potent immune suppressors, diverting specific immune responses on multiple fronts (1).

The anti-tumor immune response is balanced by the overall interactions among a broad array of immune constituents. This includes effectors such as cytolytic CD8<sup>+</sup> T cells and natural killer (NK) cells, and immune

suppressors, such as MDSCs and T regulatory cells (Tregs). In addition, the anti-tumor capacity can be bolstered by antigen presenting cells (APCs) such as macrophages, DCs, and B cells. The potent immune suppressive activities of MDSCs are evident in their interactions with other immune cells. For example, PMN-MDSCs suppress T cell functions, utilizing ROS and reactive nitrogen species (RNS) as key mechanisms (2). RNS can act as potent chemical modifiers to induce nitration of chemokines and T cell receptors, creating a chemical barrier that serves to restrict T cell infiltration into the tumor while also impairing T cell functions (3). In addition, the presence of MDSCs depletes key nutrients (L-arginine, L-tryptophan and L-cysteine) required for T cell proliferation and activation (1,2). MDSCs can interfere with NK cell cytotoxicity and interferon-gamma (IFN- $\gamma$ ) production via TIGIT signaling in a ZAP70/Syk and ERK1/2 dependent manner (4). The hypoxic milieu of the TME promotes M-MDSC differentiation into M2-type tumor-associated macrophages (TAMs), which are characterized by impaired antigen presentation and immune suppressive cytokine production (2). Moreover, MDSCs not only impede the differentiation of DCs but also render existing DCs immunosuppressive via the induction of IDO1 expression (5).

How do MDSCs impact B cells in the context of tumorigenesis? As recently reported in *The Journal of Immunology*, Wang and colleagues have found that MDSCs suppress B cell activities in a murine lung cancer model (6). They observed that both the percentage and number of B cells from the BM and spleen were reduced in tumor-

bearing mice. Interleukin-7 (IL-7) and its downstream STAT5 signaling that regulates B cell lineage commitment were also repressed. The B cell dysfunction was indicated by a decrease in serum IgG levels. This impairment of B cell development and function correlated with increased MDSC infiltration as the tumor progressed. Depletion of MDSCs not only restored B cell frequency and IL-7 signaling, but also rescued serum IgG levels. Furthermore, adoptive transfer of BM MDSCs from tumor-bearing mice into congenic recipients recapitulated the reduction of B cell subsets in the peripheral blood. These findings suggest that the accumulation of MDSCs impaired B cell responses in this murine lung cancer model. Investigation of the underlying mechanisms revealed that the production of TGF- $\beta$ , an important suppressor of IL-7, increased in the tumor-bearing mice. Inhibition of TGF- $\beta$  via neutralizing antibody rescued IL-7-mediated B cell development and function. In addition, B cell proliferation was suppressed by MDSCs in an arginase-dependent manner *in vitro*, and this suppression required cell-to-cell contact.

B cells have the capacity to either promote or inhibit anti-tumor immunity. In a study of human NSCLC, B cell density is positively correlated with patient survival (7). Activated tumor infiltrating B cells (TIL-Bs) are associated with effective anti-tumor T cell responses, whereas exhausted TIL-Bs frequently coexist with Tregs (8). Antibodies secreted from TIL-Bs are reactive against tested tumor antigens in approximately 50% of patients, suggesting an anti-tumor immune response (7). This finding is further confirmed in a murine cancer model showing that the allogeneic antibodies secreted by B cells can recognize tumor antigens and facilitate DC-mediated antigen presentation (9). On the other hand, B regulatory cells (Bregs) impose immune suppression through promotion of Treg differentiation, induction of CD8<sup>+</sup> T cell anergy and apoptosis, and facilitation of myeloid cell accumulation (10). In this study by Wang *et al.*, the authors also found increased numbers of Bregs in the lungs and spleens of tumor-bearing mice (6).

Given the multifaceted function of MDSCs in the inhibition of immune responses, a variety of potential solutions to block MDSCs have been suggested. For example, Gr-1 antibody-mediated MDSC depletion leads to enhanced anti-tumor activities in a murine lung cancer model (11). This results in an increase infiltration of functional T cells, NK cells and DCs in the TME, a switch of the secretome profile from pro-angiogenic (VEGF, CXCL2 and CXCL5) to anti-angiogenic (CXCL9 and

CXCL10), and reduced production of IL-10 by CD8<sup>+</sup> T cells. Studies have also demonstrated the anti-tumor benefit of inhibiting MDSC tumor infiltration. CXCR2 ligands are the predominant chemokines recruiting PMN-MDSCs to the tumor site. Elevation of the two CXCR2 ligands, CXCL5 and CXCL8 portend a poor prognosis in NSCLC (12). CXCR2 blockade not only impairs tumor angiogenesis but also reduces MDSC infiltration, resulting in an enhanced anti-tumor immune response (12-14).

Other studies have attempted to interfere with MDSC activation or to facilitate their maturation. While Wang *et al.* have shown that the MDSC-mediated IL-7 reduction is due to TGF- $\beta$ , we have demonstrated that IL-7 can decrease both TGF- $\beta$  production and signaling (15). These findings highlight the importance of the reciprocal relationship between IL-7 and TGF- $\beta$  in the context of tumor immunity. Importantly, IL-7 administration not only restores B cell responses but also decreases tumor burden with concomitant T cell activation and Treg reduction (6,16). Another example is cyclooxygenase 2 (COX-2), which is frequently elevated in human NSCLC. COX-2/PGE2-dependent MDSC expansion and activation may be due to COX-2-induced expression of arginase 1, CXCL5 and CXCL8 (12,17). Therefore, COX-2 inhibition can be a means to restore effective antigen presentation and anti-tumor immune responses (18). To promote differentiation of MDSCs into mature myeloid cells, therapeutic attempts have included the use of all-trans retinoic acid (ATRA), which reduces tumor ROS levels, and therefore facilitates the differentiation of MDSCs into mature myeloid cells, including DCs. The presence of Ly6C<sup>high</sup> monocyte-derived DCs in the TME correlates with CD8<sup>+</sup> T cell activation and effective immune responses in several tumor models (19). In lung cancer, directly restoring the capacity of antigen presentation plays a vital role in anti-tumor responses; in a phase I clinical trial, intratumoral vaccination of DCs elicits tumor-specific immune responses and CD8<sup>+</sup> T cell infiltration (20).

Ongoing research continues to explore the complex mechanisms underlying MDSC-mediated immune suppression. The work presented by Wang *et al.* enhances our understanding of the MDSC-dependent regulation of B cell responses in lung tumorigenesis. Blockade of MDSCs can be achieved at multiple levels and may simultaneously inhibit a broad spectrum of tumor-promoting processes. Further studies will be required to more thoroughly define the early determinants of the generation of MDSC. This will facilitate optimal targeting strategies and combination

MDSC blockade with other immunotherapies, such as checkpoint inhibition.

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## Footnote

*Conflicts of Interest:* SM Dubinett serves on the scientific advisory boards for EarlyDx, T-Cure Bioscience, Cynvenio Biosystems and the Johnson and Johnson Lung Cancer Initiative. R Li has no conflicts of interest to declare.

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