The emerging role of myeloid-derived suppressor cells in lung diseases

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ABSTRACT  Myeloid-derived suppressor cells (MDSCs) are innate immune cells characterised by their potential to control T-cell responses and to dampen inflammation. While the role of MDSCs in cancer has been studied in depth, our understanding of their relevance for infectious and inflammatory disease conditions has just begun to evolve. Recent studies highlight an emerging and complex role for MDSCs in pulmonary diseases. In this review, we discuss the potential contribution of MDSCs as biomarkers and therapeutic targets in lung diseases, particularly lung cancer, tuberculosis, chronic obstructive pulmonary disease, asthma and cystic fibrosis.

Myeloid-derived suppressor cells are involved in various lung diseases and represent promising therapeutic targets http://ow.ly/WKZKh

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Myeloid-derived suppressor cells

Definition
Suppressive myeloid cells were initially identified more than three decades ago in patients with cancer [1–3]. Later on, these cells were uniformly termed as myeloid-derived suppressor cells (MDSCs) [4] and defined by 1) their myeloid origin and 2) their ability to suppress T-cell responses. Despite a plethora of studies on MDSCs in mice and men, the precise haematopoietic origin and lineage-association still remain a matter of debate [5, 6]. Broadly accepted is the notion that MDSCs stem from immature myeloid cells (IMCs) and can be subdivided into granulocytic/neutrophilic MDSCs (G-MDSCs) and monocytic MDSCs (M-MDSCs). Current MDSC concepts suggest that differentiation of IMCs into mature granulocytes, macrophages or dendritic cells (DCs) in bone marrow is skewed towards MDSCs in cancers [7]. While tumour-derived factors, such as granulocyte/macrophage colony-stimulating factor (GM-CSF), have been proposed to induce MDSCs in malignancies, the signals that drive MDSC generation in non-malignant infectious and inflammatory conditions remain incompletely understood [7, 8]. MDSCs are not defined as a single subset of cells, but rather represent a group of phenotypically heterogeneous myeloid cells that share a common biological activity. Human MDSCs have been described to commonly express the myeloid markers CD11b and CD33 as well as CD66b/CD15 for G-MDSCs and CD14 for M-MDSCs [9]. Murine MDSCs express the surface markers CD11b and Gr1 and lack the expression of cell-surface markers that are specific for macrophages or DCs [10]. Sub-phenotyping divides murine MDSCs into monocytic (Ly-6GlowCD11b+Ly-6ChighSSClow) and granulocytic/neutrophilic (Ly-6GhighCD11b+Ly-6Cintermed) subsets [7, 11].

Expansion
MDSCs have been reported to expand in malignant, infectious and autoimmune conditions [7, 8]. The factors driving MDSC expansion comprise a broad variety of pro-inflammatory factors, including interferon (IFN) γ [12–14], cyclooxygenase (COX) 2, stem-cell factor and prostaglandin E (PGE) [15, 16], GM-CSF [17], transforming growth factor (TGF) β [18–21], and interleukin (IL) 1β [22]. Signal transducer and activator of transcription 3 (STAT3) is regarded as the main transcription factor that regulates the expansion of MDSCs. STAT3 activation increases survival and proliferation of myeloid progenitor cells and regulates MDSC expansion through the expression of S100A8 and S100A9 proteins [23, 24]. The combination of IL-6 and GM-CSF has been identified to generate MDSCs from both human and murine immune cells [25, 26]. Beyond GM-CSF and IL-6, microbial factors have been described to induce MDSCs. Particularly, the opportunistic bacterium Pseudomonas aeruginosa was found to potently induce MDSC generation through flagellin [27]. Moreover, fungal infections with Aspergillus fumigatus and Candida albicans induced a distinct subset of MDSCs through the pattern recognition receptor Dectin-1 and its downstream adaptor protein caspase recruitment domain-containing protein 9, which further involves the generation of reactive oxygen species (ROS) as well as caspase-8 activity and IL-1 production [28]. The retinoblastoma gene was found to regulate M-MDSC differentiation towards G-MDSCs in tumour-bearing mice [29]. Under hypoxic conditions in the tumour microenvironment, MDSCs suppress both antigen-specific and non-specific T-cell activity via hypoxia-inducible factor (HIF) 1α [30]. HIF-1α also redirects MDSCs differentiation toward tumour-associated macrophages, which further supports the immune-suppressive network in the tumour microenvironment [30]. MDSCs have been reported to have a shorter lifespan in comparison to their counterparts, granulocytes and monocytes, in tumour-free mice mediated by tumour necrosis factor (TNF)-related apoptosis–induced ligand receptors and endoplasmic reticulum stress [31]. LPS and IFN-γ treatment in combination has been shown to trigger the expansion of splenic myeloid precursors into functionally suppressive MDSCs, blocking their development into DCs [32]. In addition, it was reported that G-MDSCs are expanded in neonatal cord blood and efficiently modulate innate and adaptive immune responses by suppressing T and natural killer (NK) cell responses [33]. These neonatal cord blood MDSCs may weaken cellular anti-microbial host defence responses and may contribute to the increased lung infection susceptibility in neonates.

Function
The mechanisms listed below have been implicated in MDSC-mediated suppression of T-cell function:

Reactive oxygen species
ROS have been implicated in MDSC-derived T-cell suppression as common mechanism in neoplastic conditions, inflammation and microbial infections [34]. MDSCs in both tumour-bearing mice and patients with cancer produce ROS and inhibition of ROS production diminished the suppressive effect of MDSCs [35–38]. It has been further shown that ligation of integrins, expressed on MDSCs, contribute to increased ROS production following the interaction of MDSCs with T-cells [39]. Several cytokines, such as TGF-β, IL-6, and GM-CSF, have been described to induce the production of ROS by MDSCs [40].
Arginase, nitric oxide synthase and nitric oxide

Arginase (ARG) 1 and inducible nitric oxide synthase (iNOS) are involved in L-arginine metabolism. iNOS generates nitric oxide (NO) from L-arginine, and arginase converts L-arginine into urea and L-ornithine. MDSCs express high levels of arginase and iNOS, and utilise these enzymes to deprive arginine and, thereby, inhibit T-cell function [41–43]. The shortage of L-arginine inhibits T-cell proliferation by decreasing T-cellular CD3ζ expression [44] and inhibiting the upregulation of the cell-cycle regulators cyclin D3 and cyclin-dependent kinase 4 [45]. On the other hand, NO suppresses T-cell function through inhibition of Janus kinase 3 and STAT5 in T-cells [46], inhibition of MHC class II expression [47] and the induction of T-cell apoptosis [48].

Peroxynitrite

Peroxynitrite is one of the most powerful oxidants, and is a product of a chemical reaction between NO and superoxide anion (O2•−). Peroxynitrite induces the nitration and nitrosylation of the amino acids cysteine, methionine, tryptophan and tyrosine. Increased levels of peroxynitrite are associated with tumour progression in many types of cancer [49–54], which has been linked with T-cell unresponsiveness.

Induction of regulatory T-cells

MDSCs were found to promote the development of CD4+CD25+FOXP3+ regulatory T-cells (Tregs), an effect that required the activation of tumour-specific T-cells and the presence of IFN-γ and IL-10 [55, 56].

Subset-specific mechanisms

The two main subsets of MDSC employ different mechanisms to suppress T-cell proliferation. The G-MDSC expresses high levels of ROS and low levels of NO, whereas the M-MDSC conversely expresses low levels of ROS and high levels of NO, while both subsets express arginase [57]. The suppressive activity of the G-MDSCs was shown to be ARG1-dependent, in contrast to the STAT1- and iNOS-dependent mechanism of M-MDSCs [58].

Non-T-cell related mechanisms of suppression

While initially described as merely T-cell suppressive, emerging evidence suggests that MDSCs also interact with and modulate the function of other immune cells, particularly including macrophages [59], NK cells [60, 61], and Tregs [61]. Moreover, MDSCs, tumour-associated macrophages (TAMs) and DCs have been reported to interact and to cross-promote their immunosuppressive activities within the tumour microenvironment [62]. MDSCs in the tumour microenvironment were described to rapidly differentiate into TAMs through a HIF-1α mediated mechanism [31]. MDSCs, in turn, producing high levels of IL-10, downregulate macrophage IL-12 production, promote TAMs and macrophage M2 polarisation and facilitate the development of Tregs [59, 63]. Furthermore, regulatory DCs (regDCs) have been described in cancer contexts as distinct DC subpopulation, which directly inhibit effector T-cells and indirectly induce or activate Treg cells and MDSCs [64]. Mechanistically, the immunosuppressive effects of regDCs were found to be mediated through IL-10, TGF-β, COX-2, iNOS, arginase and indoleamine 2,3-dioxygenase (IDO) [65–67].

MDSC plasticity/fibrocytic MDSCs

Recent studies suggest that Gr1+ myeloid-derived monocytic cells and MDSCs can transdifferentiate into extracellular matrix (collagen type I)-producing fibrocytes, a mechanism involving CD4+ T-cells, IL-2, IL-4, IFN-γ and TNF, GM-CSF/G-CSF, Kruppel-like factor 4 and fibroblast-specific protein 1 [68–70]. Fibrocytic MDSCs were found to interact with activated T-cells in a cell contact dependent manner, resulting in the production of IDO and leading to Treg expansion [69]. Fibrocytes can migrate into the tumour stroma microenvironment and further differentiate into myofibroblasts and promote tumorigenesis [71, 72] as well as metastasis [73]. Targeting fibrocytic MDSCs could represent a strategy to prevent the formation of the pre-metastatic niches and subsequently suppress metastasis formation.

Other mechanisms

Less established mechanisms used by MDSCs to suppress immune responses include: 1) upregulation of cyclooxygenase 2 and PGE2 [16]; 2) secretion of TGF-β [22]; and 3) sequestering cysteine as well as limiting the availability of cysteine, which is an essential amino acid for T-cell activation and proliferation [74]. Several studies demonstrate that the immunosuppressive functions of MDSCs require cell–cell contact, suggesting that MDSCs act through cell-surface receptors and/or the release of short-lived paracrine mediators [7]. MDSCs produce the anti-inflammatory cytokine IL-10 and dampen both CD4+ T-cells and NK cell responses [7, 75, 76], while promoting the expansion of Treg [63] and M2-like macrophages [59].

MDSCs in lung diseases

Some of the different lung diseases in which MDCs play a role and the mechanisms that are used are shown in figure 1.
Lung cancer and lung metastasis

T and NK cells are essential for tumour elimination in the lung [77]. Accordingly, factors that regulate their activity are of high interest for lung cancer treatment strategies. Accumulating evidence suggest that MDSCs are responsible for inhibiting host T-cell activity against tumour-associated antigens and consequently impair the effectiveness of anti-cancer immunotherapeutic approaches [78]. MDSCs numbers were found to be associated inversely with responsiveness to chemotherapy and positively with shorter survival in patients with lung cancer [79, 80]. Several studies support the concept that MDSCs dampen T-cells in lung cancer through direct contact and through mechanisms involving a plethora of mediators and mechanisms, such as iNOS, ARG1, TGF-β, IL-10 and the induction of Tregs [55, 75, 81–86]. MDSCs are recruited to the tumour site by the CC chemokine ligand (CCL) 2, CXC chemokine ligand (CXCL) 12, and CXCL5 [87]. The tumour microenvironment stimulates MDSCs to acquire immunosuppressive properties, which are mediated through STAT1, STAT3, STAT6 and nuclear factor κB transcription factors [7]. Activated MDSCs, in turn, produce ARG1, iNOS2, IDO, NADPH oxidase and immunosuppressive cytokines that have the potential to inhibit cytotoxic T lymphocytes, DC, and NK cells as well as expand CD4CD25FoxP3 Tregs [88, 89].

Many tumour types show an organ tropism of metastatic outgrowth, which was first proposed by Stephen Paget’s seed and soil theory in 1889 [90]. Colon cancer, as an example, induces predominantly metastasis in the lung. A decade ago Kaplan et al. [91] first described the concept of the premetastatic niches appearing in the lung as target organ. Signalling factors and cytokines of the primary tumour, e.g. vascular endothelial growth factor, placental growth factor, lysyl oxidases, and TNF or TGF-β, lead to the recruitment of immature bone marrow derived cells, which mainly consist of G-MDSCs, and form pre-metastatic niches in organs distinct from the location of the primary tumour. Within the pre-metastatic niche the main drivers for the infiltration of circulating CXC receptor (CXCR)4 tumour cells are the remodelling of the extracellular matrix by matrix metalloproteinase 9 (MMP9), expression of the adhesion molecule fibronectin, pro-inflammatory S100A8/9 signalling and finally the release of the chemokine stromal cell-derived factor 1, the agonist for CXCR4 [91]. Also hypoxia of the primary breast tumour accompanied by angiogenesis signalling promotes the infiltration of G-MDSCs with potent immunosuppression of NK cells [92].
Data from animal lung cancer models showed that COX-2 is involved in MDSC regulation through the production of PGE2 and ARG1 [43]. Srivastava et al. [93] demonstrated that Snail, an activating transcription factor in epithelial-mesenchymal transition, induces tumour growth and metastasis by increasing MDSCs via increasing intracellular expression of ARG1 in murine lung tumour microenvironment. In other murine models of lung cancer, targeting of MDSCs using antibodies improved antitumor activity via enhancing effector and memory T-cell responses, as well as NK cell and antigen-presenting cell activities [94–96]. Peripheral blood MDSC levels were shown to correlate with a higher tumour burden and a worse prognosis [97–99]. Several approaches have been pursued to eliminate MDSCs in cancer, particularly abrogation of MDSCs using all-trans retinoic acid [100, 101], chemotherapy (gemcitabine, 5-fluoro-uracil) [102, 103], MMP9 inhibition (amino-biphosphonates) [104], MDSC proliferation inhibitors such as tyrosine kinase inhibitors (sunitinib and sorafinib) [97, 105, 106], MDSC recruitment inhibitors (CXCR2 antagonists) [109], MDSC function/activation inhibitors such as COX-2 inhibitors [16, 43, 108] and phosphodiesterase-5 inhibitors (sildanefil) [109]. Another novel approach to abrogate MDSCs, so called "peptibody" treatment showed complete depletion of blood, splenic, and intratumoural G- and M-MDSCs in tumour bearing mice, without affecting pro-inflammatory immune cell types [110]. Based on these studies, the translational and therapeutic potential of targeting MDSCs, in combination with conventional therapies, could be a promising approach for future anti-cancer therapy in human patients. Overall, the development of novel therapeutic agents that eliminate the activity of MDSCs in human lung cancer should accelerate our understanding of their biological role within the tumour microenvironment.

**Asthma**

CD11b\(^\text{+}\)Gr\(1\)^intF4/80\(^{-}\)/MDSC-like cells were found to accumulate in allergic asthma and to suppress lung DC-mediated reactivation of primed Th2 cells in a toll-like receptor (TLR) 4- and MyD88-dependent fashion, mediated by IL-10 and ARG1 [75, 111]. It has been further shown that tumour-derived MDSCs suppress Th2-dominant inflammation in asthmatic mice, reduce recruitment of inflammatory cells and suppress production of IgG and Th2 cytokines in a TGF-β dependent manner [112]. The chemokine CCL2 was found to recruit MDSCs into lung tissues in airway inflammation [112]. Aspirin treatment dampened the accumulation of G-MDSCs in the inflamed lung accompanied by increased Th2 airway responses [113]. It has further been demonstrated that COX and its product, PGE2, play an important role in the regulation of activation and accumulation of MDSCs through PGE2 and PGE3 receptors [113, 114]. MDSCs and IL-10 levels significantly increased and negatively correlated with IL-12 levels during the onset of asthma in both human and mice. IL-10 not only suppressed the production of pro-inflammatory factors by macrophages, but also reduced cytotoxic effects and decreased NO production. Therefore, it is proposed that MDSCs play a dual role in asthma by upregulating anti-inflammatory IL-10 and downregulating pro-inflammatory IL-12 [76]. In a different study, MDSCs enhanced mast cell-mediated secretion of several inflammatory cytokines, including TNF, IL-6, IL-13, macrophage inflammatory protein-1α and monocyte chemoattractant protein-1. The mutual interaction of MDSCs and mast cells enhanced the activities of each cell type, resulting in exacerbated inflammation and airway hyperresponsiveness [115]. Three different populations of CD11b\(^{+}\)Ly-6G\(^{-}\) myeloid cells infiltrated the lung in a mouse model of allergic airway inflammation where they differentially generate the reactive free radicals NO and O\(_2\). The Ly-6C\(^{−}\)Ly-6G\(^{−}\) subset (predominant NO producer) and the Ly-6C\(^{+}\)Ly-6G\(^{+}\) subset were found to suppress T-cell proliferation. In contrast, the O\(_2\)\(_{\text{−}}\) subset generates the Ly-6C\(^{−}\)Ly-6G\(^{+}\) subset enhanced T-cell responses [116]. Superoxide-producing myeloid-derived regulatory cells (MDRCs), present in high numbers in the airways of patients with mild asthma or chronic obstructive pulmonary disease (COPD), but not in healthy controls, were, on the other hand, found to enhance proliferation of CD4\(^{+}\) T-cells [117].

**COPD**

NO producing MDRSCs were found in the airways of patients with mild asthma, but not in COPD patients or healthy control individuals and, were found to suppress activated CD4\(^{+}\) T-cells [117]. Smoking upregulated and activated circulating MDSCs in COPD patients, but not in smokers with normal lung function [118]. In COPD patients the MDSC activation was accompanied by down-regulation of the T-cell receptor ζ chain expression in T-cells [118]. In addition, it has been shown that MDSCs were elevated in the bone marrow, spleens, and lungs after 4 months of cigarette smoke exposure, while this was paralleled by decreased pulmonary DCs [119]. However, these phenotypic MDSCs lacked immune suppressive activity, and thus were not bona fide MDSCs [119]. In a further study, MDSCs were also increased in patients with COPD and correlated with elevated levels of Tregs, which is in agreement with studies that suggest reciprocal control of these two cell types [120]. In summary, these studies suggest that the accumulation of MDSCs in COPD may underlie the blunted immune response observed in COPD.
Tuberculosis

Development of active tuberculosis (TB) is known to correlate with impaired T-cell responses, but the underlying immune mechanisms remained incompletely understood [121–125]. Both patients with acute (household exposure within 3 months) and chronic TB were recently described to show significantly higher frequencies of MDSCs that inhibited functions of CD4+ and CD8+ T-cells, including T-cell proliferation, altered T-cell trafficking as well as production of IL-2, IFN-γ and TNF [126]. The frequency of CD3+CD24highCD152high cells with MDSC phenotypes were significantly higher in active TB patients and were inversely associated with the activation and functionality of CD4+ and CD8+ T-cells [127]. In murine experimental pulmonary TB, MDSCs readily phagocytosed Mycobacterium tuberculosis, and released both pro-inflammatory (IL-6, IL-1β) and immunomodulatory (IL-10) cytokines, while retaining their suppressive capacity [128]. Excessive MDSC accumulation in lungs correlated with elevated surface expression of IL-4Rx and increased TB lethality, whereas targeted depletion of MDSCs ameliorated disease in this animal TB model [128]. In summary, these findings indicate that MDSCs accumulate in lungs during pulmonary TB and play a dual role in host-pathogen interaction: MDSCs phagocytose and harbour M. tuberculosis bacteria intracellularly, providing a cellular shelter, while simultaneously dampening surrounding hostile T-cell responses.

Pulmonary hypertension

Pulmonary hypertension is a progressive syndrome with dysregulated inflammatory processes [129]. Immunohistochemical analysis of lung sections from patients with pulmonary hypertension indicated that immature DCs are present in peribronchovascular regions of vascular remodelling [130]. In a rat model of monocrotaline-induced pulmonary hypertension, DCs with immature myeloid phenotype were recruited to remodelled vessels [130]. In addition, monocyte-derived DCs from patients with pulmonary hypertension were defective in their ability to stimulate T-cells in an allostimulatory mixed-leukocyte reaction assay. In this respect, abnormalities of T lymphocyte subsets have been documented in patients with pulmonary hypertension [131, 132]. In pulmonary hypertension patients, circulating activated MDSC numbers were significantly increased in comparison to control subjects and correlated with increasing mean pulmonary artery pressure [133]. A direct mechanistic role for MDSCs in pulmonary hypertension and inflammation-associated vascular remodelling has not yet been defined.

Cystic fibrosis

Cystic fibrosis (CF) patients are impaired in eradicating P. aeruginosa infections and show skewed T-cell proliferation and immune responses, but the underlying reasons remained poorly understood [134–136]. Recently, it has been shown that G-MDSCs accumulate in CF patients, particularly in patients chronically infected with P. aeruginosa and correlate with CF lung disease activity [28]. Flagellated P. aeruginosa induced MDSC generation, corresponding to TLR5 surface expression on G-MDSCs. Moreover, G-MDSCs in CF patients were further characterised by an upregulation of the chemokine receptor and HIV-correceptor CXCR4 on the surface of MDSCs. Functionally, both CF patient-isolated and flagellin-induced MDSCs suppressed T-cell proliferation and modulated Th17 cells, as key antibacterial T-cell populations in CF. Percentages of circulating activated G-MDSCs correlated with pulmonary hypertension and inflammation-associated vascular remodelling in CF patients chronically infected with P. aeruginosa. MDSCs could, therefore, represent a novel therapeutic target in CF patients, particularly in patients chronically infected with P. aeruginosa [26].

Pulmonary infection

Efficient innate host defence is crucial for the elimination of invading pulmonary pathogens [137, 138], but uncontrolled immune activation leads to collateral tissue damage. Neutrophilic cells that are rapidly recruited to the site of infection produce ROS and proteases to clear infection. However, due to a relatively short life span, neutrophils rapidly undergo apoptosis, secondary necrosis or neutrophil extracellular trap formation at the pulmonary site of infection. MDSCs have been described to efficiently effecrocytose apoptotic neutrophils, mediated by IL-10 [139]. Clearance of dead neutrophils by MDSCs may, therefore, help to resolve lung inflammation, preventing lung injury and ultimately restore tissue homeostasis. Studies in Stat1−/− mice showed that bacterial infection significantly increased pulmonary MDSCs, while decreasing neutrophils [139]. These observations suggest that increasing MDSCs via STAT1 inhibition in combination with effective antibiotic therapy may be beneficial in the context of non-resolving bacterial pneumonia. On the other hand, it has been shown that expansion of MDSCs and absence of invariant NK T-cells in influenza A infection suppresses influenza-specific immune responses [140]. These paradoxical effects in viral and bacterial infection may be due to different MDSC kinetics and/or downstream responses [139, 140]. MDSCs accumulate in the lungs during pneumocystis pneumonia (PCP) [141]. At the pulmonary site, MDSCs interact with alveolar macrophages through programmed cell death protein 1 and programmed death-ligand 1, leading to macrophage suppression through histone modification and DNA methylation of the PU.1 gene, finally resulting in PU.1 downregulation. MDSCs employ the same
mechanism to interact with monocytes, leading to PU.1 downregulation and inhibition of their differentiation into alveolar macrophages, resulting in decreased numbers and activity of alveolar macrophages during PCP [142].

**Pulmonary inflammation**

Exposure of mice to lipopolysaccharide (LPS) triggers the recruitment of a MDSC-like phenotype (CD11b+Ly6GlowLy6Cmed–F4/80−CD80+) into the lung [139], where they reside, in contrast to DCs, which traffic readily to the lymph nodes [75]. LPS-induced lung MDSCs were further shown to blunt the ability of pulmonary DCs to promote Th2 responses [75, 143–145]. It is speculated that lung MDSCs compromise Th2 cell survival, thereby reducing the size of the memory T-cell pool [75, 146, 147]. Thus, collectively, it appears that an important effector function of TLR-induced MDSCs is not directed to the lymph node to influence the development of adaptive immune functions, but rather to control local pulmonary immune responses. Recent studies further suggest that TLR4 activation by LPS induces GM-CSF and IL-6 production leading to STAT5 and STAT3 activation, which in turn drives MDSC pulmonary immune responses. Recent studies further suggest that TLR4 activation by LPS induces GM-CSF and IL-6 production leading to STAT5 and STAT3 activation, which in turn drives MDSC generation [82, 139, 148, 149]. At the cellular level, MDSCs induce Tregs [150] by increasing Foxp3 expression via an IL-10–, TGF-β– and ARG1-dependent mechanism [150]. It has been further shown that glucocorticoids induce a distinct anti-inflammatory phenotype in mouse monocytes, which phenotypically resemble MDSCs with respect to the expression of CD11b, Ly-6G and IL-4Rβ chain [151].

**Conclusions and outlook**

Emerging evidence suggests that MDSCs, as immuno suppressive myeloid cells, play a critical role in malignant, infectious and inflammatory lung diseases, particularly lung cancer, TB, COPD, pulmonary hypertension, asthma and CF. Amongst the MDSC subsets, granulocytic MDSCs appear to represent the major population accumulating in pulmonary diseases. Pathways orchestrating MDSC generation, recruitment, activation and suppressive functions are diverse and future studies are required to narrow down the most relevant ones for therapeutic targeting approaches. Mechanistically, a more precise understanding of how host- or pathogen-derived cues modulate MDSC generation and function will help to develop tailored MDSC inhibitors for conditions where MDSC cause harm to the host, such as lung cancer and pulmonary infection (for instance TB), where pulmonary MDSCs favour the survival of malignant cells or pathogens. Conversely, adoptive cellular transfer or specific activation of MDSCs may represent an attractive therapeutic strategy to dampen immune responses in the setting of immune over activation, as found in allergic, autoimmune and auto-inflammatory pulmonary disease conditions. Findings from both mouse models and human patients indicate a potential therapeutic role for vitamin A and D, tyrosine kinase inhibitors, chemokine receptor antagonists, COX inhibitors and phosphodiesterase-5 inhibitors in regulating MDSCs. Clinical interventional studies are the next consequent step to systematically assess the safety and efficacy of these MDSC-interfering approaches in pulmonary diseases.

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