

## Macrophages in bacterial lung diseases: phenotype and functions (review)

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### ABSTRACT

This literature review is devoted to the analysis of the role of macrophages in the immunopathogenesis of infectious lung diseases of bacterial etiology. The article summarizes information about the origin of macrophages, their phenotypic and functional heterogeneity. The mechanisms of impaired protective function of innate immunity are associated with the polarization of the program of maturation and activation of macrophages in the direction to tolerogenic or immunoregulatory cells with phenotype of M2. Alveolar macrophages perform a variety of functions (from pro-inflammatory to regenerative) in the development of inflammation in the respiratory organs. Their inherent plasticity suggests that the same macrophages can change their phenotype and function depending on the microenvironment in the inflammatory focus at different stages of the disease. Understanding the mechanisms that regulate macrophage plasticity will be an important step towards realizing the potential of personalized immunomodulatory therapy.

**Key words:** macrophages, monocytes, alveolar macrophages, lung diseases, innate immunity, immune response.

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## Макрофаги при бактериальных болезнях легких: фенотип и функции (обзор)

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### РЕЗЮМЕ

Обзор литературы посвящен анализу роли макрофагов в иммунопатогенезе инфекционных заболеваний легких бактериальной этиологии. В статье обобщены сведения о происхождении макрофагов, их фенотипической и функциональной гетерогенности. Механизмы нарушений защитной функции врожденного иммунитета связаны с поляризацией программы созревания и активации макрофагов в направлении толерогенных или иммунорегуляторных клеток с фенотипом M2. Альвеолярные макрофаги выполняют разнообразные функции (от провоспалительной до регенераторной) при развитии воспаления в органах дыхания. Присущая им пластичность свидетельствует, что одни и те же макрофаги могут изменять свой фенотип и функции в зависимости от микроокружения в очаге воспаления на разных стадиях заболевания. Понимание механизмов, которые регулируют пластичность макрофагов, станет важным шагом на пути реализации потенциала персонифицированной иммуномодулирующей терапии.

**Ключевые слова:** макрофаги, моноциты, альвеолярные макрофаги, заболевания легких, врожденный иммунитет, иммунный ответ.

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## INTRODUCTION

The 2011 Nobel Prize in the Physiology and Medicine nomination presented the opportunity for the creation of new ideas about the mechanisms of innate immunity activation, the role of dendritic cells and macrophages in the formation of immunological tolerance, and their regulatory influence on the

adaptive immune response. The origin and functions of macrophages and dendritic cells (DC) are very similar. However, a distinctive feature of DC is their unique function of the primary presentation of antigens to T-cells and participation in the formation of immunological tolerance. A macrophage is a key antigen presenting cell of innate immunity, which,

with classical activation, supports the course of an acute and chronic inflammatory T-cell immune response, while simultaneously performing an effector function (M1-macrophages). However, in the case of alternative activation and acquisition by the macrophage of a tolerogenic phenotype (M2, or M2-like macrophages), their functional rearrangement occurs. While blocking the transfer of the activation signal inside the T-cells, they begin to perform the immunosuppressive function, promote fibrogenesis, proliferative processes and tissue regeneration [1, 2].

The system of mucosal immunity of the respiratory tract is morphologically represented by bronchoalveolar lymphoid tissue (BALT), the structural elements of which are alveolar macrophages (AM), DC, lymphocytes, gamma-delta-T cells, lymphoid cells of the innate immunity (ILC), antimicrobial peptides, and extracellular matrix proteins. It is obvious that AM play a key role in the successful implementation of the mechanisms of mucosal immunity in the penetration of pathogen-associated molecular patterns (PAMP) and high-molecular compounds (antigens) into the mucous membranes of the respiratory tract. Macrophages are phenotypically and functionally a highly heterogeneous cell population. The formation of the macrophage phenotype, on the one hand, can be initially predetermined at the stage of monocyte differentiation in the bone marrow or directly in the blood under the influence of a complex of humoral factors released into the systemic circulation. On the other hand, monocytes differentiate into macrophages and DC at the inflammatory focus, which is the "true" territory of the immune response depending on the nature of the antigen, local cytokine and cellular microenvironment. With the development of the immune response, the plasticity of macrophages provides the possibility of their further conversion and functional reprogramming under the influence of a wide range of molecular cell factors. This review summarizes current knowledge of the types, origins, and functions of macrophages and their role in the pathogenesis of various pulmonary diseases of bacterial etiology.

## REVISITING THE ORIGIN AND FUNCTIONS OF MACROPHAGES

Macrophages mature from monocytes, which are initially formed from CD34 + myeloid progenitor cells in the bone marrow, circulate in the blood and penetrate into peripheral tissues [3]. In circulating blood, monocytes constitute up to 10%

of the total number of leukocytes. Just as is the case with macrophages, they differ from each other phenotypically and functionally. C. Tsou et al. (2007) showed that blood monocytes in mice are formed in the bone marrow from macrophage progenitor cells or DC (macrophage dendritic precursors, MDP). At the same time, the chemokine receptor CCR2 and the macrophage protein chemoattractant 3 (macrophage chemotactic protein, MCP-3) contribute to the mobilization of monocytes from the bone marrow [4]. The macrophages formed from monocytes differ depending on the degree of maturity, the area of localization, as well as their activation by antigens or lymphocytes. Macrophages are divided into fixed and free (motile). Motile, or wandering, macrophages include connective tissue macrophages, called histiocytes. There are macrophages of serous cavities (peritoneal and pleural), AM, liver macrophages (Kupffer cells), central nervous system macrophages (glial macrophages), osteoclasts. All these forms of macrophages are combined into a system of mononuclear phagocytes, whose cells are characterized by a variety of responses to changing conditions of the microenvironment [5].

The well-known fact that circulating monocytes are the central source of replenishment of the tissue macrophage pool has recently been questioned. In 2012, *Science* published an article by Christian Schulz and his research group. The authors investigated the origin of macrophages and found that some macrophages develop in the embryo before the appearance of the first hematopoietic stem cells (HSC) of myeloid origin. It has been shown that the transcription factor Myb, necessary for the development of HSCs, all monocytes and macrophages with the CD11b<sup>high</sup> phenotype, is not required for the development of the yolk sac macrophages and their descendants - embryonic macrophages of a number of organs and tissues from which Kupffer cells are formed in the liver, AM, Langerhans' epidermal cells, and microglial cells that can persist in adult mice regardless of HSC. These results indicate the presence of a line of tissue macrophages that originate from the yolk sac in embryogenesis and are genetically different from the descendants of HSC [6].

The structural feature of macrophages is a pronounced lysosomal apparatus, represented by a large number of lysosomes and phagosomes located in the cytoplasm. A feature of histiocytes is the presence on their surface of numerous folds, invaginations and pseudopodia, necessary for cell migration and phagocytosis [7].

Macrophages derived from monocytes in peripheral tissues are in an inactive state, which is characterized by low oxygen consumption, low rate of protein synthesis and moderate cytokine production. However, resident macrophages can quickly respond to environmental stimuli by significantly changing the pattern of gene expression [8]. Activation of macrophages, for example, with tissue damage and the development of inflammation, is accompanied by the secretion of cytokines, chemokines and other inflammatory mediators, which, in turn, contribute to the involvement of new macrophages to implement the effector phase of the immune response [9].

As mentioned above, two types of activated macrophages are distinguished: M1 (pro-inflammatory phenotype) and M2 (immunomodulatory and tissue remodeling phenotype). This designation is similar to the classification of activated T-lymphocytes for T-helper cells of the 1st (Th1) and 2nd (Th2) types and to some extent emphasizes the connection of the macrophages of a particular phenotype with the implementation of the corresponding type of adaptive immune response [10]. In 2014, P.J. Murray et al. proposed a nomenclature of macrophages and presented guidelines for their cultivation and reproduction of the differentiation of M1 and M2 subpopulations in vitro in the laboratory [11]. However, the classification of macrophages needs to be further revised.

## PHENOTYPIC AND FUNCTIONAL HETEROGENEITY OF MONOCYTES AND MACROPHAGES

It is known that peripheral blood monocytes are functionally heterogeneous and have different effector potentials. Among monocytes, there are 'classic' CD14 ++ CD16- cells intended for phagocytosis, 'intermediate' monocytes CD14 ++ CD16 +, which perform immunoregulatory function and interaction with T-lymphocytes, and 'non-classic' cells CD14 + CD16 ++, which have a high affinity for endothelium and called 'patrolling' [12]. The first subpopulation of monocytes actively secretes interleukin (IL) 6, IL-8, IL-10; the second secretes IL-8 and slightly less IL-1 $\beta$ , IL-6; the latter predominantly secretes IL-1 $\beta$ , IL-8, tumor necrosis factor (TNF)  $\alpha$ , and to a lesser extent IL-6. In tissues, monocytes are transformed into macrophages. At the same time, it is not known exactly how the subsets of monocytes and macrophages relate to each other. It is assumed that, due to classical monocytes, the pool of resident macrophages is replenished; intermediate cells differentiate into DC

myeloid lineage, and nonclassical monocytes into proinflammatory macrophages [13].

'Classical' activation of macrophages, leading to polarization of their maturation in the direction of M1 cells, is induced by interferon (IFN)  $\gamma$ , produced by activated CD4 + lymphocytes and natural killers (NK), as well as other proinflammatory mediators, such as TNF $\alpha$  and bacterial lipopolysaccharide (LPS) [14]. As a rule, M1 macrophages are characterized by pronounced cytotoxic and antimicrobial activity, mediated production of reactive oxygen species, nitrogen and proinflammatory cytokines (IL-1 $\beta$ , IL-6, IL-12, IL-23, TNF $\alpha$ ), characterized by low secretion of IL-10. Macrophages of the first type induce the Th1 response and provide protection against intracellular pathogens and tumor cells [15]. The main differentiation factors and humoral products of regulatory M2-macrophages are CCL18, IL-4, IL-10 and transforming growth factor (TGF)  $\beta$ . CCL18 is a protein belonging to the family of CC chemokines. CCL18 was originally known as AMAC-1 (alternative macrophage activation-associated CC chemokine-1). CCL18 is produced by macrophages and DC innate immunity, promotes the differentiation of monocytes into M2 macrophages, and is also their specific marker and secretory product [16–19]. The secretion of M2-macrophages TGF $\beta$  determines their participation in fibrogenesis and chronic proliferative inflammation. Various forms of macrophages with the M2 phenotype are characterized by low production of IL-12 and IL-23, expressing a large number of phagocytic mannose and galactose receptors [20–22].

If the classic phenotype of activated M1 macrophages is well described in the literature, the data on cells with the M2 phenotype are rather contradictory. Often, alternatively activated M2 macrophages are divided into three subpopulations: M2a, M2b and M2c [23].

Macrophages with the phenotype M2a are differentiated by the action of IL-4 or IL-13. They are involved in the activation of the reactions of the Th2-dependent immune response. M2a cells have been shown to play a major role in the anthelmintic immune response, connective tissue proliferation and wound healing when damaged by helminths, and also contribute to attracting eosinophils to the lesion parasites (possibly due to the release of leukotriene B4) [24]. The M2b phenotype is formed in case of immune complexes in combination with IL-1 $\beta$  or LPS, while the polarization of macrophages is associated with the activation of toll-like receptors (TLR) and the IL-1 receptor (IL-1R). Macrophages

with the M2b phenotype are involved in the regulation (suppression) of immuno-inflammatory processes and contribute to the activation of Th2-dependent reactions. The formation of cells with the M2c phenotype occurs under the influence of IL-10, TGF $\beta$ , or glucocorticoids. Macrophages such as M2c activate the synthesis of the extracellular matrix and are involved in tissue remodeling. Macrophages with M2a and M2b phenotypes usually show anti-inflammatory activity. Macrophages of the M2c type are very similar to M1-macrophages, except that IL-10 is secreted instead of pro-inflammatory cytokines [20, 24].

The functional phenotype of monocytes and macrophages is flexible and is determined by the expression of surface receptors and the profile of cytokines produced (expression of cytokine genes, cytokine content inside the cell and the level of their secretion into the extracellular environment), activation of nuclear transcriptional factors of signaling pathways, the nature of the antigen, its immunogenicity, and local cytokine status of the microenvironment of cells [2, 25, 26]. Receptors are functionally key for the membrane molecules of monocytes / macrophages. These include TLRs designed to recognize PAMP and lectin receptors, in particular the mannose receptor (CD206), which is characteristic of M2-macrophages and is poorly expressed on monocytes. Both on monocytes and macrophages (mainly M1) there are DC-SIGN lectin receptors (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) - CD209 and lectin-1. The functionally important group of surface molecules of monocytes / macrophages is constituted by the molecules of the major histocompatibility complex (MHC) and co-stimulation. Expression of MHC type II molecules is enhanced when cells are activated, and when CD80 and CD86 molecules, which are considered markers of M1 macrophages, act as costimulatory molecules. CD86 appears on the cell surface only after activation, and CD80 is expressed constitutively, but when it receives the activation signal, its expression increases [20, 27, 28].

Of greatest interest are scavenger receptors ('scavengers'), which, in particular, include the MSR (macrophage scavenger receptor) molecule, CD36, which has affinity for collagen, the mannose receptor CD206, stabilin-1 (mediates the processes of absorption of phagocytosed objects and their transport endosomal-lysosomal system), SR-A (CD204), SR-MARCO (expressed mainly on resident macrophages), common membrane

marker M1 and M2 macrophages CD68, and others [29–34].

Interestingly, M1 and M2 macrophages differ in the profile of chemokines expressed. Classical activation of macrophages LPS leads to the expression of genes of proinflammatory chemokines (CXCL8, CXCL9, CCL2, and CCL3). With alternative activation, IL-4 and IL-13 selectively induce the synthesis of CCL17, CCL22 and CCL24, and IL-10 – CCL16 and CCL18 [3]. S. Gordon (2003) showed that the functional activity of M1 cells is mediated through the production of chemokines, which are chemoattractants for Th1 lymphocytes (for example, CXCL9 or CXCL10), while M2 macrophages secrete CCL18 and CCL22, which are chemokines that exhibit chemotactic properties for Th2 lymphocytes and regulatory T cells [10]. The functional phenotype of macrophages determines not only the range of chemokines produced by them, but also the expression of chemokine receptors on cells. Thus, the expression of CCR7 prevails on M1-macrophages. IL-4 activated M2 macrophages are characterized by high expression of CXCR1 and CXCR2, while M2 cells activated by IL-10 carry CCR2 and CCR5 on their surface [3, 35].

Thus, macrophages of various subpopulations have multidirectional effects. On the one hand, they are involved in the processes associated with the destruction of tissues in the inflammatory focus when performing an effector function. On the other hand, when performing a regenerative function, they are involved in the healing processes.

## MACROPHAGES OF THE LUNGS AND THEIR PROTECTIVE FUNCTION

The system of macrophages in the lungs consists of several subpopulations that are located in different anatomical parts of the lungs, including the respiratory tract, alveolar spaces, and resident lung tissue. Alveolar macrophages constitute more than 90% of the population of pulmonary macrophages. Traditionally, their source is the bone marrow precursor cells. AMs have a peculiar phenotype. They exhibit a low level of phagocytic receptor CD11b expression and a high level of expression of CD11c integrin and SiglecF lectin, which allows distinguishing them among other myeloid cells of the lung tissue. M. Williams et al. (2013) found on the mouse model that AM is formed from fetal blood monocytes under the influence of the colony-stimulating factor granulocytes and macrophages (GM-CSF), but in the period of postnatal development, the maintenance of the AM population

largely depends on their ability to self-renewal [36]. Therefore, in general, the population of macrophages of the lungs is mainly supported by the self-renewal of pulmonary AM by local proliferation. Such proliferation is homeostatic and is activated in all cases of deficiency of immunocompetent cells. The local proliferation of AM in homeostatic depletion of their reserve depends on both GM-CSF and M-CSF (colony-stimulating factor of macrophages), but does not depend on signals generated by IL-4 [37]. Thus, GM-CSF and M-CSF simultaneously control proliferation and further AM survival. Along with this, the differentiation of AM and their main functions, including phagocytosis and catabolism of surfactants, are controlled mainly by GM-CSF [38].

AM express three classes of receptors for an Fc fragment of IgG class antibodies: FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) [39]. The first two of these receptors also express blood monocytes; the third is a feature of AM. Between monocytes and AM there is a difference in the expression of receptors for proteins of the complement system (CR). Thus, the expression of CR4 on AM is enhanced with a reduced expression of CR3 and CR1. AMs differ from blood monocytes by reduced expression of adhesive molecules LFA1 (*Lymphocyte function-associated antigen 1*) and the lack of proteins of the integrin family on the membrane. However, in terms of the expression level of histocompatibility antigens, MHC AM is not inferior to blood monocytes. AMs coordinate antimicrobial protection through the expression of scavenger receptors, complement, β-glycan, mannose, which facilitate the phagocytic function of AM, generate active forms of nitrogen and oxygen involved in the protection against microbial infection [40]. AMs are central regulators of the reduction of inflammation, due to their ability to absorb apoptotic cells during the effector phase of the immune response in the lungs [41].

## THE ROLE OF MACROPHAGES IN THE IMMUNOPATHOGENESIS OF LUNG DISEASES

Pulmonary tuberculosis, acute pneumonia, chronic nonspecific lung diseases, especially chronic bronchitis, and chronic obstructive pulmonary disease occupy a special place among respiratory diseases. The mucous membrane of the respiratory tract is a vast surface for the introduction of pathogens and toxic substances into the human body. An early immune response to bacterial infections triggers the activation of the expression of genes involved in

the polarization of maturation of M1 macrophages. These include genes encoding cytokines, such as IL-15, chemokines (CCL2, CCL5 and CXCL8) and the chemokine receptor CCR7. Other M1-related genes encode the enzymes indolamine-2,3 dioxygenase (IDO) and NO-synthase 2 (NOS2), which are involved in microbicidal activity of macrophages, and costimulatory molecules of the B7 group - CD80 and CD86. Probably, M1 activation is necessary as a general 'alarm signal' against bacteria that induce macrophage activity, since most of the genes of proinflammatory cytokines are expressed regardless of the type of bacteria. Polarization of macrophages in the direction of M1 is usually associated with the inclusion of the protective function of the immune system in acute infectious diseases. For example, *Listeria monocytogenes*, which causes disease in immunocompromised patients and pregnant women, induces an M1 cell activation program that promotes the formation of bacterial phagosome and stimulates the intracellular destruction of bacteria in vitro and in vivo [42].

The chronic course of infectious lung diseases is associated with the reprogramming of macrophages in the direction of the M2 profile. One of the examples confirming this differentiation of macrophages was demonstrated by A. Joshi and T. Raymond (2008). According to the authors, as a result of infection with *Schistosoma mansoni*, mice developed pulmonary fibrosis, which indicates the involvement of M2 cells in the pathogenesis of the pathological process. In mice with pulmonary granulomatosis infected with *Schistosoma mansoni*, macrophages derived from bone marrow expressed more CCL18 and MSR CD36 (macrophage markers with M2 phenotype) and less iNOS, CCL3, MIP-2, TNFα and IL-12 (cell markers with phenotype M1). The authors showed that, compared with naive M0 macrophages, macrophages differentiated under the conditions of a Th2-dependent immune response during *Schistosoma mansoni* infection show increased reactivity to the presence of specific TLR agonists that activate the expression of cytokine genes of both M1 and M2 macrophages [43].

In idiopathic pulmonary fibrosis in the alveolar tissue, the cytokines of the Th2 profile are predominantly determined, which contribute to the proliferation, differentiation and secretory activity of fibroblasts, epithelial cells, T-cells and macrophages. In humans and mice against the background of this pathology, according to immunohistochemical studies, macrophages with the M2 phenotype prevail among the cells of bronchoalveolar lavage.

However, in an experimental model of fibrosis during the development of silicosis in mice, the absence of preferential polarization of maturation of macrophages according to any phenotype, as well as the lack of polarization of T-cell differentiation in the direction of Th1 or Th2, was shown [44].

Chronic brucellosis is characterized by damage to all human organs and systems, and the respiratory tract is involved in the pathological process. After infecting the mice with *Brucella abortus*, D. Fernandes and J. Jiang (1996) found that chronic brucellosis is associated with the mediated IL-10 M2-polarization of macrophages. The experiment showed that the neutralization of IL-10 and IL-4 by recombinant antagonists in infected mice contributed to the eradication of *Brucella abortus* by macrophages due to the activation of IFN $\gamma$  production and the conversion of macrophages into M1 cells [45].

The macrophage phenotype at the inflammatory focus does not always correspond to its classification by functional activity. Different types of streptococci can cause meningitis, pneumonia, endocarditis, and necrotizing fasciitis in humans and animals. Upon primary infection by the streptococcal family of bacteria, an acute inflammatory reaction usually occurs with a predominantly TLR2-dependent pathway of innate immunity activation involving M1 macrophages [46]. Human and mouse macrophages differ in their responses to *Streptococcus pyogenes*. In humans, this pathogen induces M1 cells characterized by increased expression of the mRNA of chemokines CCL2, CCL5, CXCL8 and CXCL10 [47]. In mice, *Streptococcus pyogenes* stimulates an unusual activation program that combines the M1 and M2 profiles of macrophage differentiation [48].

Pneumonia caused by *Streptococcus pneumoniae* is an infectious disease of the lungs with a high mortality rate, especially among infants and the elderly. It accounts for 1.6 million deaths worldwide (of which 1 million are children), mostly in developing countries [49].

*Streptococcus pneumoniae* is the main causative agent of community-acquired pneumonia, meningitis, otitis media, and sinusitis. In rare cases, pneumococcus can cause infections at other sites (endocarditis, septic arthritis, primary peritonitis, phlegmons, etc.) [50]. A. Kadioglu et al. (2004) examined the mechanisms of immune protection against pneumococci during their penetration into AM, including activation of several factors: homeostatic proliferation of alveolar macrophages (M1 and M2), infiltration of the center of inflammation by neutrophils, and activation of the complement system and CD4 + T cells with the

development of an inflammatory adaptive immune response [51].

T. Menter et al. (2014) conducted a study on the causes of increased susceptibility to *Streptococcus pneumoniae* and mortality from pneumonia related to patient age. As a result of assessing the composition of cells in the outbreak of inflammation (neutrophilic granulocytes and various subpopulations of lymphocytes and macrophages), immunohistochemical analysis of lung tissue samples in young, middle-aged and elderly patients with streptococcal pneumonia revealed a higher content of neutrophilic granulocytes in the elderly. In contrast, in young and middle-aged patients a higher content of AM was found with the phenotype CD11c<sup>+</sup> and M1-macrophages (CD14<sup>+</sup>HLA-DR<sup>+</sup>). However, no significant difference was found in the number of M2 macrophages and lymphocytes [52]. It was suggested that the program for the activation of macrophages with the M1 phenotype in younger patients is associated with an effective protective function of the immune system during the development of streptococcal pneumonia. However, excessive or prolonged M1 activation can be negative, increasing the damaging effects of inflammation.

## MACROPHAGES AND MYCOBACTERIAL INFECTION. MYCOBACTERIUM TUBERCULOSIS ESCAPE MECHANISMS FROM PHAGOCYTOSIS

Active tuberculosis can occur immediately after infection or due to reactivation of a latent infection that is limited to granulomas. Further development and maintenance of inflammation within the granuloma depends on the effectiveness of a specific anti-tuberculosis immune response, the mechanisms of which are not fully understood. In immunocompromised patients, infection with *Mycobacterium tuberculosis* (*Mtb*) can lead to the development of acutely progressive forms of pulmonary tuberculosis.

There is a hypothesis that mycobacteria modulate the activation of M2-macrophages in order to effectively use the granuloma as a source of its existence [53, 54].

In addition, in the case of the presentation of the DC antigen, *Mtb* interacts with the latter via the DC-SIGN receptor (CD209), suppressing the transmission of a TLR2-dependent signal. It is shown that the interaction of the ligand with TLR2 mediates the process of maturation, DC activation and the start of the immune response, which is characteristic

of immunogenic DCs, while activation of CD209-dependent signal transduction, on the contrary, contributes to the formation of tolerogenic DCs and, as a result, the expression of costimulatory molecules [55]. L. Balboa et al. (2013) found that CD16-negative monocytes differentiate into DCs with the CD1a<sup>+</sup>DC-SIGN<sup>high</sup> phenotype, providing an effective response to *Mtb*, and CD16-positive monocytes - to DCs with the CD1a<sup>+</sup>DC-SIGN<sup>low</sup> phenotype, characterized by a weak presentation of mycobacterial antigens. At the same time, in patients with pulmonary tuberculosis an increase in the number of CD16-positive cells was noted in up to 40% of the total number of monocytes in the blood. A decrease in the number of CD16<sup>+</sup> cells was associated with the differentiation of monocytes into CD1a<sup>+</sup>DC-SIGN<sup>high</sup> dendritic cells [56].

M. Benoit et al. (2008) in several mouse models showed that the M1 polarization of macrophages dominates in the early phase of the immune response against *Mtb*, and its clinical picture resembles the one that develops in patients with active pulmonary tuberculosis [57]. In mice, in the structure of granuloma, macrophages with the M1 phenotype were found to predominate between 7 and 30 days after exposure to the *Mtb* antigen, and a high level of IFN $\gamma$  and iNOS was detected in the granuloma [58]. In general, the differentiation of macrophages towards M1 is part of the 'common host reaction' against intracellular bacteria and is characterized by high expression of iNOS M1 cells with subsequent formation of nitric oxide (NO), secretion of pro-inflammatory cytokines and chemokines, release of proteolytic enzymes and antimicrobial peptides, increased phagocytosis and the development of an intracellular environment toxic to *Mtb* [59]. Given this hostile environment created by M1-macrophages, it is not surprising that *Mtb* developed strategies that impede M1-polarization.

Some escape mechanisms of *Mtb* from the damaging activity of cells of innate immunity were investigated. B. Miller et al. (2004) revealed that some *Mtb* species are able to neutralize the effector molecules of M1-macrophages. For example, *Mycobacterium bovis* bacillus Calmette-Guerin interferes with the entry of NOS2 into phagosomes and inhibits the release of NO [60]. In the later stages of infection, the number of alternatively activated macrophages increases. This leads to the impairment of NO production and contributes to the survival of *Mtb* [61]. In addition, it was found that the virulence of *Mtb* is largely determined by the presence of *ESX-3* genes in the cluster pathogen,

the expression of which leads to the suppression of phagosome maturation [62]. Mycobacteria block the activation of M1 macrophages through the secretion of virulence factors. This has been demonstrated on the isolated from *Mtb* antigen ESAT-6, which inhibits the activation of the transcription factor NF- $\kappa$ B and IRF (interferon-regulating factors) through TLR2-dependent mechanisms [63]. As a result, macrophages are unable to destroy the highly virulent strains of *Mtb*. However, *Mtb* can inhibit the transcription of *IFN* genes with the involvement of IL-6 [64]. Although IL-6 is associated with M1 activation, it may also be involved in restrictive responses of the immune response [65].

In the process of cell-mediated immune response to *Mtb*, IFN $\gamma$  is synthesized, which activates macrophages and other anti-tuberculosis defense cells: granulocytes and natural killer cells. For the killing of *Mtb* in the cytosol of the macrophage under the influence of IFN $\gamma$ , an autophagolysosome is formed, and the pathogen is destroyed in it by the enzymes of lysosomal granules. At the same time, *Mtb* has the property of blocking phagosomal-lysosomal fusion. Thus, the autophagy mechanism is activated in response to TLR activation and IL-1 $\beta$  synthesis by macrophages. IL-1 $\beta$  restores phagosome maturation disturbed by mycobacteria by resuming production of PI(3)P (phosphatidyl inositol-3-phosphate), an important participant in the TLR2-dependent signaling pathway. In response, *Mtb* secretes ZmpA zinc metalloprotease, which inhibits the production of IL-1 $\beta$  by macrophages, which suppresses the synthesis of PI(3)P and again slows down the maturation of phagosomes. Thus, the probability of bacterial intracellular survival remains high and is determined by the outcome of the long-term opposition of the pathogen and the host organism [62].

*Mtb* reprogram M1 macrophages into M2 cells by secreting the immunosuppressive mediator IL-10. It has been found that *Mtb* can affect all TLR-dependent signals and limit the pro-inflammatory response by directed induction of IL-10 secretion through the CD209 receptor to DC [66, 67]. It has been shown that human M2 macrophages generated in the presence of M-CSF are characterized by high secretion of IL-10 against the background of a lack of production of IL-12, IL-1 $\beta$ , IL-6 and TNF $\alpha$  in response to stimulation of LPS, mycobacterial antigens, Zymosan A or IFN $\gamma$  in combination with CD40L [68].

In general, AMs are characterized by low phagocytic activity and the ability to inhibit T-cell



activation. The endogenous properties of AM are determined by the effects of TGF $\beta$ , which is formed by alveolar epithelial cells and inhibits the phagocytic, antigen presenting and proinflammatory activity of AM [69]. It was previously assumed that macrophages lose the receptor for TGF $\beta$  during the differentiation [70, 71]. However, the revealed changes in the expression of the IL17BR receptor mRNA in macrophages under the action of TGF $\beta$  suggested that under certain conditions macrophages retain the ability to respond to TGF $\beta$  [72].

The ability of macrophages to be suppressed by TGF $\beta$  is important in the pathogenesis of the development and generalization of tuberculosis infection. Thus, we previously established the molecular mechanisms of immunosuppression in pulmonary tuberculosis associated with antigen-dependent generation and activation of regulatory T cells genetically determined by the overproduction of inhibitory cytokines, TGF $\beta$  and IL-10 [73, 74].

The involvement of the innate immunity cell scavenger receptors is noted in the regulation of the adaptive immune response in pulmonary tuberculosis by directed differentiation of T-helper cells after their recognition of the antigenic peptide. Zhipeng Xu et al. (2017) in a mouse model of tuberculosis infection showed that the expression of PRR (pattern-recognizing receptor) class A (CD204) is regulated by the pathogen and suppresses translocation to the nucleus of IRF-5, shifting the polarization of macrophages from M1 to M2, and thereby switches the adaptive response of T -helpers from the Th1 path to the Th2 path [30].

Thus, on the one hand, in pulmonary tuberculosis, macrophages are located in the microenvironment containing a combination of anti-inflammatory and suppressor cytokines, which can contribute to their differentiation into M2 cells with the corresponding functional phenotype. On the other hand, *Mtb* have properties that suppress the M1-polarization of macrophages. Expression of scavenger receptors on M2 macrophages has a modulating effect on T-lymphocyte differentiation, promotes *Mtb* dissemination (with the development of a Th2 immune response) and pathological remodeling of lung tissue and its fibrosis (with the development of a Treg-immune response) [30, 75, 76].

## CONCLUSION

One of the most important unsolved problems in the pathophysiology of the infectious process is the assessment of the characteristics of inflammation, a universal reaction of innate immunity that develops

in the lung tissue in response to the penetration of the pathogen into alveolar macrophages. To a large extent, there are many unanswered questions related to the mechanisms that determine the expression of molecular factors, the direction of differentiation, activation and functional plasticity of macrophages during the development of infectious lung diseases. The mechanisms of contact interaction between myeloid and lymphoid cells of innate immunity are being actively studied. Modern methods of treatment of diseases of the respiratory system organs do not always contribute to the achievement of the desired therapeutic effect. The increasing drug resistance of bacteria to antibiotics is becoming a global problem of the 21st century, so the use of alternative antibacterial therapy of treatment methods is becoming increasingly popular in clinical practice. Since macrophages have a high degree of phenotypic heterogeneity and functional plasticity, they are the optimal target for the development of new methods of cellular immunotherapy. Considering the peculiarities of immunopathogenesis of infectious lung diseases, a compelling reprogramming of the macrophage phenotype seems to be a relevant and promising direction for solving these issues.

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