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Macrophage-derived cytokines in pneumonia: Linking cellular immunology and genetics

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ABSTRACT

Macrophages represent the first line of anti-pathogen defense - they encounter invading pathogens to perform the phagocytic activity, to deliver the plethora of pro- and anti-inflammatory cytokines, and to shape the tissue microenvironment. Throughout pneumonia course, alveolar macrophages and infiltrated blood monocytes produce increasing cytokine amounts, which activates the antiviral/antibacterial immunity but can also provoke the risk of the so-called cytokine "storm" and normal tissue damage. Subsequently, the question of how the cytokine spectrum is shaped and balanced in the pneumonia context remains a hot topic in medical immunology, particularly in the COVID19 pandemic era. The diversity in cytokine profiles, involved in pneumonia pathogenesis, is determined by the variations in cytokine-receptor interactions, which may lead to severe cytokine storm and functional decline of particular tissues and organs, for example, cardiovascular and respiratory systems. Cytokines and their receptors form unique profiles in individual patients, depending on the (a) microenvironmental context (comorbidities and associated treatment), (b) lung monocyte heterogeneity, and (c) genetic variations. These multidisciplinary strategies can be proactively considered beforehand and during the pneumonia course and potentially allow the new age of personalized immunotherapy.

1. Introduction

Monocytes and macrophages (MΦs) are among the first responders against any type of invading pathogens, primarily of viral and bacterial origin. Monocytes/MΦs are the components of the innate immune system with the essential ability for phagocytosis, cytokine production and release, and antigen presentation. Monocytes are normally present in the blood, while MΦs are found in all the tissues, including so-called immune-privileged zones (microglia of the central nervous system, MΦs of eyes, testis, and placenta). The ubiquitous location of monocytes/MΦs makes them one of the first cell populations, which encounter the invading pathogens.

Both monocytes and MΦs express Toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns, such as bacterial lipopolysaccharides (LPS) (TLR 2,4), bacterial or viral DNA and RNA (TLR3, 7–9) [1,2]. The ligand-receptor engagement leads to the monocyte/MΦ proinflammatory activation and cytokine release, which results in increased cellular phagocytic and cytotoxic activity and further regulation of innate and adaptive immune systems together with the surrounding tissues. Thus, cytokines, which include interleukins, interferons, chemokines, colony-stimulating and growth factors, are essential communication molecules involved in cellular cross-talk and signaling. Cytokines shape pro- or anti-inflammatory microenvironment and are involved in a broad number of physiological processes - cell attraction and differentiation, - and pathological events - bacterial and viral infections, autoimmunity, metabolic disorders, and cancer [3].

Abbreviations: CCL, CC–chemokine ligand; CCR, Cc chemokine receptor; CD, Cluster of differentiation; COPD, Chronic obstructive lung disorder; CXCL, Chemokine (C-X-C motif) ligand; EGFR, Epidermal growth factor receptor; GMCSF, Granulocyte-macrophage colony-stimulating factor; GWAS, Genome-wide association studies GWAS; IFN, Interferon; IL, Interleukin; IRF, Interferon regulatory factor; LPS, Lipopolysaccharides; MCP, Monocyte chemoattractant protein; MHC, Major histocompatibility complex; MIF, Macrophage migration inhibitory factor; MRC, Mannose receptor C-type; MΦ, Macrophage; NFκB, Nuclear factor kappa-light-chain-enhancer of activated B cells; PAMP, Pathogen-associated molecular pattern; PPAR, Peroxisome proliferator-activated receptor; PTX, Pentraxin-related protein; RNA, Ribonucleic acid; SNP, Single nucleotide polymorphisms; STAT, Signal transducer and activator of transcription; TF, Transcription factor; TGFβ, Transforming growth factor beta; TLR, Toll-like receptor; TNFα, Tumor necrosis factor alpha.

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In pneumonia the cytokine signaling network is formed by multiple cell populations, including airway epithelium, fibroblasts, and MΦs. Here, we address the roles of lung resident MΦs and monocytes in cytokine network in the context of cell microenvironment, disease history, and genetics.

2. Diversity of lung monocytic subsets and cytokine profiles

Host response to viral or bacterial pathogens, which generally penetrate the lungs via inhalation or swallowing, requires the activation of local and systemic components of inborn (monocytes/MΦs, neutrophils, natural killer cells) and adaptive (T- and B-lymphocytes) immunity together with nonimmune resident cells (fibroblasts, airway epithelium) to counteract the pathogen and promote tissue recovery. While all of the cell populations are essential for proper antiviral and antibacterial responses, lung MΦs and infiltrated blood-derived monocytes represent an important cytokine source and remain in focus of attention for understanding the lung homeostasis in health and disease [1].

In the physiological conditions, only tissue-resident MΦs - alveolar and interstitial - populate lungs (Fig. 1). Although the precise origin of alveolar MΦs is yet to be established, the developmental studies suggest that they migrate from two independent sources, yolk sac and fetal liver, and populate the alveolar and airway lumen [2,3]. Interstitial MΦs are also essentially present in the lung tissue and comprise around 5–10 % of all lung monocyte cells [4]. Various genomic and single-cell studies in mice and humans distinguish from 2 to 3 various subsets of interstitial MΦs basing on major histocompatibility complex (MHC) II and CD11c expression levels, antigen presentation and phagocytic activities [5–7]. When compared with alveolar MΦs, interstitial MΦs show higher mRNA levels of cytokine (interleukin (IL) 4, IL6, IL10) and interferon (IFN) (IFN A, G) receptors and chemokines (CC-chemokine ligand (CCL) 3,4,6−9; chemokine (C-X-C motif) ligand (CXCL) 1314; CC chemokine receptor (CCR) 1,2) in a non-activated state and increased cytokine (CXCL 1, 2, 9−11, IL11, IL33) expression upon LPS stimulation [5,6,8]. IL10-producing MΦs, predominantly represented by interstitial MΦs, are reduced in asthma patients, and are, thus, believed to play an essential role in physiological and pathological immunoregulation [9,10].

While pathological inflammation arises resident MΦ subsets are supplemented with the peripheral monocytes infiltrated from the blood (Fig. 1). Lymphocytes and eosinophils are also recruited to the lungs, and their amounts gradually decrease with time, while monocytes can remain in the lung tissue for longer periods and convert into MΦs. To address the functional activity monocytes / MΦs can be roughly classified into unprimed (non-stimulated), pro-inflammatory (M1-like) or anti-inflammatory (M2-like) cells (Fig. 2).

Recent works show that monocytic cell roles throughout pneumonia course significantly depend on the phenotypic subset and origin together with the microenvironment, as different activating stimuli show similar outcomes within one tissue/organic location, but not throughout the whole organism [11]. Alveolar and interstitial MΦs vs. monocytes have different potency for cytokine production in healthy lungs and during the early disease stages (Table 1, Fig. 1). Blood-derived monocytes produce the highest levels of proinflammatory cytokines (Fig. 1). Of note, younger patients exhibit higher levels of peripheral monocytes and inflammatory cytokines in the nasal lavage than adults, and these parameters are not associated with disease severity and outcome. However, the presence of proinflammatory monocytes in the systemic circulation is a risk factor of uncontrolled cytokine storm and sepsis in all cohorts of patients [12]. During later stages of the disease lung-resident myeloid cells become a predominant source of immunosuppressive cytokine IL10 and effectively control T helper 2 cell activity [13]. Further, lung-resident MΦs, but not monocytes, exhibit reduced capability for phagocytosis long-term after recovery from infectious pneumonia, and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) transcriptional regulation seems to be among the major mechanisms of this dysfunction [14]. This can be one of the key reasons of chronic lung inflammation and fibrosis, when alveolar MΦs become dysfunctional and fail to remove the damaged cells and debris and perform physiological surfactant turnover. MΦs originated from the

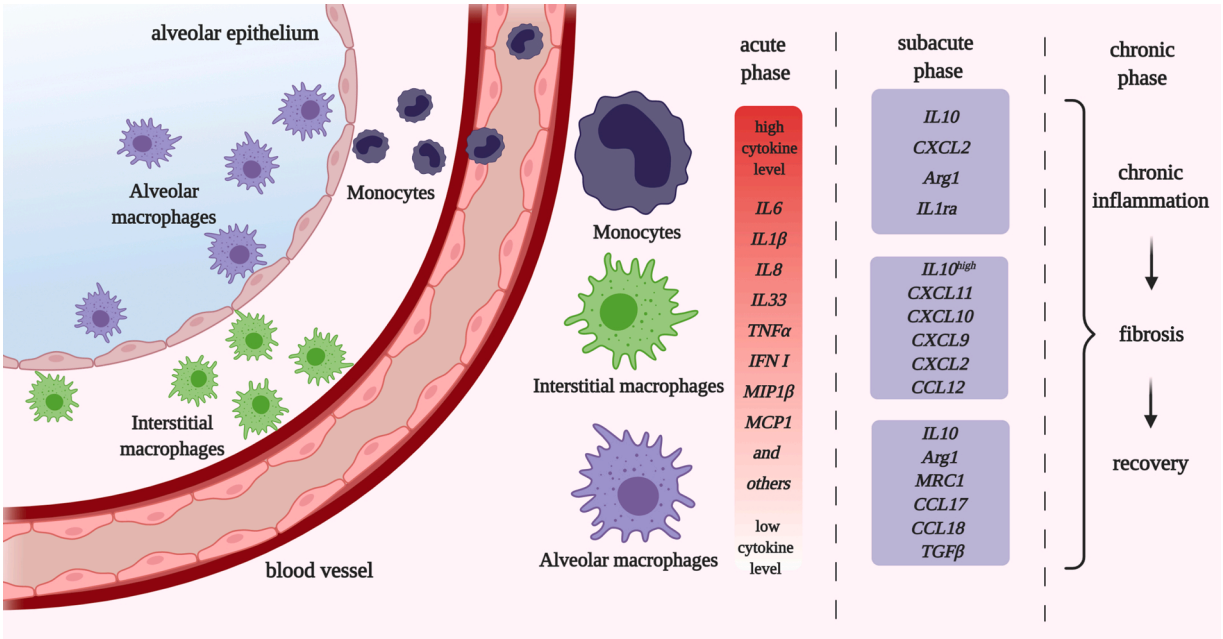

Fig. 1. The monocyte / macrophage (MΦ) activity throughout the pneumonia course. Under physiological conditions lung monocytic populations include resident alveolar and interstitial MΦs, located in the alveolar and airway lumen and interstitial space, respectively. During infection, the blood derived monocytes penetrate the lung tissue. During the early, or acute, stage monocytes / MΦs develop proinflammatory phenotype and produce proinflammatory cytokines essential for attraction of other immune cell subsets. Among monocytic cells, infiltrated monocytes are the major source of pro-inflammatory cytokines. Later during subacute phase macrophages switch towards anti-inflammatory profiles, which support the lung tissue reorganization (chronic phase) and/or recovery.
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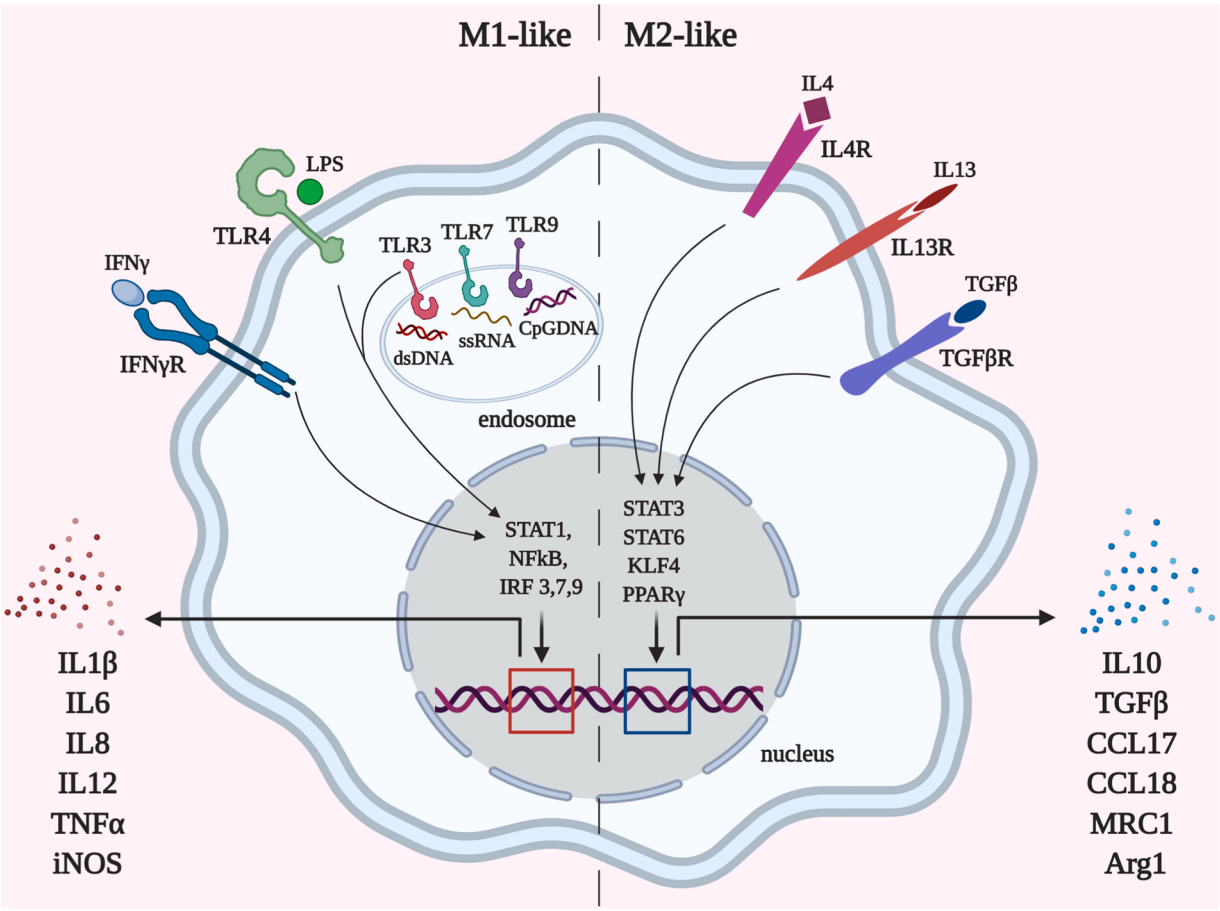

Fig. 2. Functional polarization of monocytic/macrophage cell subsets. Macrophages can obtain the distinctive phenotype depending on the microenvironment. Polarization towards pro-inflammatory (M1-like) macrophages is triggered by pathogen-associated molecular patterns (PAMPs) such as LPS, bacterial or viral DNA, and some cytokines (IFNγ) via STAT1, NFκB and interferon regulatory factor (IRF) transcription factor signaling, which leads to high pro-inflammatory cytokine production. M1-like monocytic cells are responsible for anti-pathogen defense, acute inflammation, other immune subset attraction and can provoke cytokine storm. Anti-inflammatory (M2-like) polarization of macrophages is elicited by cytokines IL4, IL13, and TGFβ and leads to the resolution of inflammation, tissue reorganization, and regeneration. The balance between M1/M2 states is required for proper pathogen elimination and efficient structural and functional recovery. Created with BioRender.com

infiltrated monocytes can unlikely replace them since blood-derived MΦs more intensively undergo Fas-dependent apoptosis and are thus eliminated from the lung microenvironment [15]. Initially, Fas signaling cascade is required for IL1β production via caspase-mediated inflammasome formation in monocytes exclusively and is associated with strong antiviral activity [16,17]. CD44-expressing blood-derived MΦs are more resistant towards Fas-dependent apoptosis, and MΦ migration inhibitory factor (MIF)/CD44 signaling axis can thus be used to expand this cell population and to eliminate the viral/bacterial pathogens more efficiently if needed [18]. Less is known about the distinctive features of interstitial MΦs. Considering their location and predisposition for high IL10 production in the resting state, it may be suggested that this subset prevents systemic monocyte activation, as anti-inflammatory IL10 can be released by interstitial MΦs both into alveolar space and blood flow to restrict cytokine storm on both local and systemic levels [19].

Importantly, the cytokine contribution to the disease pathogenesis is completely rearranged if a joint bacterial infection develops. For instance, cytokines, such as IL33, which are considered as negative factors and are associated with the cytokine storm in viral infections, become essential for bacterial clearance and further recovery after associated bacterial pneumonia [47]. Moreover, while IL33 is considered as highly proinflammatory, as it promotes γδT cells via IL9 axis in COVID19 disease, can also act as immunosuppressor long-term during and after sepsis [48–50].

Whether the cellular source of IL33 in the listed situations is diversified remains unclear. Conclusively, the functional outcomes of cytokine signaling have to be considered when cytokine profile is shaped in pneumonia therapeutics. With that, it is particularly important to address the monocyte cell origin together with the pathological context for targeted subset re-polarization and controllable cytokine regulation in personalized and stage-dependent modes for further clinical implementations.

3. Proinflammatory cytokine network in pneumonia

The overstimulation and prolonged activation by proinflammatory stimuli lead to overproduction of cytokines and emerged inflammation, which can also impact surrounding tissues and provoke lung and cardiovascular damage, and even septic-like conditions. An anti-inflammatory cytokine network is on hand for restriction of M1-like polarization at the later stages of pneumonia. Certain cytokines, such as granulocyte-monocyte colony stimulating factor (GMCSF), can be used to redirect MΦs towards less inflammatory and more protective phenotype, and suppression of cytokine storm remains a major therapeutic strategy against pneumonia [51,52].

In general, monocytes/MΦs release a broad spectrum of proinflammatory cytokines (Table 1). The major contributors to the disease course during bacterial or viral-induced pneumonia are IL6, IL1β, tumor necrosis factor alpha (TNFα), IL8, IFNI, and others, which are produced under control of signal transducer and activator of transcription 1

Table 1
General Characteristics of Lung Monocytic Cell Subsets.

Mononuclear cell subset	Transcription factor	Secretory profile	Functional role
Alveolar macrophages (SiglecF + CD11c + CD11b − CD71+)			
Unprimed alveolar macrophages	PPARγ, STAT6, STAT3, FOXP3, SOCS3 [20]	Immunosuppressive prostaglandins, TGFβ, GMCSF, retinoic acid, IL10	Lung microenvironment maintenance; Debris phagocytosis, surfactant turnover. Low antigen presenting activity, suppression of T cell activation [1, 21]
CD206+CD14+CD169+			
M1-like alveolar macrophages	STAT1, NFκB, IRF3,7 9 [22]	IFN I, IL6, TNFα, IL1β, IL8, MCP1, MIP1β, IP10, CCL5,CXCL1	Anti-pathogen defense, acute inflammation and immunoregulation; Attraction of cytotoxic T cells, T helper cells, B-lymphocytes [1,23]
CD40+CD80+CD86+			
M2-like alveolar macrophages	PPARγ, STAT6, STAT3, KLF4, c-MYC, IRF4 [22, 24,25]	Arg1, MRC1, CCL17, CCL18, IL10, TGFβ	Alveolar formation in embryogenesis
CD71+ CD206+ RELMα + CD163			Regulatory T cell infiltration, resolution of inflammation; lung tissue reorganization and regeneration [26]
Interstitial macrophages (SiglecF − CD11b+HLADR + CD71low)			
Unprimed interstitial macrophages	PPARγ, Maf, Maf B, HIF1 [4,5]	IL7, IL10^{low}, IL6, IL4, TNFα, CCL3, CCL4, CCL6−9, CXCL13−14, CCR1, CCR2, IFNA, IFNG	Lung immune homeostasis
CD11b + CD11c + CD14+			Relatively high antigen presenting activity [4,9,10]
M1-like interstitial macrophages CD206-	STAT1, NFκB, IRF3	PTX3, IL-12, CXCL13, CCL5, CXCL1,2,9−11, IL11, IL33	Th1 cell activation T and B lymphocyte chemoattraction Phagocytosis [6,27]
M2-like interstitial macrophages CD206+	STAT6 STAT3 KLF4	IL10 ^{high}, IL1-Ra, CXCL11, CXCL10, CXCL9, CXCL2, CCL12 [6]	Immunoregulation,lung tissue reorganization and regeneration [6,28]
Blood-derived monocytes CD14+ CD16+/- CCR + CCR5+ CD62L+			
Unprimed monocytes CD80+CD163+ (CD14++CD16-CCR2+ classical, CD14dimCD16++CX3CR1+	Irf8, Klf2, Klf4, C/EBPβ, Nur77 [31,32]	IL1β low, IL6, TNFα, CCL2, CCR2, CCL24 [33]	Blood homeostasis
Non-classical, CD14++CD16 + C × 3CR1+ (intermediate) [29] [30]			Maintenance of macrophage and dendritic cell populations [34]
M1-like monocytes/macrophages	STAT1, STAT2,NFκB, IRF1,3,5 [37]	IL6, IL1β, IL8, TNFα, MCP1, MCP3, MIP1β, IP10, GMCSF, CXCL10, GBP1 [38]	Acute inflammation
CD14+ CD16+/- HLADR + CD80+ CD163- (predominantly from classical monocytes) [29,35,36]			CD8+ T cell attraction Reactive oxygen species production Pro-inflammatory activity during late stages of pneumonia Maintenance of dendritic cell pool [30,39,40,41]
M2-like monocytes/macrophages	STAT6, STAT3, KLF4, IRF4 [44]	IL10, CXCL2 (MIP2), Arg1, IL1ra [45]	Immunoregulatory activity
CD14DIM CD16- CD80- CD163+ (predominantly from non-classical monocytes) [29,42,43]			Alveolar epithelium restoration Lung tissue reorganization and regeneration Fibrosis [28,45,46]

(STAT1) and NFκB transcription factors (TFs). Another important group of TFs is an IFN regulatory factor (IRF) family, primarily, IRF 3, 7, and 9, which positively regulate of viral-induced IFN transcription. Altogether, activation of these proinflammatory TFs is a double-edged sword, as they promote proinflammatory M1-like polarization, cytokine release, and attraction of other immune cells for antibacterial or antiviral activity but may also lead to poor recovery and damage of lung tissue, vasculature, heart, and even more distant organs if sepsis arises. For instance, the high levels of antiviral interferons α and β increase the disease severity, lung damage, and mortality in animal models [53].

It is known that viral components actively modify the cytokine network and can shape the immune microenvironment [54,55]. For instance, numerous works report that viral proteins, such as ORF and NSP families (severe acute respiratory syndrome CoV, SARS-CoV-2) and H5N1, can suppress STAT1 phosphorylation and promote antagonistic STAT3 signaling, which results in impaired IFNI production and signaling in airway epithelium and dendritic cells during pneumonia [55–57]. Of note, STAT3 signaling is also related to apoptotic escape in H5N1 (avian influenza)-loaded bronchial and alveolar epithelial cells. Interestingly, STAT3 signaling is more IL6-dependent and proinflammatory in peripheral monocytes, while STAT3 of MΦs is associated with IL10-mediated response and results in immunoregulatory profile, so that viral STAT3 manipulation may lead to infiltrated monocyte survival and excessive inflammation or development of immunosuppressive microenvironment, which has to be further investigated [58, 59]. Moreover, the dysregulated STAT signaling is a hallmark feature of MΦs during various viral infections, other than respiratory: hepatitis B, hepatitis C, human cytomegalovirus, oncolytic vesicular stomatitis [60–63]. However, the details of the interaction between viral proteins and monocytes/MΦ transcriptional machinery in pneumonia remain poorly investigated, so that the viral impact onto M1/M2 polarization is not fully understood.

3.1. Cytokine network in monocyte-to-macrophage transition

As it has been mentioned, alveolar MΦ origin from the fetal liver and

yolk sac monocytic precursors during the development, while in adulthood majority of alveolar MΦs are maintained without bone marrow cell contribution unless lung pathology develops (Fig. 3) [64,65]. An embryonic monocyte-to-MΦ switch is not passive but occurs in cytokine (transforming growth factor beta (TGFβ), GMCSF)-dependent mode and requires activation of a specific transcriptional program, which relies on key TFs peroxisome proliferator-activated receptor γ (PPARγ) and STAT6, which, in their turn, form a MΦ cytokine profile, distinct from those of monocytes [64–67].

TFs PPARγ and STAT6 are highly expressed in alveolar MΦs of healthy subjects; PPARγ and STAT6 constitutively orchestrate autophagic activity and cytokine production and are thus required for normal MΦ activities [68]. TFs PPARγ, STAT6, and others downregulate proinflammatory cytokine transcription via direct DNA binding or suppression of M1-related TFs STAT1 and NFκB [69] (Fig. 3). Disruption of PPARγ or STAT6 machinery could lead to certain pathologies. For instance, the PPARγ deficiency was found in patients with pulmonary alveolar proteinosis, a condition when lung surfactant deposits within alveoli likely due to MΦ insufficient phagocytic activity [65]. In pneumonia pathogenesis, resident MΦ activation and peripheral monocyte infiltration also require the transcriptional program switch and improve antipathogen response during the early stages and restrict tissue regeneration in later stages [70].

Indeed, mouse research models show that the factors, involved in monocyte-to- MΦ differentiation, can be connected to pneumonia severity. While infiltrated monocytes are major contributors of IL6 during pneumonia, monocytes can become one of the risk factors when the recirculation from the blood to lung tissue is prolonged or monocyte-to- MΦ differentiation is suppressed [70]. The decreased activities of PPARγ and STAT6 are associated with the prolonged inflammation, higher levels of proinflammatory cytokines IL6, IL1β, IL12, CCl2, TNFα, and reduced pathogen burden at the same time complicated with the extensive lung tissue damage during viral infections; therefore, it likely impacts the destiny of resident and infiltrated cells [25,71–73]. Moreover, infiltrated monocytes are exposed to local cytokines such as granulocyte-macrophage colony-stimulating factor (GMCSF) within the lung tissue, undergo transcriptional reprogramming, and become functionally indistinguishable from resident cell populations, once inflammation is completely resolved [51,74]. Indeed, increased levels or externally (intranasal) delivered GMCSF are protective against viral and bacterial pneumonia, first of all during the most severe pneumonia cases, including COVID19 [51,75–79]. Interestingly, Ly6Clo lung MΦs exhibit even higher proinflammatory activities in the absence of type I interferons deactivating stimulus, than newly infiltrated Ly6Chi monocytes during influenza A and SARS-CoV-2 [80,81]. Moreover, certain viruses, such as middle east respiratory syndrome coronavirus, but not SARS-CoV-2, utilize PPARγ activity to stimulate the production of anti-inflammatory cytokines (primarily IL10) and suppress the host immune system [82–84]. The alterations in the cytokine spectrum itself may also participate in various antipathogen responses. TGFβ-TGFR is a cytokine axis, which regulates the monocyte repopulation of lung tissue exclusively [64,85]. TGFβ promotes immune cell infiltration to the lung during bacterial and viral infections, while also worsening the lung injury [86,87].

4. Personalized look onto cytokine profiles in pneumonia

The emerging amount of data shows the substantial roles of genetic signatures, expression levels, and functional activity of cytokines and their producing machinery during pneumonia pathogenesis. While the majority of patients survive pneumonia and completely restore the normal lifestyle, the substantial cohort undergoes undesired complications such as cytokine storm, excessive fibrotic tissue formation, and chronic lung dysfunction, which may be due to individual genetic

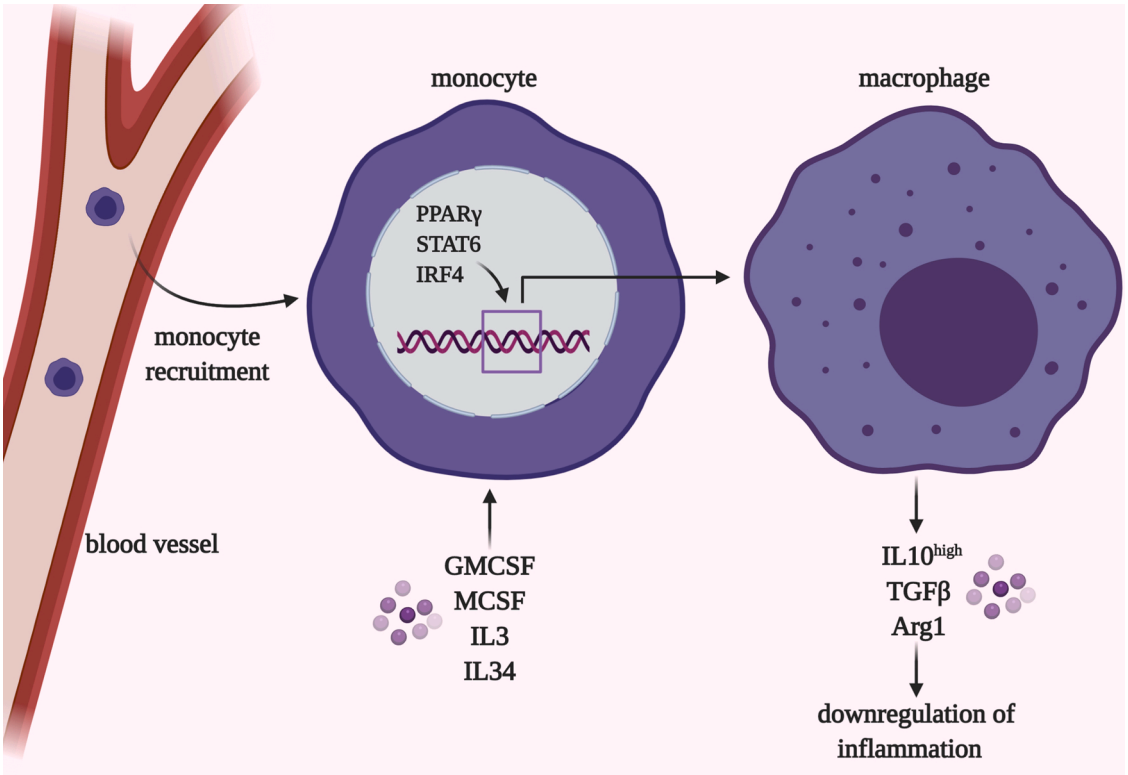

Fig. 3. Monocyte-to-macrophage differentiation within lung tissue. Switch from monocytes to macrophages occurs during embryonic development or upon acute inflammation or lung damage. This process is governed by locally produced GMCSF, MCSF, IL3, IL34, and others under control of the transcription factors PPARγ, STAT6, and IRF4. In long-term periods cells of peripheral origin become phenotypically similar to the lung-resident macrophages.
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variations and preliminary history.

In general, the severity and negative outcomes of viral-induced pneumonia are associated with the high cytokine levels, primarily, IL33, IL6, TNFα, IL10, monocyte chemoattractant protein (MCP) 3, which can be detected in plasma, bronchoalveolar fluid, and nasal lavage of patients [12,88–91]. At the moment, the plasma cytokine patterns, which reflect systemic events and risk of cytokine storm and sepsis, are considered more suitable for evaluation of disease course and hospitalization pre-requisite. Moreover, transcriptional profiles of the peripheral blood mononuclear cells are also reflective for disease severity and outcome [92]. Bronchoalveolar fluid and nasal lavage can also be of use, while some patients with high local levels of proinflammatory cytokines show fast viral removal and efficient recovery after infection [12].

4.1. Altered cytokine network within risk groups

Many bacterial and viral infections, including COVID-19, showed that certain comorbidities - chronic pulmonary and cardiovascular disorders, diabetes, autoimmune conditions - are increased risk factors of cytokine disbalance and severe pneumonia [93]. Additionally, the patients undergoing regular therapy such as in cancer are also at risk and have to be considered with particular attention. The substantial cohort of patients (around 60 %) hospitalized with pneumonia undergo medical interventions for other reasons [94]. Here, we address the most common examples of correlations between chronic conditions and cytokine signaling networks involved in pneumonia.

4.2. Systemic disorders

Diabetes. Current studies on COVID-19-related pneumonia show that diabetic patients comprise 5 to more than 50 % of total cases [95]. Such a high disease prevalence can be explained by altered immune status, as well as applied therapeutic interventions against diabetes. Patients with diabetes using PPAR-γ agonists have decreased levels of proinflammatory cytokines during lung infections; however, develop severe forms of bacterial pneumonia with high bacterial burden [96]. Elevated IL6 levels are often found in diabetic patients, suggesting the increased risk for cytokine storm [95]. Statins are commonly used to control hypercholesterolemia and may inhibit NFκB signaling preventing excessive inflammation; however, most studies show no impact of statins in pneumonia prevalence or severity [95,97,98].

Autoimmune conditions require the life-long intake of immunosuppressive medications, such as corticosteroids or hydroxychloroquine [99,100]. In general, autoimmunity is associated with impaired IFN signaling and reduced production of cytokines, such as IL1α and IL6 [101,102]. Indeed, patients with inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis are more susceptible to pneumonia [103–105]. At the same time, the therapeutic interventions used to control autoimmunity relapses may be on hand to restrict cytokine storm severity in pneumonia, which is becoming particularly prominent in COVID-19 treatment [99]. For instance, corticosteroid treatment, which reduces the systemic levels of IL6, IL1RA, and MCP, is widely used in pneumonia management [106].

Cancer. In general, oncological conditions are strongly associated with an immunosuppressive status of the patients due to cancer-related processes and relevant radio- or chemotherapeutic treatment. Lung tumors are among the most prevalent cancer types found in COVID-19 patients. Interestingly, patients after several pneumonia episodes have a lower risk of lung cancer development, which is probably due to their prolonged hyperactivated immune responses within lung tissue [107]. For patients already diagnosed with cancer-specific treatment approaches significantly impact cytokine profiles, as well as other parameters. Anti-epidermal growth factor receptor (EGFR) therapy, for example, is one of the most common approaches in lung cancer patients. However, EGFR signaling is protective against TNFα-induced airway epithelium apoptosis, and anti-EGFR treatment leads to pneumonitis development, the major death cause in lung cancer patients [108]. On the other hand, the excessive activity of the EGF/EGFR axis, found in patients with severe pneumonia course, leads to the risk of lung tissue fibrosis, chronic pulmonary obstruction, and poor recovery prognosis [109,110]. Anti-programmed cell death protein 1 (PD1) immunotherapy is also found to cause pneumonia with subsequent cytokine storm and risk of lung fibrosis and organ failure in various forms of cancer [111–113]. This side effect, which can be corrected by anti-IL6 treatment, is a matter of concern and has to be considered as a dramatic risk factor for prospective patients. Cytokine-based therapies, which implement the antitumor activities of IL2, IL15, IL21, GMCSF or suppress tumorigenic properties of CCL2, 3 and 5 chemokines, are under development and applied in combination with other approaches in clinical trials [114,115].

4.3. Chronic lung pathologies

Chronic obstructive lung disorder (COPD) is associated with an increased predisposition and a less favorable outcome of pneumonia. COPD patients exhibit elevated CXCL1 levels in response to external proinflammatory stimuli, while serum levels of TNFα, IL1β, and IL6 are reduced when compared with patients with pneumonia alone [116,117]. In accordance with these data, peripheral monocytes of COPD patients have reduced cytokine release following ex vivo total bacterial extract or LPS stimulation [118]. Suggesting that COPD is associated with functional deficiency of peripheral monocytes, this cell subset has to be a primary therapeutic target for these patients.

Asthma is also reported as a susceptibility factor for pneumonia by numerous studies, while the underlying mechanisms of this connection are not fully understood [119]. One possible factor is IL17 production by Th17 cells, and high levels of IL4 and TNFα, which leads to MΦ / monocytes and neutrophil recruitment with subsequent excessive inflammation [120–122]. Second, corticosteroid-based therapy is often used in asthma management and can be relevant to insufficient immune responses, including cytokine production, and increased bacterial/viral burden in infectious pneumonia [123,124].

The major challenge of cytokine profiling in respect to comorbidity-pneumonia correlations is that the exact cellular cytokine source cannot be precisely determined in the patients. The subset contribution can only be accessed by 1) isolation of peripheral blood monocytes and myeloid cells of bronchoalveolar fluid and their further ex vivo stimulation with bacterial/viral pathogens, 2) by translational research derived from animal model studies, or 3) computational modeling of the cell behavior in microenvironmental and genetical contexts. The first two approaches are not universal as in vitro cellular responses significantly differ from those in the organism, while cytokine profiles and monocyte/MΦ subsets are not uniformed in humans and animals in health and disease. Genetic analysis may assist this issue implying a side-by-side comparison of individual genetic variations and linking them with the functionality of desired cell populations. Moreover, the same genetic variations may overlay pneumonia predisposition and comorbidities, as it will be further discussed (Table 2).

4.4. Genetic predisposition of pneumonia risks

The growing numbers of evidence suggest that genetic background including variations in viral/bacteria-host interactome and the host immune profile is an important factor that impacts disease predisposition and progression. While adaptive immunity is pathogen-dependent, factors of the innate immune system are more universal and can be used for a generalized prediction of inflammatory processes. The genetic component of the infectious conditions, such as pneumonia, can be detected via single nucleotide polymorphisms (SNPs) of the receptors, which form the first line of anti-pathogen defense (TLRs, pathogen-associated molecular patterns (PAMPs), and cytokine networks, which

Table 2
Genetics of cytokine network and viral pneumonia pathogenesis.

Gene	Genetic background	Pneumonia and comorbidity states / prognosis (+/-)
Cytokines and their receptors		
IL1A	A114S (rs17561)	H1N1 influenza A pneumonia predisposition / - [132] Cancer (lung, ovarian, breast) predisposition / - [133,134,135]; Asthma prevalence / - [136]
IL1B	rs1143627 rs16944 (511*C/T)	Influenza A pneumonia / - [137] Cancer (lung, cervical) / + [138, 139]; Autoimmunity / - [140] Systemic inflammatory response syndrome / - [141] Diabetes / + [142]; Asthma / - [143]
IL1R1	rs3917254; rs2160227	Invasive pneumococcal disease / - [144,145]
IL1RA (secreted inhibitor for IL1)	A1A1 genotype	Community-acquired pneumonia / + [146]
	A2A2 genotype	Asthma / - [147]; Diabetes / - [148] Community-acquired pneumonia / - [146] Sepsis / - [149]
IL4	C−590 T (rs 2,243,250) rs2070874	Respiratory syncytial virus / - [150] Respiratory infection predisposition / - [151] Asthma / - [152]; Autoimmunity (rheumatoid arthritis) / - [153]; Cancer / - [154]
IL4RA	Q551R (rs1801275)	Respiratory syncytial virus / - [151] Asthma / - [155]
IL6	GG genotype, G allele of IL6−174 G/C SNP (rs1800795)	Community-acquired pneumonia / - [156] Immunodeficiency / - [157] Pneumonia-induced sepsis /- [158] Sepsis / + [159]; Cancer (various) / - [160]; Asthma / + [161] PMCID: PMC4612856
IL9	rs2069885	Respiratory syncytial virus / - [162] Asthma / - [163]; COPD / - [164]; Lung inflammation (cystic fibrosis) / - [165]
IL10	rs1800896-A	Community-acquired pneumonia / + [156]
	rs1800871 (−819 T/T genotype)	Diabetes / - [166,167]; Asthma / - [168]; Breast cancer /- [169] Postoperative pneumonia / - [170]
IL12B	rs2195940, rs919766	Invasive pneumococcal disease / - [145] Acute chest syndrome / - [171]; Inflammatory cardiomyopathy / - [172]
CCL5	rs2107538*CT	Respiratory syncytial virus / - [173] Cancer (breast, prostate) / - [174, 175]
CCL2	rs1024611 (G-2518A)	SARS-CoV / - [176] Autoimmunity (multiple sclerosis) / - [177]; Cancer / - [178,179]
CCR5	CCR5-Δ32 allele	Influenza A / - [180] Diabetes / - [181,182]; Breast cancer / - [183,184]
TNFα	rs361525 308*G/A (rs1800629)	Influenza A / - [185] Systemic inflammatory response syndrome / - [185]; Pneumonia-induced sepsis /- [158]
	−238A allele (rs361525)	Diabetic nephropathy / - [185,186]; Pneumonia in patients with systemic lupus erythematosus / - [187]
TNFRSF1B	TNFRSF1B + 676 (rs1061622)	Community-acquired pneumonia / + [188] Autoimmunity (systemic lupus erythematosus, rheumatoid arthritis) / - [189,190] Lung cancer / + [191]
MIF	C allele at −173 G/C (rs 755,622); rs5844572	Pneumonia-induced sepsis / + [89] Meningitis and bacterial pneumonia / - [192] Autoimmunity (systemic lupus erythematosus, rheumatoid arthritis) / + [193,194]
Transcription factors		
NFκB cREL	rs842647*G	sepsis / - [195,196]
NFκB RelA (p65)	−94delATTG (rs28362491)	autoimmune (Behcet's Disease) / - [197] acute respiratory distress syndrome / - [198] cancer / - or + [199,200]; diabetes / - [201]
STAT1	L706S, Q463H, E320Q, P293L Complete Stat-1 deficiency	mycobacterial disease / - [202,203] pneumonia / - [204] autoimmunity / - [204]; viral infections / - [205,206]
IRF5	rs77571059, rs2004640, haplotype GTAA	community-acquired pneumonia / -
	rs77571059	autoimmunity (systemic lupus erythematosus, systemic sclerosis) / - [207,208,209,210,211] diabetes / - [212]; melanoma / - [213]
IRF7	F410 V (rs 786,205,223) rs375323253; Q421X	influenza A / - [214]
IRF9	Loss-of-function IRF9 allele loss-of-function c.991 G > A	Influenza A, parainfluenza virus, respiratory syncytial virus / - [215] Influenza A, respiratory syncytial virus / - [216]

are responsible for correct pathogen elimination and tissue repair and are described in the current review [125,126].

The genetic predisposition to pneumonia can be associated with the dysfunction in both pro- and anti-inflammatory cytokine systems and lead to excessive (cytokine storm) or insufficient (increased bacterial/viral burden) immune responses. The major gene polymorphisms found in cytokine network genes and associated with pneumonia are summarized in Table 2. IL6 and TNFα can be listed among the major proinflammatory cytokines, and the positive correlation between the severity of illness and the IL6/TNFα allele frequency was demonstrated in the cases of community-acquired pneumonia [127]. In progressive pneumonia and sepsis, anti-inflammatory cytokines such as IL10 are produced to control excessive inflammation. IL10 SNP, which is located in the ETS-like transcription factor recognition site for ETS-like TF, can be used as diagnostic criteria since the increase in its level is also closely related to the severity of disease symptoms. The IL10 level is also higher in patients with sepsis [128]. Pro-inflammatory cytokines including IL1α and β, IL6, IL8, and TNFα can also bear SNPs in the promoter regions. For instance, the presence of SNP in IL1β, IL10, IL17, and IL28 genes determines the outcome of the H3N2 (influenza A) virus-driven pneumonia, and similar results are shown for other viral strains [129]. Interestingly, the same polymorphisms are linked to the predisposition to cancer, asthma, autoimmunity, diabetes, as well as other chronic conditions (Table 2) [130,131]. This connection has to be considered in personalized medicine, as the same genetic background can link together acute (pneumonia or other infections) and chronic immune-related disorders.

The study of SNP contribution has been demonstrated via implementation in-silico studies of pro- and anti-inflammatory cytokine genes as well as of transcription factors. In particular, rs1800795 in IL6 genes can aggravate the course of the disease, leading to sepsis and septic shock due to the cytokine storm. Oppositely, certain polymorphisms can be protective against pneumonia. For instance, SNP rs1800896 in IL10

protects the body from weighting the symptoms of these diseases [217]. Interestingly, some genetic factors can be either harmful or protective throughout the disease course. For instance, GG genotype and G allele of IL6−174 G/C SNP are associated with higher pneumonia rates, while the risk of sepsis is significantly reduced (Table 2). This may be explained by the increased IL6 activity with the suppressed initial antipathogen response and negative prognosis during the early stages of pneumonia, while later the reduced pro-inflammatory activity lowers the risks of cytokine storm [218]. Accordingly, the genetic background contributes to the development of infectious diseases and their phenotypic manifestations. The activity of TFs relies on their interaction with the relevant DNA binding sites and TF-encoding genes. SNPs in the DNA binding sites or target gene promoters can affect TF-DNA interactions, thus impacting transcriptional regulation. These alterations can be predicted by bioinformatics approaches. In particular, it has been identified that out of 80 polymorphisms found in STAT1 or IRF1 motifs, about 34 SNPs impact the TF-DNA interactions [219]. The in-silico experiments predicted that IRF1 can bind T rs9260102 allele, located in the HLA-A promoter, but TF is unable to interact with another allele (G) and fails to perform its transcriptional activity. Later, similar results were obtained by in vitro experimentations [220]. In this way, in-silico methods allow highly efficient and time- and resource-saving prediction of SNP effects on cytokine transcriptional machinery and cytokine functionality [156].

We can also conclude about the impact of SNP on the development of concomitant diseases, which was demonstrated by the example of pneumonia. However, it has to be specified one more time that contribution of each particular protein and corresponding gene polymorphisms is a matter of spatiotemporal factor and disease origin. With that, the additional computational analysis of the SNP association with pneumonia origin (viral, bacterial, or mixed) and its stage (acute, subacute, or chronic) is also essential.

5. Cytokine network in COVID-19 lung pathology

Cytokine storm is a key feature of COVID-19 pathology associated with local lung injury and systemic organ failure if inflammation goes to the systemic level. Anti-cytokine therapy, for instance targeting the IL6-IL6R axis, improves survival and milds symptoms and adverse events throughout the disease course [221]. Cytokine network during COVID-19 course shows some distinctive features when compared with other pneumonia types. For example, the peripheral monocytes from COVID-19 patients are enlarged in size, comprised of mixed M1/M2 polarization with higher, than in influenza, levels of cytokines and their receptors (TNF, IL6R, IL10R) and certain TFs (STAT1, IRF3) [222,223]. At the same time, other researchers report the presence of peripheral myeloid-derived monocyte-like cells, which exhibit signs of immunosuppression with impaired antigen presentation and cytokine production [224,225]. Alveolar MΦs of all Covid19 patients are highly pro-inflammatory, while levels of anti-inflammatory cytokines are elevated only in severe disease cases [224,226].

Transcriptional profiles of SARS-CoV-2-infected human cells and tissue samples reveal the dysregulated chemokine and cytokine (primarily, various interleukins and TNFα) networks, and this dysregulation - at least partially – is mediated by viral protein impact onto host TFs (STAT1, STAT3, IKKβ – NFkB inhibiting protein) [56,227–229]. For instance, the most severe COVID-19 patients exhibit de-mono-ADP-ribosylation of STAT1 by viral nsp3 protein [229]. Additionally, alveolar monocytes and MΦs show the repressed activity of PPARγ TF complex, which is required for maintenance of physiological cytokine levels and resolution of inflammation [230]. Current studies suggest that although monocytes express Ace2 receptor, the SARS-CoV-2 replication does not occur within monocyte/MΦ subsets, and transcriptional alterations are expected to fade gradually once the viral particle number is lowered in the organism [231].

Similar to other viral infections, chronically dysregulated transcriptional factors can be risk factors for increased cytokine production, as it is observed for increased NFkB activity and IL1, IL6, and TNFα cytokine production in the elderly and people with metabolic disorders [232]. Particularly, sensitized IFNα and IL6 signaling pathways of monocytic cells can be associated with the higher predisposition for severe disease course in aged patients [233]. The lung microenvironment is altered in pneumonia higher glycolytic activity alterations triggered during infection lead to metabolic switches in alveolar MΦs with higher glycolytic activity and reactive oxygen species generation, thus, directly connecting the glucose levels – and diabetes – with disease pathogenesis [234]. While the risk factors, such as age, cardiovascular and metabolic disorders, have to be considered for therapeutic design in individual patients, the therapies applied for immunomodulation in a general situation also have a potential for new coronavirus disease management. For instance, tocilizumab (anti-IL6R monoclonal antibody applied in rheumatoid arthritis), metformin, fenretinide (used in type 2 diabetes and metabolic syndrome), and other drugs have been suggested as promising adjuvant therapies in COVID-19 disease [235–237].

At the moment the major attention is attracted to the studies of the genetic variations and expression patterns of proteins responsible for SARS-CoV-2 intracellular entrance to follow disease predisposition and clinical picture [238]. At the same time, the SNPs within the cytokine network are potential predictive markers of cytokine storm accidents and multiorganic failure in individual patients. As for today, the SNPs in chemokines CCR9, CXCR6, in *TMEM189–BE2V1* and *TEMEM189–UBE2V1* gene loci (involved in IL1 signaling) have been connected to increased COVID-19 risks [238–240]. It is worth noting that no links between SNPs in TFs STAT1, NFkB, and IRFs have been reported so far, and the search on individual predispositions for COVID-19 predisposition and severity has to be continued. Of note, the genes and SNPs mentioned in the review reflect the distinctive features of cytokine network and can appear to be universal clinical markers for viral-induced pneumonias (Table 2, Fig. 4).

6. Conclusions and future directions

Modulations of cytokine levels remain one of the most important strategies in pneumonia treatment [241]. First, cytokines are required for proper antiviral responses (proinflammatory) and further tissue repair (anti-inflammatory). Second, dysregulated cytokine profiles are risk factors for pneumonia predisposition and severity. Improper cytokine signaling may arise from hereditary factors, chronic metabolic and immune disorders, and therapeutic interventions, and consideration of all the listed factors is essential for pneumonia prognosis and successful treatment. Moreover, the associations between a growing number of newly discovered SNPs for cytokines, their receptors and TFs have not been found; however, these genetic variations can still be connected to certain forms of viral or bacterial pneumonias, and have to be considered in case of further epidemics. Moreover, the cytokine profiles are not uniformed within monocyte/MΦ subsets and other lung cell populations, and this diversity can serve as an important and more sensitive mechanism of immunomodulation. Phenotypic and genetic screening of individual patients may establish the most efficient cellular and molecular targets to prevent and overcome pneumonia and link the genetic variations found in comorbidity conditions and pneumonia.

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CRediT authorship contribution statement

Marina Dukhinova: Conceptualization, Writing - original draft, Writing - review & editing. **Elena Kokinos:** Visualization, Writing -

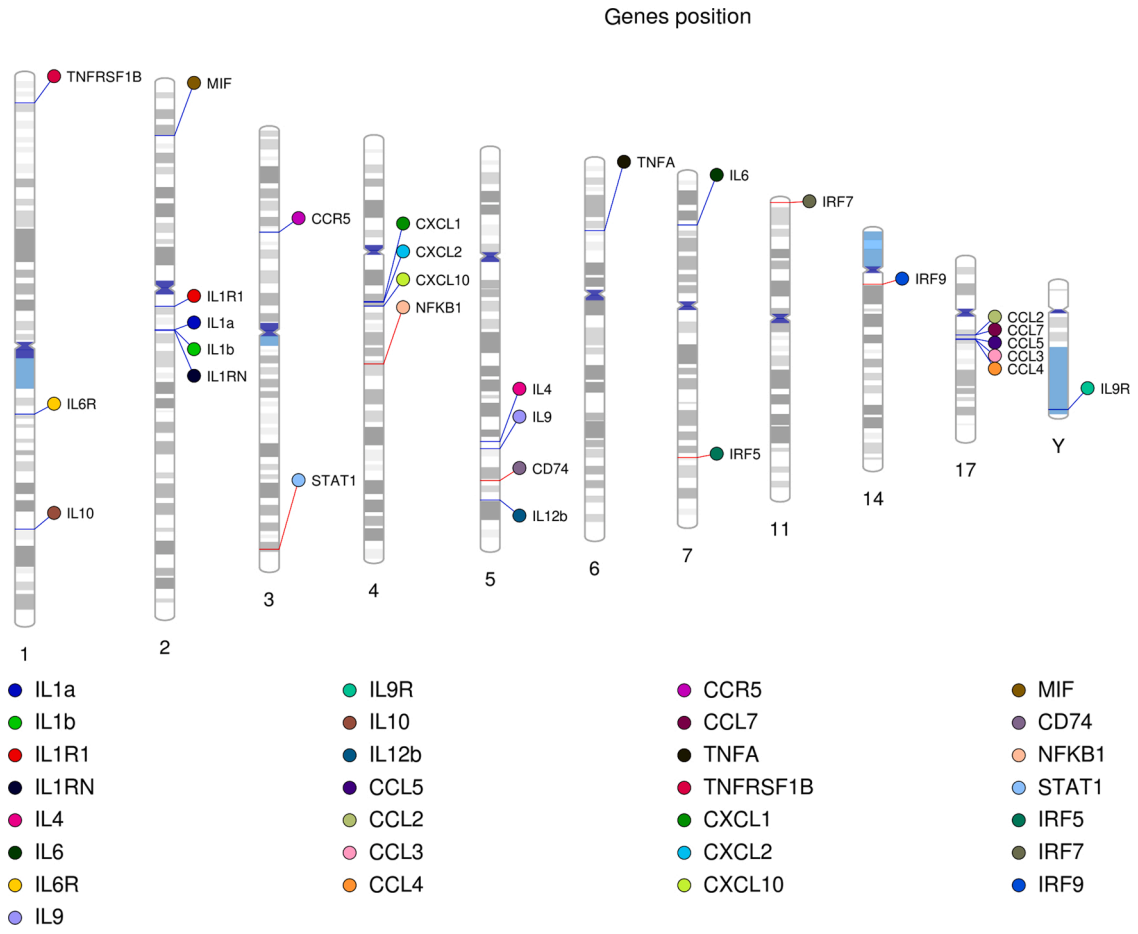

Fig. 4. Arrangement of cytokines and relevant transcription factors in the human genome. Certain genes are grouped in several genomic loci positioned on chromosome 2 (IL1α, IL1β, and their receptor), 4 (CXCL 1, 2, and 10), and 17 (CCL2-7). Transcription factors STAT1 and NFκB have been mapped to chromosome 3 (STAT1) and 4 in the proximity to the CXCL cytokine gene family (NFκB). The IRF transcription factors do not form a single group and are distributed between different chromosomes. Other cytokines and their receptors highlighted in the review also do not show any spatial correlations.

original draft. **Polina Kuchur:** Visualization, Writing - original draft. **Alexey Komissarov:** Writing - original draft, Writing - review & editing. **Anna Shtro:** Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest, financial or otherwise.

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