Chapter 2

# Macrophage Polarization in Lung Biology and Diseases

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Additional information is available at the end of the chapter

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## 1. Introduction

Lung is a major site of continuous immune reactions as it encounters various foreign particles and antigens entering the respiratory system. It is the main internal organ constantly exposed to the external environment that contains an array of microbes and particulate matter. Typically an adult exchanges 4.2 liters of air per minute amounting to almost 6000 liters per day [1In fact ventilation and respiration generates an environment where both inflammatory and anti-inflammatory response takes place continuously. However, a delicate balance is maintained between eliciting an immune response followed by resolution and repression of further immune reactions. Uncontrolled responses may result in injury or collateral damage to the lung whereas a subdued immune reaction may lead to unchecked infection. Hence, an efficient inflammatory reaction followed by precisely controlled resolution and fine-tuned remodeling process has evolved to minimize the effects of such challenges. The immune system of the lung is well developed to encounter this continuous challenge and disparate demands. Both innate and adaptive immune responses contribute to the surveillance of overall immune function in the lung. The respective immunological effector cells, T-lymphocytes, mast cells, dendritic cells (DCs) and macrophages are present within the lung interstitium, as early as from the pseudoglandular stage of development [2].

Macrophages are strategically distributed all over the body, present virtually in all tissues. They represent an important part of the immune system as tissue resident cells. Macrophages can differentiate from circulating peripheral blood mononuclear cells which migrate into tissue in the steady state or in response to inflammation. As the most plastic cell of the hemapoetic system, macrophages are classified depending on the milieu and specialization. Macrophages are of various types such as alveolar (lungs), microglia (brain), kupffer cells (hepatic), splenic, intestinal, intraocular (eyes) and bone marrow. Macrophages represent a spectrum of activated

phenotypes rather than defined stable subpopulations. During homeostatic conditions, the tissue resident macrophages remain in a quiescent state. Upon requirement, monocytes get recruited and differentiated into macrophages and DCs at the site of inflammation. Mature macrophages can further get polarized into either M1 macrophages (classical activation) or M2 macrophages (alternative activation) and attain their respective phenotypes. They are characterized based on their surface markers, secreted cytokines, nitric oxide enzymes, transcription and epigenetic factors.

Macrophages serve as an effective component of innate immunity for their ability to recognize, engulf and kill potential pathogens. Macrophages are commonly derived from monocytes and play a crucial role in both innate and adaptive immunity [3]. They contribute to the activation of these immune responses by synthesis and secretion of a range of pro-and anti-inflammatory mediators thereby establishing protective immunity. Macrophages also play an important role in the defense system as antimicrobial warriors against invading microbes such as bacteria. Uncontrolled macrophage activity in the host is however noxious and has been linked to various pathogenic conditions such as artherosclerosis, granulomatous disease and macrophage activation syndrome [4-9]. The pivotal role of macrophages during the initiation, regulation and termination of inflammation makes them a major target for the prevention, control and resolution of inflammatory processes in various chronic lung diseases such as chronic obstructive pulmonary disease (COPD) [10-13], asthma [14-16] and idiopathic pulmonary fibrosis (IPF) [17-20].

The alveolar macrophages (AMs) are the predominant leukocyte phenotype in the lung among all age groups (> 89%). Bronchoalveolar lavage (BAL) from healthy adults contains an average of 91% of alveolar macrophages, 7% of lymphocytes, 1% neutrophils and 1% of mast cells [21]. In the lungs, cells of lymphoid origin are sparse when compared to cells derived from the myeloid lineage during an acute immune response. Macrophages initiate phagocytosis and subsequently release cytokines along with other products which orchestrate host cellular defence. Understanding the molecular basis of macrophage polarization is an important aspect to deal with inflammation. The microenvironment plays an important role in the phenotypic polarization of macrophages. This polarization is driven by various factors, signals and diseased conditions. However, the molecular basis of macrophage polarization has not been fully explored. A major question that remains to be answered is about the function of the different macrophage types under various conditions such as steady state, diseased and tissue-repair. The need to understand the polarization of macrophages becomes mandatory in order to improve the therapeutic strategies for different chronic respiratory diseases. In this chapter, the heterogeneity of macrophages, its classification under different conditions, and the status of its polarization in chronic respiratory diseases along with their respective functions are discussed.

## 2. Monocyte heterogeneity

The mononuclear phagocyte system represents a subgroup of leukocytes described as a population of bone marrow derived CD4+(cluster of differentiation 4) myeloid progenitor cells

that circulate in the blood as monocytes [22]. They act as immune effector cells, equipped with chemokine receptors and pathogen recognition receptors on its surface that mediate migration from blood to tissues. These cells do not proliferate in a steady state condition but circulate in blood stream, bone marrow and spleen [23, 24]. They enter the peripheral tissues during inflammation and mature into either macrophages or inflammatory DCs which are significant mediators of inflammatory reaction in the lung tissue. The differentiation of recruited blood monocytes into macrophages depends on the characteristics of inflammation and is also governed by the pulmonary microenvironment. Newly differentiated macrophages can also activate resident macrophages or epithelial cells to secrete more inflammatory cytokines, chemokines and other inflammatory factors which in turn result in more monocyte recruitment to the site of inflammation.

Peripheral-blood monocytes show morphological heterogeneity, such as variability of size, granularity and nuclear morphology [25]. In human blood, monocytes are divided into two subsets depending upon the differential expression of cell surface markers CD14 and CD16, commonly detected by means of cytometry. Monocytes which are $CD14^{hi}$(High) and $CD16^{-}$ (negative) represent the classical subset whereas monocytes with $CD14^{hi}$ and $CD16^{+}$(positive) expression represent the other type characterized by higher expression of major histocompatability complex class II (MHCII) and CD32 antigen [26]. The monocyte heterogeneity in mice is differentiated with the expression of chemokine (C-C motif) receptor 2 (CCR2) and lymphocyte antigen 6 complex (Ly6C). Monocytes which express CCR2, CD62, $CX3CR^{low}$ (chemokine [C-X3-C motif] receptor 1), Ly6C correspond to $CD14^{hi}CD16^{-}$ (classic) human monocytes [27]. Although monocyte heterogeneity is not completely understood, one theory suggests that monocytes continue to develop and mature in the blood and can be recruited into the tissues at various points during maturation continuum [28].

Plasticity is the hallmark of monocytes and it responds to various microenvironmental signals and mount specific phenotypic functional programs. Monocytes in response to the pro-inflammatory signals migrate to the inflamed tissue and differentiate into inflammatory macrophages and DCs. Also in the absence of inflammation, monocytes have been thought to enter the tissues and replenish the pool of tissue resident macrophages and DC populations [29]. However, recent evidences suggest that tissue resident macrophages proliferate and maintain their pool locally, independent of the circulating blood monocytes [30]. However, the precise mechanism for this switch in the role of monocytes from one type to another is not clear. Granulocyte macrophage-colony stimulating factor (GM-CSF) and interleukin 4 (IL4) are able to induce the differentiation of human and mouse monocytes into DCs, irrespective of their subsets [31, 32]. These striking similarities in the characteristic features of mouse and human monocyte subsets establish the conserved mechanisms among the two species. However, since most of our understanding about macrophage biology relies on in vitro studies or severe pathological conditions of animal experimental disease models, one needs to overcome the difficulties in establishing the in vitro and in vivo studies to have a clear mechanistic understanding of the phenotype switching in monocytes under homeostatic conditions. In this context, significant progress has recently been achieved in mice thereby improving our understanding of the weak connection between circulating blood monocytes

and resident tissue macrophages. For example it has been shown that AMs originate from fetal monocytes, thus establishing a locally independent, self-maintained pool of highly specialized resident tissue phagocytes. The pool is maintained by local proliferation, mainly triggered by GM-CSF stimulation and under steady state conditions exist independent of replenishment by blood monocytes [30, 33, 34].

## 3. Populations of macrophages

Macrophages can be derived from circulating monocytes and exhibit a high degree of heterogeneity like their precursors [35, 36]. However, it is still not clear whether in this way differentiated cell will be able to functionally replace resident tissue macrophage. Heterogeneity refers to the ability of macrophages to embark on different phenotypic functional specialization depending upon the anatomical location and its microenvironment. For example, the AMs express high pattern recognition receptors to counter the environmental microbial challenge in the lungs. Likewise, each tissue resident macrophage has its typical functional characterization. It is clear that macrophages represent a spectrum of activated phenotypes rather than discrete stable subpopulation. The main function of immune surveillance remains the same for all the macrophages irrespective of its location. Macrophages play a central role in inflammation and host defence [3] and are characterized by considerable diversity and plasticity [37, 38].

In the lung, distinct macrophage subpopulations have been characterized primarily in infectious disease and asthma models [39-43]. The local conditions present in the lung dictate the differentiation and activation of monocytes and macrophages in addition to the specific developmental pathways [25]. Two unique populations of monocytes are present in circulation. The monocytes enter lungs under steady state conditions and develop into resident tissue interstitial macrophages and AMs [44, 45]. Inflammatory monocytes are recruited in a CCR2-dependent manner at the time of inflammation, and develop into either an activated macrophage population, known as exudative macrophages (ExMacs) or into monocyte-derived dendritic cells (moDCs) [46]. Resident macrophages differ markedly from inflammatory monocyte-derived macrophages in terms of morphology, phenotype, and effector functions [42].

Resident lung interstitial macrophages and AMs express relatively lower MHCII and costimulatory molecules [47]. After activation, they produce low levels of inflammatory cytokines and do not promote T-cell activation. In contrast, ExMacs are a major source of inflammatory cytokines and chemokines, expressing high levels of MHCII and costimulatory molecules. Further, they also stimulate T cell activation [46]. It is hypothesized that ExMacs are recruited to the lung early after noninfectious lung injury and have effector functions distinct from resident macrophages [46]. AMs in the lung provide the first line of defense against inhaled organism and irritants [16, 44]. In addition to their phagocytic role, AMs are known to be a critical modulator of the lung inflammatory response through the production of various pro-inflammatory and anti-inflammatory modulators.

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## 4. Activation and recruitment of macrophages

The presence and evolution of distinct macrophage subsets in the lung serve specific niches in regulating the inflammatory response and its resolution. Based on the patterns of gene expression, protein secretion and roles in host defense mechanisms, macrophages are classified into classically activated macrophages (CAM) and alternatively activated macrophages (AAM). The two main macrophage subsets namely CAM (also termed as M1) and AAM (termed as M2) have been described in analogy to T helper (Th)1 and Th2 lymphocyte archetype activation [3]. In response to various signals, macrophages may undergo M1 classical activation [by toll like receptor (TLR) ligands and interferon gamma (IFNγ)] or M2 alternative activation [by IL4 and IL13]. M1 and M2 activation phenotypes represent two ends of the functional spectrum of macrophage polarization [48] (Figure 1). In addition to these stimulants, various other cytokines and interferons have also been documented in the polarization of macrophages. Addition of transforming growth factor beta 1 (TGFβ1) to monocytes confers the phenotype of leukocytes during in vitro condition [49], whereas exposure to macrophage colony stimulating factors (M-CSF) induces monocytes to differentiate into macrophages under the same condition. Addition of IFNγ [or lipopolysaccharide (LPS)] to M-CSF induces the differentiation of M1-like macrophages whereas addition of IL4 induces the differentiation of M2-like macrophages [50, 51]. A continuum of macrophage polarization is likely to exist beyond these discrete in vitro based classifications [38].

The immune system of alveolar blood barrier in the lungs has to be tightly regulated as pulmonary edema and inflammation can lead to thickening of alveolar walls and thereby compromise gas exchange efficiency [52]. Alveolar macrophages play an important role in maintaining the immune system of the lungs. Multiple subsets of monocyte derived macrophages contribute to distinct stages of inflammation [23, 27]. A fully differentiated macrophage subpopulation can change its phenotype in response to the microenvironment [48, 53, 54]. Each signal from the microenvironment has its specific role in the process of macrophage polarization and the macrophages change their phenotype based on the duration of exposure to the stimulus [53-57]. Macrophages which are exposed to the environment favoring alternative activation, switches its phenotype to M1 when it encounters activation by IFNγ or TNF [58-60]. Various molecules such as 7-oxo-cholesterol (7oxo-C), P50 have been recognized as stimulants of polarization. 7oxo-C has a prominent impact on the phenotype of polarized M1 and M2 macrophages. It stimulates the expression of MHCII by M1 macrophages resulting in upregulation of macrophage function as antigen presenting cells (APC) that favor activation of adaptive immune responses [61]. 7-oxoC affects human macrophage biology by skewing the M1/M2 macrophage balance towards a pro-inflammatory profile. P50 in nuclear factor kappa B (NF-κB) play an essential role in the orientation of macrophage polarization both in vitro and in vivo. This regulatory subunit may play a crucial role in the control of M1 and M2 driven inflammation [62]. Other key transcription factors for polarization are interferon regulatory factor 5 (IRF5), signal transducer and activator of transcription 1 (STAT1) for the M1 and IRF4, STAT6 and peroxisome proliferator activated receptor gamma (PPARγ) for the M2 pathway [63].

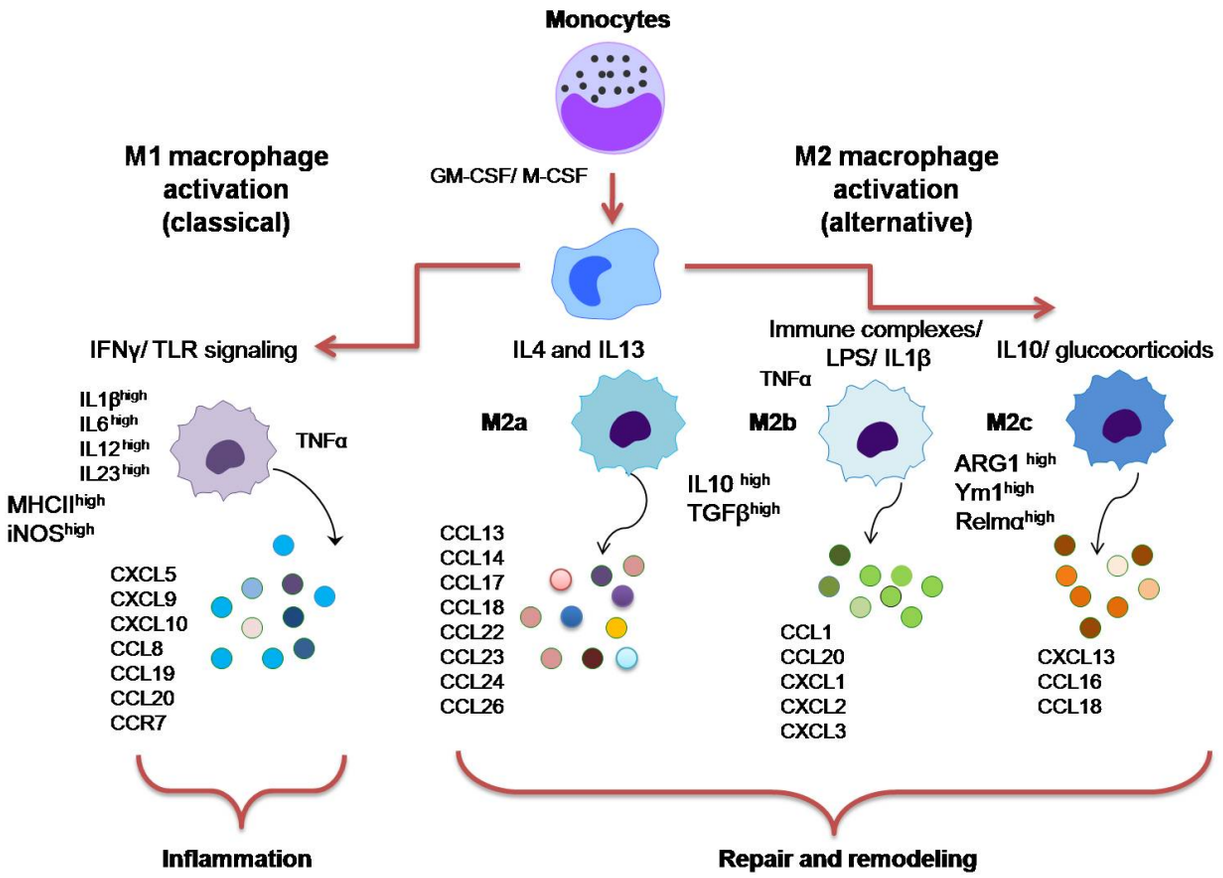


**Figure 1. Schematic representation of M1 (classical) and M2 (alternative) macrophage polarization**. Several cytokines and chemokines are involved in the classical and alternative activation of macrophages. Monocytes gets differentiated into macrophages which in turn polarize to M1 type on exposure to interferon gamma (IFNγ). Various signals define the different forms of alternative activation of macrophages. Interleukin 4 (IL4) or IL13 induces M2a subtype; IL1β or lipopolysachharide (LPS) or immune compelxes induces M2b macrophages; and IL10 or glucocorticoids results in M2c macrophages [38, 48, 64]. **GM-CSF:** granuloctye macrophage-colony stimulating factor, **M-CSF:** macrophage-colony stimulating factor, **MHCII:** major histocompatibility complex II, **iNOS:** induced nitric oxide synthase, **TNFα:** tumour necrosis factor alpha, **ARG1:** arginase 1, **Ym1:** chitinase-like 3, **Relmα:** resistin like alpha, **CXCL:** chemokine (C-X-C motif) ligand, **CCL:** chemokine (C-C motif) ligand, **CCR:** chemokine (C-C motif) receptor.

## 5. Classical activation of macrophages (CAM)

M1 macrophages are induced by IFNγ. Other factors which results in the activation of M1 macrophages are LPS, cytokines such as TNFα and GM-CSF. IL12 and IL23 are upregulated while IL10 is down-regulated during M1 macrophage activation [65]. IL1β and TNFα act as inducers as well as effector molecules during this process. It is also observed that Th1 response is involved in classical macrophage activation. M1 macrophage development results in elevated expression of the enzyme induced nitric oxide synthase (iNOS/NOS2) [66] thereby causing production of an excess amount of nitrogen and oxygen intermediates. These cells mediate the resistance against microbes, intracellular parasites and tumours by eliciting tissue disruptive reactions. M1 macrophages, whose prototypical activating stimuli are IFNγ and

LPS, exhibit potent microbicidal properties and promote strong IL12-mediated Th1 responses. M1 macrophages express reduced levels of mannose receptor and Fc receptor for IgG (Fc$\alpha$R)II [67]. Classical polarization of macrophages by cytokines affects lymphocyte proliferation. It also determines the cytokines to be produced by activated macrophages. Pro-inflammatory M1 macrophages release higher amounts of active matrix metalloproteinases (MMPs) such as MMP1 and MMP9 compared to anti-inflammatory M2 cells.

## 6. Alternate activation of macrophages (AAM)

Macrophages activated in the presence of IL4 are known as alternatively activated macrophages. IL4 along with IL13 are the major cytokines of Th2 immune responses. Macrophages treated with IL4 and IL13 fail to present antigens to T cells and produce low levels of cytokines in vitro [68, 69]. These macrophages are also termed as wound healing and tissue regeneration macrophages because of their ability to produce growth factors contributing to the development of extracellular matrix (ECM). The main properties of M2 like macrophages are expression of higher levels of surface scavenger, mannose and galactose type receptors that are involved in debris clearance. It is worthy to note that although murine M1-and M2-polarized macrophage subsets are relatively easy to distinguish based on combinatorial gene expression profiles, the identification of equivalent subsets in humans is a more challenging task [61]. There are various forms of AAM [70]. Immune complexes along with IL10, glucocorticoids activate M2 macrophages besides IL4 and IL13. Contrary to the M1 macrophages, during polarization IL12 and IL23 are released at lower levels whereas scavenger, mannose and galactose-type receptors are expressed at higher levels. IL4 was initially believed to act as anti-inflammatory for its ability to suppress TNF$\alpha$ and IL6 production in macrophages. AAMs also downregulate host protection against selected pathogens, but promote parasite encapsulation.

There are three distinct subtypes of AAMs namely M2a, M2b and M2c (Figure 1). This classification is mainly based upon the interaction between the specific ligands and receptors of the macrophages. The subtypes of AAMs are characterized based on the cell surface markers and specialization. Low amounts of IL4 promote a Th2 cell response. If the stimulus persists, it results in sufficient production of IL13, which is a dominant Th2 effector cell cytokine. IL13 in turn induces responses in both hemapoietic and non-hemapoietic cells. The diversity of macrophage function is indicated by their polarized states, distinct subpopulations and localization in the lung. Signals inducing M2 polarization downregulate the activities of NF-$\kappa$B and STAT1. IL4 and IL13 selectively induce CCL24, CCL17, CCL18 and CCL22 in M2a macrophages with inhibition by IFN$\gamma$ [70]. M2b macrophages express high levels of IL10 and low levels of IL12. M2c macrophages express high levels of CXCL13, CCL16 and CCL18 [70]. Unlike other discrete leukocyte populations, macrophages maintain their plasticity and can alter their phenotype based on the microenvironment, including the cytokine milieu among the other factors. Importantly, M1 cells can repolarize towards M2 after the phagocytosis of apoptotic neutrophils [71, 72] suggesting that reprogramming of inflammatory macrophage towards M2 phenotype may be involved in the resolution phase of acute lung injury.

The markers of polarized macrophage were originally identified by Becker and colleagues using membrane proteomics of macrophages [73]. AM induces high IL10 production and also weakly express the surface receptors for M2 cells. This suggests that an early recruitment or activation of a resident population can serve to balance the pro-inflammatory milieu. A population of pro-inflammatory M1 cells within the interstitium is also found to be resident cells. During the resolution phase of lung injury, this population ($CD11b^{low}$ and $CD45^{hi}$) up regulates the M2 markers, transferrin receptor (TFRC), chitinase –like 3 (YM1) and arginase 1 (ARG1) expression representing M1 cells in transition. A similar trend of repolarization markers is observed among these cells located in the alveolar space. $CD11b^{hi}$ expressing population of cells demonstrates higher iNOS, IL12 and ARG1 gene expression. This subpopulation coexpressing iNos and ARG1 may be regarded as representative cells which share M1 and M2 markers [74]. The $CD11b^{hi}$ cells also express high amounts of IL12, another factor by which these cells can regulate T cell responses. Cu, Zn superoxide dismutase (Cu, Zn-SOD) polarize the macrophages to M2 phenotype, and Cu, Zn-SOD-mediated $H_2O_2$ levels modulates M2 gene expression at the transcriptional level by redox regulation of a critical cysteine in STAT6 [75].

## 7. Resident alveolar macrophages (AM)

The lung provides an appropriate example of macrophage heterogeneity within an organ and effects of the microenvironment on the respective functions of macrophages located within that particular environment. Based on the anatomical location within the lung, there are three types of macrophages viz., alveolar, interstitial, and the intravascular macrophages. Each macrophage performs specific functions, as for example, the primary function of alveolar macrophage is the removal of particulates and microorganisms from the alveolar space. The pulmonary intravascular macrophages perform the same function but in the circulation whereas the interstitial macrophages might have a role in limiting inflammation, fibrosis, and antigen presentation [76, 77]. However, the role of macrophage heterogeneity in development of various macrophage population and its subsets is not clearly understood. As described above, resident alveolar macrophages are derived from fetal monocytes but not blood monocytes. However, it is still not clear whether the ExMacs are differentiated after inflammation from recruited monocytes can actually replace those developed under steady state conditions. Further, it remains unclear whether resident macrophages in the respective tissue niche are terminally differentiated or remain flexible to change their phenotype from one niche to another according to the respective signals and microenvironment.

In summary AMs are an unique type of mononuclear phagocytes that populate the surface of the lung in steady state. It forms the first line of defence against foreign particles invading the alveolar space. AMs get activated on pathogen recognition, thereby releasing early response cytokines such as TNF$\alpha$ and IL1 $\beta$. The early response also stimulate the neighboring alveolar cells to produce chemokines. These chemokines mediate the recruitment of neutrophils, ExMacs and lymphoctyes [78, 79]. AMs contribute to respiratory tolerance by inducing Fox3 expression in naïve T cells [80]. Noteworthy, the bone marrow with derived blood monocytes

does not significantly contribute to the alveolar macrophage compartment during steady state conditions. Previous alveolar macrophage half-life studies were confounded by the facts that they did not account for the inflammatory and stimulatory effects of irradiation conditioning regimens [79].

## 8. Molecular basis of macrophage polarization

Macrophage polarization is associated with significant changes at the transcriptional level, although the two polarizing conditions are very different. M1 polarization profoundly affects the transcriptional profile while M2 polarization results in only subtle adjustments [65]. The investigations on the transcriptional events associated with M-CSF-dependent monocyte-to-macrophage differentiation and subsequent M1 or M2 polarization induced by LPS and IFN$\gamma$ or IL4 demonstrated the existence of a complex network of gene regulation. Modulation of genes involved in general cellular metabolic activities is a prominent feature of macrophage differentiation and polarization. The enzymes such as sphingosine 1 phosphate and ceramide 1 phosphate are used to distinguish the polarized forms of macrophages as sphingosine and ceramide kinase are selectively present in M1 and M2 macrophages respectively [65].

Classically activated macrophages include prototypic M1 polarization markers, such as the indoleamine-pyrrole 2,3 dioxygenase, the lysosomal associated membrane protein 3, IL7R and CCR7 [81]. Classically activated macrophages are characterized by increased expression of the solute carrier family member SLC21A15 and SLC31A2, while alternatively activated macrophages exhibit increased SLC4A7, SLC38A6 expression. In case of humans, membrane expression of the markers CD80 and CD200R are specific for M1 and M2 polarized macrophages respectively whereas mannose receptor (CD206) expression does not vary between M1 and M2. Transcript analysis further identified six markers of M1 polarization [IL-12p35, CXCL10, CXCL11, CCL5, CCR7 and indoleamine 2,3-dioxygenase 1 (IDO1)]; five markers of M2 polarization [TGF$\beta$, CCL14, CCL22, scavenger receptor class B, member 1 (SCARB1)] and several transcription factors IRF4, IRF5, STAT1, STAT6 and PPAR$\gamma$] involved in macrophage polarization. Ability of human M-CSF generated macrophage to polarize toward M1 or M2 subtype is also associated with enhanced secretion of TNF$\alpha$, IL1$\beta$, IL12p40, CXCL10 and IL10 (for M1); or CCL22 (for M2). Moreover, the comparison of the expression of M1 markers in M-CSF and GM-CSF macrophages polarized towards M1 subtype has revealed similarities [82].

Chemokine receptors are differentially expressed on polarized Th cells. Typically, CXCR3 and CCR5 are preferentially expressed on polarized Th1 cells, whereas CCR3, CCR4 and CCR8 have been associated with the Th2 phenotypes. Distinct chemokines are associated with M1 and the various forms of M2 macrophage activation. LPS and IFN$\gamma$ induce the expression of CXCL10, CXCL9 and CCL5 [83-85]. In addition, LPS mediates induction of the CXCL10, CXCL9 and CCL5 genes through the activation of the transcription factor IRF3, which results in IFN$\gamma$ expression and subsequent STAT1 activation [85]. Further, LPS activation of monocytes or macrophages results in the NF-$\kappa$B dependent transcription of inflammatory chemokines such as CXCL1,2,3,5,8,9 and 10; and CCL2, 3,4,5,11,17 and 22 [86]. Resistin like alpha (Relm$\alpha$),

YM1 are also expressed in higher levels and are used as phenotypic markers for M2 polarized macrophages. CCL13, CCL14, CCL17, CCL18 and CCL24 [87] are specifically induced in M2a macrophages [64, 88], whereas M2b macrophages rather characterized by expression of high levels of CCL20, CXCL1, CXCL2 and CXCL3; whereas M2c macrophages express high levels of CXCL13, CCL16 and CCL18 [64].

## 9. T cells and Alveolar macrophages

T cell mediated immunity is important in the lung in order to protect the host from inhaled pathogens and environmental antigens [89-91]. Furthermore, most of the environmental antigens encountered by the lung are innocuous. Hence it is crucial for the resident immune cells to distinguish such inert antigens from those derived from pathogens and respond appropriately. The immunoregulatory mechanisms employed by the lung include the components for surfactant lining [92], products secreted by alveolar type II epithelial cells as well as alveolar macrophages which altogether actively suppress T cell proliferation. Moreover, AM induces anergy (immune unresponsiveness) in T cells which is reversible upon its removal from culture [91]. T cells isolated from lungs of rodents express low levels of IL2 receptor (IL2R/CD25) [91]. The Immunoregulators associated with AM include prostaglandins, leukotrienes, IL1 and nitric oxide [89]. AMs also downregulate local pulmonary immune responses against intratracheally administered T cell dependent antigens [93].

AMs from rat, mouse and human differ markedly in its potency to inhibit mitogen-induced T cell proliferation. However, T cells stimulated in the presence of AMs display a similar phenotype in all species examined, i.e. CD3 downregulation, upregulation of IL2R, increased IL2 production and inability to respond to IL2 [94]. Thus, AMs appear to allow T cell activation and effector functions, while selectively inhibiting T cell proliferation. The suppressive activity of AMs is restricted to the final step in the activation process, (i.e. proliferation). Through CD3 downregulation, IL2R expression and IL2 secretion appear to proceed normally [94].

T cells from humans produce less IL2 than autologous blood-derived T cells [95]. FoxP3 is a master regulator of regulatory T cells (Treg). FoxP3 expression is regarded as definitive marker for cells with regulatory function in mice and humans [96, 97]. AMs obtained from BAL of mice or humans enhance FoxP3 expression in CD4+FoxP3-T cells in vitro. Activation of naïve T cells in the presence of either AMs or AM-conditioned media prevents T cell proliferation. This effect can be reversed by inhibiting binding of retinoic acid to its receptor or by blocking TGFβ1 signaling [80]. AMs induce intracellular FoxP3 expression in CD4+T cells. It promotes IL10 while suppressing IFNγ production by the same T cell in vitro [80]. AMs induce an immune unresponsiveness in T cells and also affects its proliferation.

## 10. Role of macrophages in chronic respiratory diseases

Macrophages have the ability to elicit an immune response and resolve the inflammatory processes. The macrophages of the respiratory system are involved in the pathogenesis of

different respiratory diseases such as COPD, asthma and pulmonary fibrosis. Different phenotypes of macrophages are involved in these respiratory diseases which play an important role in either inflammation and / or resolution process.

## 11. Chronic obstructive pulmonary disease (COPD)

COPD is a global epidemic, mainly caused by cigarette smoke exposure (smokers disease) and high particulate air pollution (as associated to in-house cooking) with an alarming increase in its mortality rate [98]. COPD is characterized by an inflammatory airway obstruction and loss of alveolar tissue thereby causing reduced respiratory surface area (emphysema). Macrophages are elevated and accumulate in small airways, bronchioles and alveoli during COPD irrespective of the disease severity. Macrophages monitor and respond to their microenvironment that can define tissue remodelling and possibly control other inflammatory events. AMs in the lung are an important source of both proteinases and antiproteinases. They secrete a series MMPs (1,9 and 12) [10, 99-101] and tissue inhibitor of metalloproteinases (TIMPs). In addition, they also secrete lysosomal cysteine proteinases [Cathepsin K, L, S (CTSK, CTSL and CTSS respectively)] and their inhibitor cystatin C (CST3) [10, 102]. An imbalance between proteinase and antiproteinase is considered to be an important event in the pathogenesis of COPD [103].

Macrophage derived MMPs as well as cathepsins are elastinolytic [10, 102, 104] and are important in airway inflammation and development of emphysema [9, 10, 101].Elastinolysis, an essential event of emphysema [105] results in the destruction of lung tissues during COPD [106, 107]. AMs have also been shown to release neutrophil elastase in vitro [102, 108]. There is a positive association between macrophage numbers in the alveolar walls and the presence of mild to moderate emphysema as well as the degree of small airways disease in patients with COPD [109, 110]. Dysregulated expression of macrophage MMPs either directly or indirectly by cigarette smoke exposure can lead to lung parenchyma destruction, characteristic of emphysema.

The role of different subsets of AMs in the pathogensis of COPD is yet to be fully ascertained. Increased expression of iNos in AMs is found in patients with COPD [111-113]. Smoke exposure enhances the release of pro-inflammatory cytokines such as IL1β, IL6, IL8 and TNF$\alpha$ [114-118] in the lungs which are markers of M1 macrophage polarization. There is also contradictory transcriptome based evidence that M2 polarized alveolar macrophage may contribute to COPD pathogenesis [119]. Further, COPD exacerbation, characterized by severe shortness of breath, is a common occurrence, which is usually caused due to an infection or exposure to environmental pollutants. Impaired phagocytosis, a characteristic feature of M1 polarized macrophages is also considered to be an important cause for increased COPD severity [120]. Analysis of BAL fluid of COPD patients suggests that smoking cessation partly changes the macrophage polarization from a pro-inflammatory M1 towards an anti-inflammatory M2 macrophage phenotype [121]. M2 polarized alveolar macrophage have been shown to produce MMP12 which plays an important role in cigarette smoke induced emphysema

[122-124]. It could be considered that COPD pathogenesis is largely contributed by dysfunction of macrophages rather than a single subset of AMs.

## 12. Asthma

Asthma is characterized by airway inflammation and airway hyperresponsiveness (AHR). Macrophages also contribute significantly to the development of asthma [125]. The inflammatory process of asthma is dominated by Th2 inflammation, but there is also involvement of both types M1 and M2 macrophages [14]. The balance between different phenotypes of macrophages changes with the severity of asthma [126]. In case of acute exacerbation of chronic asthma, AMs are found to significantly enhance the expression of AAM markers along with pro-inflammatory cytokines (IFN$\gamma$ and TNF$\alpha$) and cell surface proteins. Ironically, the cell surface proteins associated with antigen presentation are M1 inducers [127, 128]. Elevated serum IFN$\gamma$ correlates with the severity of airway inflammation in atopic asthma, and IFN$\gamma$ has been linked to mechanisms inducing AHR [129]. It was demonstrated that IL33/ST2 plays a significant role in the amplification of AAM polarization and chemokine production which contribute to innate and Ag-induced airway inflammation [130].

The ability of AMs to phagocytose apoptotic cells is known as efferocytosis. Macrophage efferocytosis is impaired in non-eosinophilic asthma to a similar degree as in COPD [131]. In mice with less severe asthma, M1 macrophage numbers were higher and correlated negatively with M2 macrophage counts. Lower numbers of M2-like macrophages were found in mice exposed to house dust mites. The balance between macrophage phenotypes changes as the severity of allergic airway inflammation increases. Influencing this imbalanced relationship could be a novel approach to treat asthma [126]. CCL18 and YKL40 (chitinase 3-like 1) levels and CHIT1 (chitinase 1) activity are enhanced in allergic airway inflammation and thus may contribute to airway remodelling in asthma [132]. M2 macrophages play a role in eosinophil and potentially other leukocyte migration patterns into asthmatic airways [133]. Dysregulation of alveolar macrophage function results in dendritic cell-mediated mechanisms of allergic airway inflammation [134]. AMs can also contribute to the genetic susceptibility to allergic asthma [39].

## 13. Pulmonary fibrosis

Fibrosis is the result of persistent or dysregulated wound healing, usually in response to some type of repeated injury. It is often associated with chronic inflammation, alveolar epithelial hyperplasia and excessive deposition of ECM [135]. Lung macrophages and circulating monocytes play an important role during pulmonary fibrosis. AMs are involved in the removal of accumulated collagen. AAM play an important role in the development and resolution of lung fibrosis after injury, but their growth promoting activity raise the intriguing possibility that persistent M2 activity might contribute to the failure in resolving fibrosis in IPF patients.

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Sun and coworkers [136] reported that increased numbers of AAMs induced by over expression of IL10 results in induction of lung fibrosis in mice. Accordingly increased expression of CD206 (another marker of AAM) and IL4 is observed in patients with IPF and systemic sclerosis [137, 138]. Secretion of IL4 and IL13 by T cells is required for fibroblast migration and proliferation and their subsequent differentiation into myofibroblasts. IFN$\gamma$, in contrast, attenuates the fibrotic response and induces collagen degradation [139]. Paired immunoglobulin like receptor beta (PIRB) contributes to the pathogenesis of pulmonary fibrosis via the negative regulation of macrophage effector function and fibrogenic mediator expression. PIRB negatively regulates IL4-induced macrophage activation. Various studies have also demonstrated the role of AAM production in pulmonary fibrosis [140]. Relm$\alpha$, a hallmark M2 macrophage marker is upregulated in pulmonary fibrosis which is controlled by IL4/ IL13-and STAT6-dependent pathways [141].

The Th2 cytokines IL4 and IL13, like TGF$\beta$1, directly stimulate collagen synthesis in mouse and human fibroblasts [142]. They also promote the development of the classic myofibroblast phenotype in human lung fibroblasts [143]. Macrophages accumulate in areas of fibrotic injury but their role remains incompletely understood. A study using silica-induced model of lung fibrosis found that the IL4R$\alpha$-dependent differentiation of AAM is critical for the induction and maintenance of the $CD4^{+}$Th2 response required to trigger fibrosis [144]. Chitotriosidase, an enzyme especially expressed by M2 macrophages is also overexpressed in patients with IPF, especially in a progressing stage suggesting that this enzyme plays a role in the pathogenesis of diffuse lung disease-associated fibrosis [145, 146].

Polarization of macrophages to the M1 phenotype attenuates pulmonary fibrosis [65]. Fibrosis may be independent of monocyte and lung macrophage activity during the inflammation phase of bleomycin injury, a frequently used animal model for IPF. The depletion of lung macrophages during the inflammatory phase of bleomycin injury has no effect on the early as well as peak stage of lung fibrosis. However, during the progressive phase, lung macrophage depletion reduces the degree of pulmonary fibrosis. Depletion of lung macrophages during the resolution phase of bleomycin induced lung fibrosis slowed down the process [147]. Macrophages may promote resolution during the reversible phase of bleomycin induced pulmonary fibrosis [148]. Overexpression of MMP9 by AMs has the capability to attenuate the fibrosis induced by bleomycin [149]. ExMacs are recruited to the lung after noninfectious injury by bleomycin and are the major source of macrophages derived CXCL10 [46]. ExMacs are $CD11c^{+}$, $MHCII^{in}$ Gr-1 int and are separated from resident AMs by high expression of both CD11b and CX3CR1. Everson and colleagues [147] separated AMs into 18 density defined subpopulations. Bleomycin altered the proportions of these subpopulations and enhanced the production of TNF$\alpha$ production in these specific subpopulations. Bleomycin-treated *Pirb*$^{(-/-)}$ mice displayed an increased expression of collagen and IL4 associated profibrogenic markers Relm$\alpha$, MMP12, TIMP1, and osteopontin, which were localized to AMs. Thus, macrophages may have a role in resolution during the reversible phase of bleomycin induced pulmonary fibrosis [148].

## 14. Environmental exposure to particle inhalation

Epidemiologic and occupational studies show that exposure to high concentrations of ambient particulate matter cause cardiopulmonary health effects, including exacerbation of pre-existing lung disease as well as the development of respiratory infections. Particle related oxidative stress and inflammatory responses are considered to be key for the subsequent health effects, but the precise mechanism how inhaled poorly soluble, sterile, endotoxin free particle induce pulmonary inflammation is not well understood [150]. Since the size of the inhaled material determines their penetration depth into the lungs, smaller particle (<100nm) cause higher alveolar lung burden than bigger sized particles. Lung surface macrophages (i.e. AMs) do not efficiently phagocytose small, sub-100nm sized, so called ultrafine particles (UFP) or nanoparticles (NP), but take them up in a rather sporadic and unspecific way [151]. But the evidence that UFP bypass the most important clearance mechanism for particles deposited in the alveoli, namely phagocytic uptake by macrophages, requires further clarification as to whether these results are specific for the material, the size or other characteristics of the particles. A rethinking of clearance pathways for inhaled UFP is therefore considered necessary [151].

Inhalation of ultrafine carbon particles triggers a biphasic pro-inflammatory process in the lung, involving the activation of macrophages and the upregulation of immunomodulatory proteins [152]. Higher doses cause a distinct inflammatory response characterized by the release of pro-inflammatory cytokines and accumulation of inflammatory leukocytes [153]. A single exposure to these carbon particles however causes only a transient inflammatory response, which resolves within one week after treatment [154]. Black carbon laden AMs however are observed even at much later time points when no inflammatory stimulation in the lungs is detectable. Whether the immunological activity of these long-living tissue macrophages gets changed remains unknown. In animal experiments, when lung inflammation for example is induced by titanium di oxide (TiO2) particles in rats, AMs induce the production of IL-13 and IL-25 production. This in turn modulates the inflammatory response [155]. When exposed to gold NPs, it is found that AMs efficiently internalize NPs by endocytosis, and rearrangements of vesicles and of NPs within the vesicles of macrophages occurred [156]. The uptake of gold particles by AMs is limited, though to a low degree, systemic particle translocation is reported. To summarise, inhaled NPs or UFPs pose high burden to the integrity of lungs as these particles penetrate into the susceptible alveolar region due to the ineffective clearance mechanisms. Whether an activation of lung macrophages, potentially caused by particle-cell interactions, results in a change of their immunological properties thereby increasing the susceptibility for secondary infection warrants further investigations.

## 15. Conclusion

Macrophages are essential to host defense mechanism. The alveolar macrophages exhibit unique properties, including uncharacteristic phenotypic features, remarkable plasticity and

functionality. Various factors of the lung microenvironment define the polarization of macrophages. The temporal changes in the polarization of macrophages during chronic pulmonary diseases help in the regulation of tissue repair and remodeling. Thus understanding of the molecular mechanisms and microenvironment biology of macrophage polarization is a crucial step in evolving novel therapeutic strategies for treating chronic respiratory diseases.

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