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REVIEW

Mechanisms and Effects of Macrophage Polarization and Its Specifics in Pulmonary Environment

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Summary

Macrophages are a specific group of cells found in all body tissues. They have specific characteristics in each of the tissues that correspond to the functional needs of the specific environment. These cells are involved in a wide range of processes, both pro-inflammatory and anti-inflammatory ("wound healing"). This is due to their specific capacity for so-called polarization, a phenotypic change that is, moreover, partially reversible compared to other differentiated cells of the human body. This promises a wide range of possibilities for its influence and thus therapeutic use. In this article, we therefore review the mechanisms that cause polarization, the basic classification of polarized macrophages, their characteristic markers and the effects that accompany these phenotypic changes. Since the study of pulmonary (and among them mainly alveolar) macrophages is currently the focus of scientific interest of many researchers and these macrophages are found in very specific environments, given mainly by the extremely high partial pressure of oxygen compared to other locations, which specifically affects their behavior, we will focus our review on this group.

Key words

Macrophage • Polarization • Pulmonary tissue • Surfactant • Hypoxia

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Basic populations of macrophages

Macrophages were first described in 1883 by Metchnikoff and were characterized as a population of phagocytic cells involved in the development of inflammation [1]. All macrophages and tissue-specific cells derived from them, belong to the monocytic phagocytic system. It includes cells circulating in the blood that are able to infiltrate various tissues on demand and differentiate into different forms depending on the local presence of various stimulating factors. These cells are also described as so-called exudative macrophages and their source are bone marrow haematopoietic progenitors in adulthood [2]. The second group is represented by the so-called resident macrophages. These are long-lived cells settled in various tissues (e.g. Kupffer cells in the liver, microglia in the brain, Langerhans cells in the epidermis) and have the ability to self-renew [3-5]. In the lung, these cells are localized directly in the tissue of pulmonary system (interstitial (IM) and pleural macrophages) or in the bronchoalveolar space (classified as alveolar macrophages (AM)). [6,7]. The environment of AMs is quite different compared to that of tissue macrophages in other locations, characterized primarily by a significantly higher partial pressure of oxygen, which may be one of the reasons for their quite different functional properties. Therefore, we will focus on this population and use interstitial macrophages as a representative of tissue macrophages to highlight their specifics.

Origin of pulmonary macrophages

The colonization of tissues by these resident macrophages starts already during early embryonic

development from yolk sac progenitor cells, later from the liver and from bone marrow in the fetal period [8-10]. It seems that further colonization by this type of cells arising from bone marrow cells is possible also postnatally. [2,11,12]. In the case of AM, the increase is highest in the early postnatal period. [13]. During senescence, there is usually a decrease in their number and the number of macrophages is compensated by newly recruited cells [14,15].

In comparison with AM, IM arise mainly from blood and lung monocytes with a small portion of cells originating from the yolk sac (as demonstrated in mice) [16]. During life, they are slowly replaced by circulating monocytes [17,18]. The different origin of these macrophages may be the reason for their different representation in the lung tissue and their distinct characteristics, including their specific energy metabolism (see below). [19].

Unfortunately, most of the knowledge on the development of tissue colonization is based mainly on murine experiments [20-27] due to the limited ability to obtain experimental samples from humans. Nevertheless, we can assume that the processes leading to the establishment and behavior of resident macrophage populations are similar in animal and human models. In the fetal and postnatal periods, colonization of tissues, including the lung, and macrophage differentiation occurs primarily under the influence of granulocyte-macrophage colony-stimulating factor. (GM-CSF), macrophage colony-stimulating factor (M-CSF), transforming growth factor β (TGF-β), and peroxisome proliferator-activated receptor γ (PPARγ) [24, 26, 28, 29]. While M-CSF probably plays a greater role in tissues, the key substance in AM differentiation appears to be GM-CSF, secreted by type II alveolar pneumocytes, where its production is under control of miR133a and b [30]. This molecule subsequently influences PPARγ expression and, through it, a number of other functions including control of lipid metabolism. TGF-β is formed directly by AM and not only promotes further tissue colonization, but is implicated in the maintenance of homeostasis in the lung by promoting immune tolerance. The effect of M-CSF is mediated primarily via colony-stimulating factor receptor 1 and interleukin (Il)-34 [31-33], which, through transcription factors identical to those involved in the proliferation of pluripotent stem cells (*c-MYC*, Krüppel-like factors (KLF) 2 and 4) [5,34,35] directly affects the proliferation and therefore self-renewal of these cells. Since GM-CSF is more important for AM homeostasis compared to other macrophage populations, where the key role is played by CSF receptor 1, stimulation of CSF receptor 2 is more important in the self-renewal process of this population. From the above, it is likely that a possible cause of the decline of resident macrophages, including AM, during aging is again the change in the activity of the above-mentioned transcription factors [15].

Specifics of the macrophages populations in the lungs

As we mentioned above we center our interest especially on macrophages populations in lungs. In the lungs, we distinguish two basic types of macrophages: alveolar and tissue (if we omit the macrophages present in the pulmonary circulation). Tissue macrophages are found directly in lung tissue (IM) but are also part of the pleural membrane (pleural macrophages, which are mainly involved in controlling the development of inflammation and neutrophil recruitment in the following situations [36]). Each of these types is settled in a different area of the lung tissue, perform various functions and exhibit different specific features. Although we will mainly focus on the properties of AM, it is necessary to highlight their specifics to mention some basic characteristics of pulmonary tissue macrophages.

Interstitial macrophages

IM are a population that is less studied due to their more complicated acquisition by tissue digestion [37]. IM have a shorter lifespan compared to AM (observed in rhesus macaques) [38]**.** The IM pool recovers faster after the depletion of both populations, (describted in mice) [17]. This is probably supported by the recruitment of monocytes from circulation that preferentially differentiate into IM under the influence of M-CSF.

This population is characterized by the presence of high levels of CD11b [18,39,40]. Other features characterizing this group have also been described in human tissue: human leukocyte antigen – DR isotype (HLA-DR)+, CD36+ cells with lacking CD169 [17]. However, the IM population is not completely compact, comprising multiple subsets settled in various parts of pulmonary tissue. These subpopulations can also be characterized by specific features such as the presence of mannose receptor (CD206) or main histocompatibility complex II (MHCII). Cells with different combinations of

these features are then found in typical locations. For example, CD206–MHCII+ IM can be detected in vicinity of nerves, whereas CD206+, MHCII– cells can be found in a perivascular space [17]. They produce IL-10 under physiological conditions [41,42]. Thus, they are not only a second line of defence against foreign agents, but participate in immunoregulatory processes modulating T cell activity provided through this factor. In their native environment, they are unlike AM in contact with the extracellular matrix, which, according to observations of Laskin *et al.* [43], may also be affecting their basic settings. Last but not least a specific feature of IM is their energy metabolism, dependent on glycolysis, which differs from the metabolic pathways used mainly in the resting state in AM [44, 45].

Alveolar macrophages

As for AM, it is a very specific group of cells that exhibits a number of differences from other tissue-localized macrophages and is one of the best studied macrophage populations due to the relative ease with which they can be collected by bronchoalveolar lavage. Airway macrophages represent a distinct subgroup of AM. They occur in an environment with a similar partial pressure of oxygen as alveolar macrophages, but their environment lacks the presence of surfactant. Their main function is to balance the pro-inflammatory and anti-inflammatory immunological response to foreign substances entering the bronchial space of the lung, thereby preventing the acceleration of the development of pulmonary inflammation. Like other macrophage types, they regulate this activity through their phenotypic change - polarization. They are mainly involved in the regulation of inflammation in mucobstructive lung disease, where changes in their function are related to their epigenetic reprogramming [46]. This review article will focus mainly on the specificities of macrophages residing directly in the alveolar space. The specific characteristics of macrophages in the alveolar space are likely to result from the specific environment in which AMs are found compared to other tissue macrophages. Both direct factors related to the specificities of the alveolar space (e.g. high oxygen concentration, presence of pulmonary surfactant - see below) and changes in histone modifications (probably mediated through regulation of toll-like receptor (TLR) 4 [47]), i.e. the epigenetic environment that controls the expression of alveolar macrophage-specific genes, are at work here [13,48]. Epigenetic modification of macrophages has been demonstrated in AM patients with chronic obstructive pulmonary disease and asthma. Increased expression of inflammatory markers in these patients may be due to increased histone acetylation in the promoter regions of inflammatory genes and/or increased enzymatic activity of histone acetylation enzymes, leading to increased transcription of inflammatory genes [46]. Immediately after delivery, there is a large increase in the partial pressure of oxygen in the alveolar space and local macrophages are placed in conditions quite different from other tissue locations.

Adaptation of alveolar macrophages to increased oxygen concentration is associated with activity of Von Hippel-Lindau protein, which directly affects their maturation and function. Thus responses different from the behavior of other groups of macrophages, resulting from this special setting of AM, will be manifested especially in situations associated with a change in oxygen tension in the alveolar environment [49,50]. In a normal situation, AMs show a rather immunosuppressive, inflammation-suppressing phenotype (see below) [51]. However, under specific conditions, they are also capable of changing to a type that promotes inflammation.

Exposure to other foreign agents during life, including bacterial and viral particles, can trigger further recruitment of monocytes, which can differentiate into so-called recruited AM. These cells differentiate in response to the original stimulus that caused their recruitment, primarily into macrophages that promote inflammation (see below). Over time, however, these monocyte-derived alveolar macrophages may persist in the lung and/or replace the original resident AM [13].

AM are characterized by the presence of the markers CD11c, SiglecF and CD169 [18,39,40] and, as mentioned above, while the energy metabolism of IM is dependent on glycolysis, alveolar macrophages primarily use fatty acid oxidation [28,44]. This is especially true in the resting state, when the anti-inflammatory phenotype predominates. If they become part of the inflammatory response, their phenotypic change involves a change in their energy metabolism via glycolysis [52].

AM also interact with a number of other cells – e.g. epithelial cells - through their products. Through regulation of ion and fluid transport [51,53] and AM-derived fibronectin may act as a proliferative factor for airway epithelial cells [54]. Vesicles containing suppressor of cytokine signaling (SOCS) released from

AM can regulate epithelial reactivity to, for example, TLR ligands [55,56]. AMs also interact with various other cells, including vascular wall cells, immune cells or fibroblasts, and thus participate in processes in lung tissue related to changes in the activity of these cells (including response to the presence of pathogens, inflammatory responses induced by arbitrary stimuli, tissue remodeling, etc.) [8,57-61].

Macrophage plasticity – polarization

If macrophages are in a resting, non-polarized state, we talk about the so-called M0 type, which is characterized by the presence of only markers common to all types of macrophages (including monocytes) – CD11, CD68 and also HLA-DR [62-64]. However, their specific feature is the ability of phenotypic change. They are able to switch into the M1 ("classically-activated", "pro-inflammarory") or M2 ("alternatively activated", "anti-inflammatory", "wound healing") macrophages. This classification was introduced by Mills 2000 based on differences in arginine metabolism [65]. This classification was based on the fact that M1 macrophages express the enzyme nitric oxide synthase, which metabolizes arginine to nitric oxide and citrulline. According to this classification, M2 macrophages are characterized by the expression of the enzyme arginase, which hydrolyzes arginine to ornithine and urea [66]. In the following years, other subtypes of M2 macrophages have been recognized: M2a, M2b, M2c and M2d [67,68]. Polarization changes can be induced in vivo and *in vitro* by exposure to various stimuli, often released from T-cells. M1 polarization is mainly promoted by helper T-cells (specifically Th1 cells), M2 polarization is promoted by helper T-cells (Th2 for M2 and macrophages) and regulatory T-cells. The polarization is also reversible unlike other terminally differentiated body cells [69]. The type M2b is able to convert back to other M2 macrophage subtypes while inhibiting the polarization of other cells from M0 to M1 [70]. However it remains unclear whether newly recruited cells are also subject to this change.

General classification of polarized macrophages, their markers and typical products

This section, concerning the classification of macrophage polarization, was mainly based on [67, 71-73]. Each type can be characterized by the typical presence of surface markers, intracellular features (including increased activity of enzymes such as inducible nitric oxide synthase and cyclooxygenase (COX) 2) and secreted products (summarized in Table 1).

M1 macrophages

Polarization to M1 type typically occurs after stimulation with bacterial products (e.g. lipopoly-saccharide) or pro-inflammatory cytokines such as interferon γ or tumor necrosis factor (TNF) [74,75]). It is also supported by the GM-CSF [76], whose expression is under the influence of miR-133a and miR-133b in mice [30]. This polarization is mediated primarily via the interferon γ receptor and activation of signal transducer and activator of transcription protein (STAT) 1 or TLR4 causing increased production of pro-inflammatory cytokines via interferon regulatory factor (IRF) 5 and nuclear factor-kappa B (NFκB) signaling pathways [77,78]. These processes result in increased expression of surface receptors molecules CD80, CD86, CD16, CD32, CD64 [79-85], CD40, CD64, CD68, HLA-DR [86, 87] and MHCII molecules and in transcription of a set of genes coding expression of pro-inflammatory substances [67, 71, 88], including increased expression of TLR4, which is also part of several activation pathways and high levels of MHCII. This way polarized macrophages produce interleukins-1, 6, 12, 23, TNFα, high concentrations of reactive nitrogen and oxygen compounds [71,77,78], a number of other chemokines (CCL2, 3, 4, 5 [89]), and intracellular protein SOCS3, which suppresses the tendency to polarize to the M2 type. Macrophage polarization to the M1 type supports the activation of Th1 cells and further development of inflammation, which is mainly mediated by CD80 and 86 [90].

M2 macrophages

The group of M2 macrophages is more heterogeneous. This type of polarization is promoted by M-CSF [91], compared to M1 macrophages, for which the main growth factor is GM-CSF (as mentioned above). Its receptor may also be the target of other molecules such as miR-22, miR-34a, and miR-155, as demonstrated in mice, substances that can modulate its activity [92]. However, which growth factor is used is not entirely relevant to the differences in final gene expression

between these two main groups of polarized macrophages [76]. M2 polarization is also associated with increased expression of for example miR-146a, miR-511-3p, miR-223 and let-7c [93-95]. "Alternatively activated" macrophages are generally formed by the action of IL-4 and IL-13 [73] and produce high IL-10, low IL-12 and IL-23 and low levels of reactive oxygen species (ROS) [96]. M2 polarization triggered by its typical activators IL-4 and IL-13 results in both mice and humans to stimulation of transcription factors KLF4 and STAT6, which in turn leads to stimulation of PPARγ. The latter regulates aerobic fatty acid metabolism, one of the hallmarks of this cell type [97-100]. These cells are generally considered to be proliferation-promoting cells in the tissue (not only during diseases leading primarily to the development of pulmonary fibrosis, but also inappropriate fibrosis as a secondary complication of healing inflammation). This is promoted by their products (tissue inhibitors of metalloproteinases and fibronectin) as well as, the capability to switch into fibrocyte-like cells that express collagen [101-104]. Their pro-proliferative effects are probably also associated with the expression of arginase-1 (Arg1) and resistin-like-α (Fizz1) [105]. However, this group is subdivided into other subtypes, differing in their specific characteristics.

M2a macrophages

M2a arise under the influence of IL-4 and 13. They suppress the expression of genes for the production of pro-inflammatory mediators and molecules producing reactive oxygen and nitrogen compounds. These substances further regulate the activity and presence of beta2 integrins, MHCII molecules, metalloproteinase 1 and tissue-type plasminogen activator [106-109]. The presence of CD163, CD206 and 209 and CXCR 1 and 2 is typical for this group [110]. They produce IL-10, TGF-β and chemokines CCL 17, 22, 24. Intracellularly, high arginase activity [67] and increased expression of IRF4, PPARγ and STAT6 proteins can be detected, molecules having a part in signaling pathways supporting the increased expression of genes typical for M2 polarized macrophages [111]. Their activation further mediates the activation of Th2 cells [112].

M2b macrophages

M2b macrophages also affect Th2 activity and participate in immunomodulatory processes. Therefore, they arise primarily under the influence of immune complexes and Il-1 R or TLR agonists [113]. They express the surface markers as CD80 and CD86, typical of M1 macrophages. In the M2 macrophage group, however, its presence is characteristic of M2b macrophages, and also CD14. These molecules participate further in the activation of Th cells, and MHCII and Il-4R alpha [67,70,71,114,115]. They release high levels of IL-10, the production of which is the most massive among all M2 types in M2b macrophages [113,116], followed by IL-1 and 6 [117,118] and TNFα [119] and compared to other types of macrophages high levels of CCL1 [120].

Increased COX2 and IRF3 and 4 activity can be detected intracellularly, limiting polarization of cells to M1 type [111,121,122]. The increase in SOCS3, which is more typically found in M1 macrophages, leads here through STAT3 inhibition to modulation of the expression of the aforementioned Il-4Rs and consequently to a reduction in arginase activity, which according to the original classification should be typical for M2 cells, but is not present in this type [70].

M2c macrophages

M2c, involved not only in immunomodulatory processes, but especially in processes resulting in tissue remodeling associated with proliferation of both cellular components and extracellular matrix (including e.g. tumor growth), are again polarized under the influence of IL-10, but also TGF-β or glucocorticoids [123]. TGF-β induces M2c polarization via SNAIL (transcription factor)-mediated suppression of the switch to a pro-inflammatory phenotype [124]. Since the source of both IL-10 and TGF-β may be M2c macrophages themselves, this may potentiate the polarization of macrophages present on M2c and significantly promote proliferative activity in the tissue. This stimulation results in, among other things, an increase in arginase activity. Although this property should be typical of M2 macrophages in general, not only does it not appear in M2b type, but as mentioned above, an increase in arginase activity was not observed even when polarization to M2c type was induced by another possible stimulator, glucocorticoids [125]. However, they share a number of common features with other M2-type macrophages. They show the presence of CD163 and 206, TLR1, IL-4R. The presence of CCL2 receptor is specific to them. They other important products include

versican and alpha-antitrypsin are probably involved in extracellular matrix remodeling [67]. Regarding intracellular features, they again show similar representation as the other M2 types: high IRF4 and SOCS3 positivity.

M2d macrophages

M2d macrophages are mainly found in the environment of tumours. Their polarization occurs under the influence of stimulation by TLR1, IL-6 and adenosine and/or tumor-associated factors and they express high levets of CD14 and CD163 [126,127]. In contrast, they do not express to a large extent the features that are generally considered typical of M2 polarization - M2d macrophages do not express Fizz1, CD206, chitinase 3-like 3 (Ym1) and the adenosine-dependent angiogenic switch of macrophages to an M2-like phenotype is independent of interleukin-4 receptor α signaling [127].

M2d macrophages secrete low levels of IL-12, and high levels of IL-10. Another important product characteristic of this type of macrophage is vascular endothelial growth factor. This substance is involved in the promotion of angiogenesis, a process that accompanies tumour growth, in which this type of macrophage plays an important role. [127, 128].

Both groups of lung macrophages are capable of polarization into the above-mentioned types, and therefore alveolar and interstitial macrophages may share some common features (e.g. CD206, CD169 – see [17,45]).

Table 1. Basic activators, markers and products characterizing macrophage subtypes in general.

Type		Stimulator	Marker	Product
M1		GM-CSF INF γ, TNF	CD80, CD86, CD16, CD32, CD40, CD64, CD68, HLA-DR+, MHCII+	IL-1, 6, 12, 23, TNFα, ROS, NOS
M2	*M2a*	IL-4, 13	CD163, CD206, CD209, CXCR 1, CXCR2, Arg-1	IL-10, TGF-β CCL 17, 22, 24
	M2b	immune complexes, IL-1 R or TLR agonists	CD14, CD80, CD86	IL-1, 6, 10, TNFα, CCL1
	M2c	IL-10,TGF-β, glucocorticoids	CCL2, CD163, 206, TLR1, IL-4R, Arg-1	IL-10, TGF-β
	M2d	TLR1 agonists, IL-6, adenosine	CD14, CD163, VEGF	IL-10, VEGF

Epigenetic regulations involved in macrophage polarization

However, polarization to the M1/M2 type leads not only to the expression of genes mediated by the aforementioned mediators (e.g. IL-4) along with the direct activation or inhibition of their signaling pathways, but also by epigenetic regulation of the expression of genes involved in the production of their specific markers. Changing the activity of factors of these signaling pathways is able to affect the expression of demethylases, which ultimately leads to a change in histone methylation and, therefore, in the transcriptional activity of M2 marker genes [129]. An second area that has been extensively studied recently is epigenetic modification of RNA itself. In the context of macrophage polarization, attention has focused mainly on N6-methyladenosine methylation, as one of the most prevalent post-transcriptional mRNA modifications. This is evidenced by the rapid increase in the number of recent works focusing on this topic [130,131]. However, one of the most studied and described epigenetic regulations involved in macrophage polarization is the role of miRNAs.miRNAs are mainly involved in the control of transcription factor activity, resulting in differential expression of macrophage markers and their cytokine production. These molecules play a role as potent regulators of the inflammatory response [132], their other forms, in turn, participate in its suppression and M2 polarization [133]. For example, the proinflammatory

state associated with the M1 polarization is characterized by an increase in expression of miR-155 and miR-125b. In addition, miR-155 is able to repolarize M2 back to M1-type. Contrary miRNAs such as miR-16, miR-124, miR-133a/b or miR-142-3p are able to attenuate polarization towards M1 type. The other group of miRNAs, e.g. miR-146a and miR-511 promotes M2 [134, 135]. The principle of their action is the down-regulation of genes involved in pro-inflammatory pathways. The amount and activity of transcription factors, especially NfκB, AP-1, hypoxia inducible factor (HIF)-1α or STAT, play a key role in modulating the pro- and anti-inflammatory state and thus macrophage polarization. These factors are themselves under the control of a number of miRNAs, but they also influence the expression of other miRNAs, which are then directly involved in changes in the expression of the final products (surface markers, cytokines, etc.) For an overview of these signaling pathways, see [136]**.** At the same time, it must be acknowledged that there is no sharp boundary between macrophage membership in M1 or M2 type according to the detection of the above-mentioned features, because under in vivo conditions, genes constituting both M1 and M2 type markers can be expressed simultaneously [137].

Specifics of AM polarization

AMs are in constant contact with the external environment and therefore represent the first line of defense of the respiratory system. Their second most important function is to ensure surfactant homeostasis. One of their specific functions is to catabolize lung surfactant [138]. On the other hand surfactant regulates their immunomodulatory activity - the binding of surfactant proteins A and D to AM surface receptors is able to inhibit macrophage activation and phagocytosis [49,139-142]. The modulation of AM activity can be also mediated by the binding of free fatty acids of surfactant to PPARγ receptors of AM [143, 144]**.** It results in the blunting of the respiratory burst in these cells [145,146]. This occurs in cooperation with dendritic and T-cells, whose activity they are able to regulate e.g. *via* TGF-β release [147-149]. These functions are mainly provided by the resident macrophages population. Conversely, recruited monocytes tend to express number of proinflammatory and profibrotic genes [150]. Their ratio depends on the primary cause of recruitment, in the case of acute inflammation the polarization of these cells is predominantly M1, in later stages rather M2 type. They may upregulate MHCII, making them capable of activating effector T-cells through antigen presentation [151,152], thus participating to a greater extent in the organism's defence responses.

In summary, the balance between AM polarization to M1 and different M2 cell subtypes is crucial for lung tissue homeostasis. An inappropriate pro-inflammatory response of AM, as well as an inappropriate activation of wound healing processes that potentially result in lung fibrosis, can lead to consequences that are difficult to reverse. In addition, the appropriate timing of onset is important in these processes. Of note here is the importance of AM in one of the most serious disorders of the respiratory system, the adult respiratory distress syndrome (ARDS), which accompanies many infectious and non-infectious lung diseases. The role of macrophages in the development of this syndrome is summarized in [153]. Briefly, in the first phase, there is primarily an overall massive increase in the number of M1 AM. On the one hand, there is a phenotypic change in resident AMs, which release factors that promote the recruitment of circulating cells. These newly recruited cells are also transformed into M1 AM and participate in the removal of pathogens and inflammatory debris. Although this pro-inflammatory function of AM is absolutely necessary to eliminate the primary cause, its inadequate level can unfortunately result in severe lung tissue damage with fatal consequences already at this early stage of the disease. The second phase of the disease is characterized by a change in AM from M1 to M2, which probably occurs mainly under the influence of regulatory T cells and a subset of CD4+ lymphocytes, [154,155], leading to a change in AM polarization through activation of the pathways mentioned above. However, this excessive “wound healing” reaction of AM may result in the development of pulmonary fibrosis characterized by collagen deposition mediated by TGF-β and Arg-1 pathways in the late stages of the disease [156,157]. This syndrome, like many other pulmonary and extrapulmonary diseases, especially those accompanied by pulmonary edema, is also associated with hypoxia. The latter is itself is also capable of altering the functional state of AM and promotes polarization to M2 type [49,105]. Which subtypes are induced by hypoxia has not yet been determined, although it can be assumed that polarization to M2c or M2a type is likely, given that macrophages exposed to hypoxia show higher

expression of surface marker CD206 or Arg-1 [49,58]. Hypoxia-induced polarization to the M2 type likely promotes proliferation of pulmonary artery smooth muscle cells, thereby promoting the development of hypoxia-induced pulmonary hypertension. This mechanism is supported by our observations, where we observed a massive increase in M2 AMs during hypoxia exposure, the elimination of which subsequently reduced the development of this pulmonary vascular disease [49,58].

Redox state and role of ROS

Macrophage polarization seems to be related to a change in the redox state of AM. However, the role of redox balance as a key factor determining macrophage polarization during hypoxia remains controversial. It is known that hypoxia is associated with an increase in tissue ROS generation [158] and that hypoxia promotes polarization to M2. However, this polarization is (as mentioned above) in macrophages associated inversely with a decrease in their ROS production. The decrease in ROS production in this type of macrophage is associated with inhibition of NADPH oxidase-2 activity [159]. However, the initial stages of hypoxia are in contrast associated with an increase in ROS production by this molecule [160]. This is also consistent with our experimental results where early exposure to hypoxia resulted in increased ROS production from AM. It seems that their production is reduced only in later stages, when M2 cells starts to predominate (our preliminary, unpublished data are consistent with this). However, the redox state and thus the polarization of macrophages may also be influenced by ROS from other sources - mainly from mitochondria. Here, the electron transport chain (ETC) and the monoamine oxidase system (MAO) [161] are the main players. MAO increases its activity mainly under the influence of pro-inflammatory stimulators and is thus more involved in polarization to M1 [162-164]. As Wiese *et al.* demonstrated, ETCs also exert significant effects during hypoxia via alteration of ROS release. Thus, ETC activity may be significantly involved in changes in macrophage activity and thus macrophage polarization [165]. However, not only ROS sources and their levels, but also their further processing by the cell play an important role in ROS signaling and subsequent polarization. The activity of Cu,Zn-superoxide dismutase (Cu,Zn-SOD) seems to be the key element here. Regardless of which source is behind the increased superoxide charge, an excessive increase in Cu,Zn-SOD activity leads to an increase in H_2O_2 production, which promotes M2 polarization via activation of STAT6 [166].

Role of HIF

The next key factor influencing the change in polarization under hypoxic conditions is probably the increased concentration of HIF. Under normal circumstances, one of its subunits is destabilized by post-translational hydroxylation by prolyl-hydroxylase [167]. In conditions of hypoxia (for review see [168], degradation is reduced. This can be caused by a reduced activity of the enzyme, an increase in the "oxidation" of this molecule due to the increased presence of ROS, a phenomenon typical of tissue hypoxia. The subunit undergoing this degradation can be represented in two different forms (HIF-1α or HIF-2α). Unfortunately, only a minority of papers distinguish between the influence of these different subunits on macrophage function, moreover in association with hypoxia (for review see [169]**)**. When these mechanisms are described in detail, they are mostly related to tumor growth (accompanied by tumor tissue hypoxia) and the function of tumor-associated macrophages. In the lung, HIF-2 appears to be a critical factor underlying the development of changes associated with exposure to hypoxia. Their source, determining the amount of HIF-2α in the result, can be not only macrophages themselves, but also other cells of the surrounding tissue. This substance has been shown to affect monocyte recruitment and vascular cell proliferation in the early stages and the overall development of hypoxic pulmonary hypertension in the later stages [170]. However, the extent to which these effects are mediated by the influence of this HIF-2α on the function of lung macrophages or other cells present in lung tissue remains unclear. If we focus on the effect of HIF-2α in macrophages, it seems to support the polarization of macrophages to the M2 type via activation of STAT3 pathway [171]. Another accompanying phenomenon of tissue hypoxia is an increased amount of lactate. It has been proven that this substance also increases the expression of HIF-2α, which results in an increase in the expression of features typical for polarization to the M2 type [172]. A second form of this molecule, HIF-1α, also affects the polarization state of alveolar macrophages. Changes in its activation (together with changes in the activation of the transcription factor STAT3) occur e.g. under the influence of IL-6 released

from fibroblasts during the development of many inflammatory lung diseases. As a result, AM shifts to the M1 pattern [173]. Moreover, as Woods *et al.* demonstrated HIF-1α provides also the metabolic reprograming of AM [174]. Whereas M1 macrophages express high levels of glycolytic enzymes, M2 macrophages oxidative phosphorylation [175].

Hypoxia undoubtedly induces also epigenetic changes in AM. Hypoxia induces changes in microRNA expression in AM, which varies depending on the specific location of the lung [176]. However, their effects have not yet been sufficiently studied. Therefore, we will not go into detail in this review.

Effects o hyperoxia

Not only hypoxia but also hyperoxia significantly affects AM function. Since administration of high oxygen is one of the most common therapeutic interventions in critical care in both adults and children, including neonates, attention should be paid to the changes induced by this mechanism.

Exposure to high concentrations of O2 (up to 95 %) induces a change in the production of a number of cytokines in AM (e.g. decrease of TNFα, IL-1 beta, IL-6, increase of IL-8). Moreover, this phenomenon was observed both in samples collected from patients and by induction under *in vitro* conditions. However, these changes in cytokine production are not the same during the entire period of hyperoxia. While the changes described above occur within a few days, early phases of exposure, on the order of hours, can have quite the opposite effect [177]. These are accompanied by changes in the expression of markers determining the AM phenotype. Exposure to several days of hyperoxia promotes an increase in the proportion of CD206-positive cells (a marker representing polarization to the M2 phenotype) in the bronchoalveolar lavage [178] as well as an increase in the number of CD68, CD44, CD11c and CD205-positive cells [179]. Hyperoxia does not only affect the state of resident AMs, but also promotes the influx of newly recruited cells into the bronchoalveolar space [178].

In addition, hyperoxia higher than 40 % oxygen in the early postnatal phase also limits the colonization of the alveolar space by macrophages. The lower number of AMs is a direct consequence of their reduced proliferation in a given space; the question remains whether a higher oxygen percentage also results in an immediate limitation of their recruitment [180]. However, hypoxia or hyperoxia may not only affect macrophage polarity per se, but also through changes in the composition of the tissue environment that accompany it. AM are normally found in the presence of surfactant which significantly affects their activity as mentioned above.

Surfactant proteins A and D are known to bind to signal regulator protein alpha on the surface of macrophages and thereby inhibit macrophage activation and phagocytosis. Given that the composition of surfactant is modified by hypoxic exposure [181], AM-surfactant interaction may play a central role in disease pathophysiology is in the setting of not only ARDS but other lung diseases associated with hypoxia [182]. This is where M2 polarization provides not only positive effects, but may result in significant adverse development of tissue fibrosis [183,184].

The potential possibility of reprogramming the macrophage phenotype thus seems to be a very interesting possibility in the future to influence the rate of various, not only pulmonary, but also other inflammatory, immunomodulatory and fibrotic processes. Basically, this involves inducing or inhibiting M1 and M2 polarization or affecting the recruitment of circulating cells. A number of agents that may affect macrophage polarization are currently being studied. However, most studies have focused on the effect of macrophage polarization mainly on tumor growth [185]. Whether these strategies could be used to influence the function of lung macrophages remains unclear, given the aforementioned specificities of this cell population. Surface structures, whose stimulators and inhibitors have already been used for other purposes, subunits of intracellular pathways and directly miRNAs are offered as general potential targets [134,186]. Therefore, further research into the principles of these cell functions and the possibility of influencing them certainly deserves attention and has the potential for broad clinical application in the treatment of a wide range of lung diseases.

Conflict of Interest

There is no conflict of interest.

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Abbreviations

AM, alveolar macrophage; Arg1, arginase-1; C-MYC, transcription factor; CCL1, small inducible cytokine A1; CCL2, chemokine (C-C motif) ligand 2, also referred to as monocyte chemoattractant protein 1; CCL3, chemokine (C-C motif) ligand 3, macrophage inflammatory protein-1α; CCL4, macrophage inflammatory protein (MIP-1β); CCL5, chemokine (C-C motif) ligand 5; CD, cluster of differentiation; COX, cyclooxygenase; CXCR, C-X-C motif chemokine receptors; ETC, the electron transport chain; Fizz1, found in inflammatory zone 1; GM-CSF, granulocyte macrophage colony stimulation factor; HIF, hypoxia inducible factor; HLA-DR, human leukocyte antigen – DR isotype; IL – interleukin; IM, interstitial macrophage; INF, interferon; IRF, interferon regulatory factor; KLF, Krüppel-like factor; M-CSF, macrophage colony stimulation factor; MAO, monoamine oxidase system; MHC – main histocompatibility system; miRNA (miR), microRNA; NFκB, nuclear factor-kappa B; NOS, nitric oxygen species; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription protein family; TGF-β, tumor growth factor β; Th, helper T-cells; TLR, toll-like receptor; TNF, tumor necrosis factor; Ym1, Chitinase 3-like 3.

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