Review

UDC 616.23/.24-007.17-053.2-002+577.218+612.112.95+611.018.53
https://doi.org/10.56871/CmN-W.2026.48.58.016

Bronchopulmonary dysplasia: inflammation induced by exogenous factors and myeloid cells

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For citation: Loshkova E.V., Zhelev V.A., Yankina G.N., Mikhalev E.V., Budkin A.V., Terentyeva A.A., Lyulka T.S., Doroshenko I.V., Rafikova Yu.S., Golikova E.V., Rebrienko M.V., Fedosova M.V., Popova A.D., Khatkevich A.A. Bronchopulmonary dysplasia: inflammation induced by exogenous factors and myeloid cells. *Children's Medicine of the North-West.* 2026;14(1):200–218. (In Russ.). https://doi.org/10.56871/CmN-W.2026.48.58.016.

Received: 10.11.2025 **Revised: 16.01.2026** **Accepted: 20.03.2026**

ABSTRACT. Inflammation in the immature lung, triggered by oxygen toxicity and the formation of reactive oxygen species early on, is the primary cause of bronchopulmonary dysplasia in premature infants. Inflammation is characterized by activation of the innate immune response, with migration of predominantly macrophages and neutrophils and the release of proinflammatory cytokines. The degree of damage and disruption of subsequent lung development determine the severity of bronchopulmonary dysplasia, which leads to limited lung function. Based on observational studies of premature infants and experimental work in preclinical models, it has been demonstrated that excessive stimulation of proinflammatory signaling pathways leads to lung injury, but at the same time, the physiological activation of these pathways underlies physiological lung growth. This pathophysiological concept explains why suppression of individual pathways leads to an imbalance in the complex signaling network in the immature lung, with more severe inflammation and lung injury affecting the alveolar, mesenchymal, and vascular compartments. Therefore, the number of available drugs with proven efficacy for the prevention of bronchopulmonary dysplasia is currently limited. Evidence is accumulating that global suppression of the inflammatory response with corticosteroids leads to more severe limitations in lung function later in life, despite its high short-term effectiveness in improving gas exchange. Therefore, a detailed analysis of the immunophenotypes of myeloid cells and their associated gene and immune signatures will be useful for understanding the cellular and molecular genetic mechanisms of disease development and progression.

KEYWORDS: *bronchopulmonary dysplasia, preterm infant, inflammation, differential gene expression, monocytes, macrophages, gene signatures, immune signatures, M1/M2 macrophages*

Funding. This study was not supported by any external sources of funding.

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ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

Обзор

https://doi.org/10.56871/CmN-W.2026.48.58.016

Бронхолегочная дисплазия: воспаление, индуцированное экзогенными факторами и миелоидными клетками

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Для цитирования: Лошкова Е.В., Желев В.А., Янкина Г.Н., Михалев Е.В., Будкин А.В., Терентьева А.А., Люлька Т.С., Дорошенко И.В., Рафикова Ю.С., Голикова Е.В., Ребриенко М.В., Федосова М.В., Попова А.Д., Хаткевич А.А. Бронхолегочная дисплазия: воспаление, индуцированное экзогенными факторами и миелоидными клетками. *Children's Medicine of the North-West*. 2026;14(1):200–218. https://doi.org/10.56871/CmN-W.2026.48.58.016.

Поступила: 10.11.2025 **Одобрена: 16.01.2026** **Принята к печати: 20.03.2026**

РЕЗЮМЕ. Воспаление в незрелых легких, спровоцированное кислородной токсичностью и образованием активных форм кислорода на начальном этапе, является основной причиной бронхолегочной дисплазии у недоношенных детей. Воспаление характеризуется активацией врожденного иммунного ответа с миграцией преимущественно макрофагов и нейтрофилов и высвобождением провоспалительных цитокинов. Степень повреждения и нарушение дальнейшего развития легких определяют тяжесть бронхолегочной дисплазии, которая приводит к ограничению функции легких. Основываясь на наблюдательных исследованиях недоношенных детей и экспериментальных работах на доклинических моделях, доказано, что чрезмерная стимуляция провоспалительных сигнальных путей приводит к повреждению легких, но в то же время физиологический статус активации этих путей является основой физиологического роста легких. Эта патофизиологическая концепция объясняет, почему подавление отдельных путей приводит к дисбалансу сложной сигнальной сети в незрелом легком с более тяжелым воспалением и повреждением легких, затрагивающим альвеолярные, мезенхимальные и сосудистые отделы. Именно поэтому количество доступных препаратов с подтвержденной эффективностью для профилактики бронхолегочной дисплазии пока ограничено. В настоящее время накапливаются доказательства того, что глобальное подавление воспалительной реакции кортикостероидами приводит к более серьезным ограничениям функции легких в дальнейшем, несмотря на высокую краткосрочную эффективность в улучшении газообмена. И поэтому детальный анализ особенностей иммунофенотипов миелоидных клеток и ассоциированных с ними генных и иммунных сигнатур будет полезен для понимания клеточных и молекулярно-генетических механизмов развития и прогрессирования заболевания.

КЛЮЧЕВЫЕ СЛОВА: *бронхолегочная дисплазия, недоношенный ребенок, воспаление, дифференциальная экспрессия генов, моноциты, макрофаги, генные сигнатуры, иммунные сигнатуры, M1/M2 макрофаги*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that develops in preterm infants [1–5]. BPD affects up to 70% of children born extremely preterm and represents the second most common chronic lung disease in children after bronchial asthma (BA) [4, 6]. Our understanding of BPD pathophysiology has evolved continuously since the condition was first described as pulmonary fibrosis and emphysema by W.H. Northway in 1967 [5–8]. The consequences of BPD can be long-lasting and severe. In childhood, they include susceptibility to respiratory infections, an elevated risk of BA, and delayed physical and neurodevelopmental growth. In adolescence and adulthood, BPD is associated with diminished lung function and physical working capacity, as well as chronic non-communicable diseases [4, 5, 8–13]. Given the growing number of surviving preterm infants and the stable incidence of BPD with no downward trend, improving the monitoring and prognostication of this disease is critically important [14–18]. Identifying targets that minimize primary lung injury in preterm infants and restrain the damaging immune response, thereby promoting early repair, constitutes a critically important and unresolved clinical challenge. Myeloid cells, acting as immunoregulators, can fulfill these functions in the developing lung [19–21].

This literature review provides a detailed analysis of the mechanisms of lung injury, starting with hyperoxia as a factor that triggers inflammation. It also examines the phenotypic diversity of monocytes and macrophages migrating to the focus of pulmonary inflammation and thoroughly characterizes the differential gene expression and gene and immune signatures underlying BPD development. The literature search was performed in the Medline, PubMed, PubMed Central, and ClinicalTrials.gov databases using keywords that included the following search strings: "bronchopulmonary dysplasia is inflammation of the lungs," "bronchopulmonary dysplasia, monocyte inflammation in the lungs," "bronchopulmonary dysplasia, macrophages, inflammation in the lungs," "bronchopulmonary dysplasia is an inflammation of the lungs and myeloid cells," "bronchopulmonary dysplasia, inflammation, hyperoxia," "bronchopulmonary dysplasia inflammation immune signatures," and "bronchopulmonary dysplasia inflammation gene signatures." The search in international databases was focused on the period from 2019 to 2025.

FROM HYPEROXIA TO INFLAMMATION

Bronchopulmonary dysplasia is a multifactorial disease, and exposure to hyperoxia in the lungs of preterm infants contributes to immune response dysregulation, impaired alveolarization, and abnormal vascular development [22–28]. The adverse effects of hyperoxia include the generation of reactive oxygen species (ROS), which negatively affect the immature lung. These ROS-induced effects lead to mitochondrial dysfunction, alterations in gene expression, and an inflammatory response with the migration of myeloid cells into the pulmonary parenchyma (Fig. 1).

Numerous studies demonstrate the effect of hyperoxia on gene expression. In a hyperoxic mouse model of BPD, the expression levels of the angiogenic markers *FOXF1* and *c-KIT* were reduced. *FOXF1* is a forkhead family transcription factor important for the development of lung and gastrointestinal tract mesenchyme, while *c-KIT* encodes a receptor tyrosine kinase that plays an important role in hematopoiesis. Hyperoxia exposure during the first seven days of life decreased the number of *c-KIT* endothelial progenitor cells. Adoptive transfer of *c-KIT* endothelial cells improved angiogenesis and alveolarization [29].

Substantial changes in expression across all cellular compartments were observed in the largest study to date of developing mice exposed to hyperoxia, conducted by M. Hurskainen et al. [20]. In the lung parenchyma, the authors identified transcriptomic shifts in myofibroblasts, pericytes, and *Col13a1* fibroblasts. Col13a1 encodes the alpha chain of one of the non-fibrillar collagens, and these fibroblasts were among the most active cells in the hyperoxic lung model. The study further revealed a significant depletion of endothelial cells and an increase in alveolar type 1 cells following hyperoxia exposure [20, 21].

C. Revhaug et al. identified changes in gene methylation and transcriptome regulation in the lungs of mice ventilated with 85% oxygen from birth for 14 days. The PI3K-AKT pathway (an intracellular signaling pathway important in cell cycle regulation), associated with the immune system and the inflammatory response, was identified as a major target. Suppression of this pathway

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

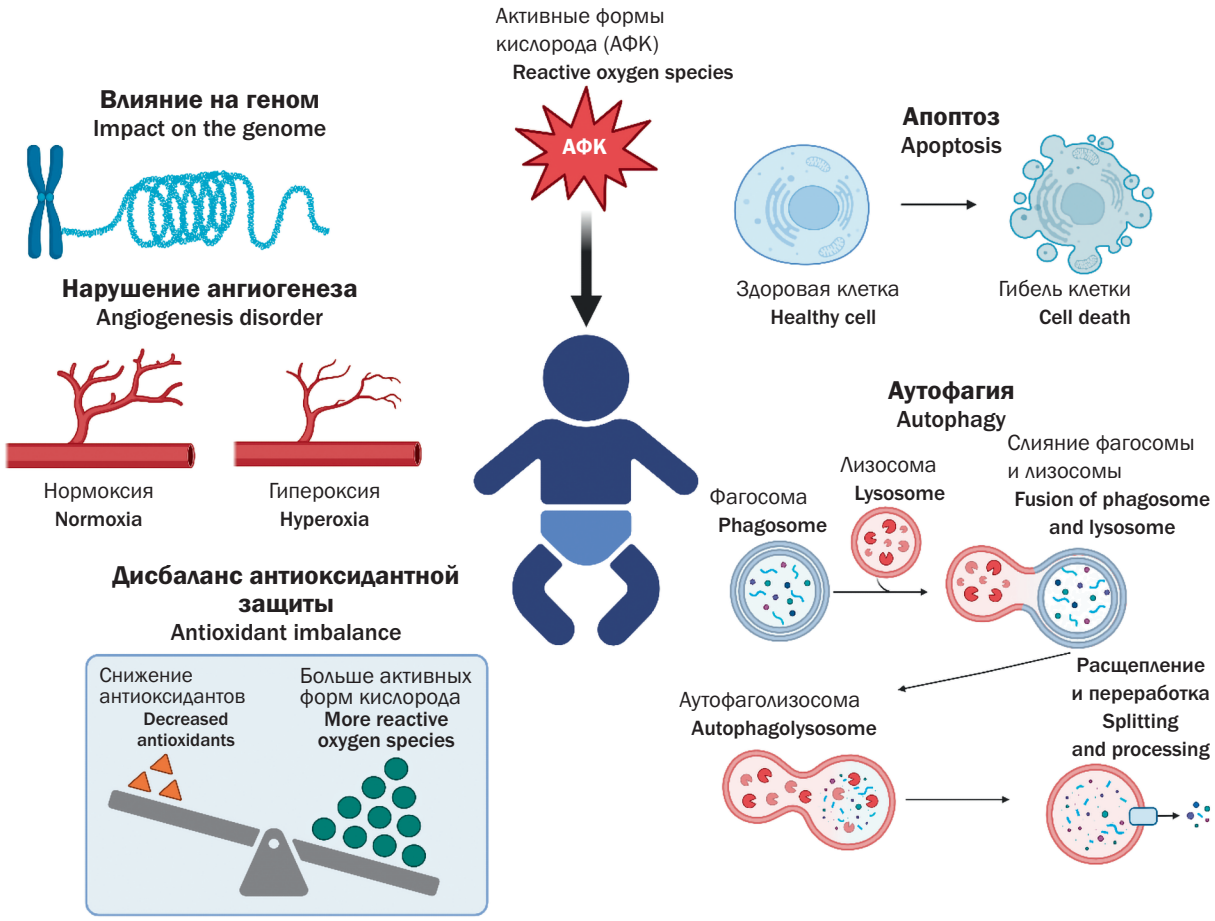

Fig. 1. The contribution of oxygen toxicity to the pathogenesis of bronchopulmonary dysplasia (created by I. Doroshenko, 2024)

Рис. 1. Вклад кислородной токсичности в патогенез бронхолегочной дисплазии (составлено И. Дорошенко, 2024)

contributed to increased susceptibility and an abnormal response to respiratory viruses [30].

In another experimental study conducted in 2017, the process of DNA methylation in genes involved in lung tissue growth and differentiation was analyzed. The researchers divided rat pups into two groups: group 1 was raised in room air (n=24), and group 2 was raised in an atmosphere containing 85% O_2 (n=26) from postnatal day 1 to 14. The rat pups exposed to hyperoxia had larger airspaces and thinner septa than those maintained in room air [31]. Further analysis revealed activation of the TGF-β signaling pathway involving key genes such as *TGFBR1, CREBBP,* and *CREB-1*. *CREBBP* functions as a transcriptional coactivator, linking various protein transactivators of transcription to the core transcriptional complex through protein–protein interactions, while *CREB-1* binds cyclic adenosine monophosphate (cAMP) and the DNA nucleotide sequence present in many viral and cellular promoters [31]. Overexpression of TGF-β1 during postnatal alveolarization in rat lungs leads to morphological, pathological, and biochemical changes corresponding to those observed in BPD in children.

IMBALANCE OF ANTIOXIDANT DEFENSE

When the balance between ROS production and antioxidant capacity is disrupted, oxidative reactions progress, ultimately resulting in cell and tissue damage through lipid peroxidation, DNA damage, and protein oxidation. The toxic effect of oxygen leads to the death of alveolar epithelium and capillary endothelium, the development of capillary dysplasia, impaired alveolarization, fibrosis, and pulmonary hypertension. It should be noted that the development of the antioxidant system occurs in parallel with surfactant synthesis during the third trimester of pregnancy; therefore,

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

the lung cellular structures of preterm infants remain insufficiently protected against peroxidation processes [1–5].

Inadequate activity of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) and endogenous antioxidants (vitamin E, glutathione, ceruloplasmin) has been reported [32]. Within the framework of antioxidant defense mechanisms, the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) represents a critical regulator of cellular defense mechanisms against xenobiotic and oxidative stress. However, studies show that the levels of antioxidants (vitamin A, vitamin E, and catalase) in preterm infants with BPD are significantly lower, whereas the level of malondialdehyde (a marker of lipid peroxidation), by contrast, is higher compared with term infants [8, 9, 32].

Research into the role of antioxidant enzymes such as SOD3 (superoxide dismutase 3) is ongoing. Notably, serum SOD3 levels are reduced in infants with extremely low birth weight, and the loss of SOD3 leads to dysregulation of gene expression involved in lung development [32].

Thus, at present, neonatal diseases can be classified as belonging to the spectrum of "oxygen radical diseases." Extremely preterm infants constitute a high-risk group due to the immaturity of their antioxidant system. Currently, active research continues not only into the role of the latter in the development of perinatal diseases but also into the design of therapeutic interventions [33].

IMPAIRED ANGIOGENESIS

Hypoxia-inducible factor HIF-1α is one of the principal transcription factors governing the expression of a number of genes required for cellular adaptation to hypoxia [34]. This factor regulates fetal growth and development under hypoxic conditions and is, therefore, rapidly degraded under hyperoxia or normoxia. Loss of HIF-1α in mice leads to embryonic lethality; the surviving embryos exhibit multiple cardiac malformations and abnormally dilated blood vessels.

VEGFA (vascular endothelial growth factor A) is a key factor in vascular development and a mediator of endothelial NO synthesis. Vascular growth encompasses two main processes: vasculogenesis, the formation of new blood vessels from endothelial cells in the mesenchyme, and angiogenesis, the formation of new blood vessels from sprouts of pre-existing vessels [15, 35]. Both hyperoxia and mechanical ventilation inhibit pro-angiogenic VEGF signaling in rodents and rabbits, and the inhibition of VEGF signaling is accompanied by reduced alveologenesis and angiogenesis in many animal species [35]. For example, the expression of VEGF and one of its receptors (VEGF-R1) is decreased in a BPD model in preterm baboons. Ventilation of two-day-old mice with 40% O_2 reduces the expression of VEGF-A and VEGF-R2 genes and proteins in the lungs and leads to structural lung abnormalities corresponding to BPD [35].

A number of studies demonstrate reduced levels of additional pro-angiogenic factors. Specifically, NO acts downstream of HIF and VEGFA in the signaling cascade and is suppressed by ROS-induced injury; ROS attenuate NO signaling and stimulate the growth and phenotypic modulation of smooth muscle cells, as well as pulmonary vascular remodeling. eNOS expression levels are decreased in lambs exposed to hyperoxia [23].

Reduced levels of Tie-2 (the angiopoietin receptor, expressed exclusively in endothelial cells of mice, rats, and humans) and Ang-1 (a member of the family of vascular growth factors that play a role in embryonic and postnatal angiogenesis) have been detected in preterm infants on mechanical ventilation. Moreover, Ang-1 expression is decreased in mouse pups exposed to hyperoxia [21, 23].

MYELOID CELL DYSFUNCTION

It has been shown that macrophage activation in mice with hyperoxia-induced BPD leads not only to epithelial cell apoptosis and pulmonary parenchymal injury but also affects fibroblasts and endothelial cells, causing matrix remodeling and impaired pulmonary vascularization [23]. The transcription factor Klf4 is known to participate in transcriptional regulation in many diseases, including BPD, and Klf4 can induce macrophage polarization by interacting with Stat6. Klf4 can influence not only monocyte differentiation but also the expression of genes characteristic of M1 and M2 macrophages, such as iNOS and Arg1 [36]. In a study by Y. He et al., increased M1 macrophage infiltration and decreased Klf4 expression were detected in the lungs of mice with BPD [24].

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

C. Leek et al. found that immediately after birth and on day 7 of hyperoxia exposure, a significant reduction in the total number of alveolar macrophages (AMs) was observed in the hyperoxia-exposed lung compared with the normoxic control. This reduction was observed in both male and female mice. SiglecF-low AMs (SiglecF, sialic acid-binding Ig-like lectin F) represent monocyte-derived macrophages that exhibit an intermediate phenotype along the continuum of differentiation into AMs [37]. Siglecs (sialic acid-binding immunoglobulin-type lectins) are sialic acid-specific lectins with an immunoglobulin-like structure that interact with sialic acid on the cell surface. They are expressed predominantly by immune cells and regulate cell proliferation, differentiation, apoptosis, and intercellular interactions. Interestingly, the number of SiglecF-high AMs decreased following hyperoxia exposure, and this was followed by a corresponding increase in the number of SiglecF-low AMs. No depletion of AMs was observed by day 14 or day 21 in either female or male mice. On day 21, the number of interstitial macrophages in the hyperoxia-exposed lungs was reduced compared with the control group. Overall, neonatal hyperoxia exerts differential effects on the abundance of myeloid cell subpopulations, with the most marked changes observed in AMs [37].

MONOCYTES AND MACROPHAGES IN THE MECHANISMS OF BRONCHOPULMONARY DYSPLASIA DEVELOPMENT

To understand the early changes in the neonatal immune response that give rise to the persistent inflammation associated with BPD development at the cellular level and beyond, research attention has been focused on one of the inflammatory mechanisms — the characterization of monocyte subtypes at birth and throughout the neonatal period. Pulmonary monocytes and macrophages are key players in innate immunity that undergo a complex maturation process and, in newborns, perform diverse functions, including lipopolysaccharide (LPS)-induced activation, IFN-γ-mediated and IL-10-mediated responses, and Fc receptor-dependent phagocytosis [28, 38, 39]. Several macrophage immunophenotypes are distinguished. Thus, M1 macrophages represent a pro-inflammatory macrophage phenotype (classically activated), the key cells of innate immunity responsible for host defense. They are activated by interferon gamma (IFNγ) and lipopolysaccharides, eliminate pathogens (bacteria and viruses) and tumor cells, and produce reactive oxygen species and pro-inflammatory cytokines (TNF-α, IL-12). M2 macrophages represent a functional macrophage phenotype that mediates an anti-inflammatory response, tissue repair (regeneration), and the suppression of immune reactions. They are activated by IL-4 and IL-13, promote wound healing, tissue remodeling, and the clearance of apoptotic cells, and can also stimulate tumor growth.

A.C. Windhorst et al. established that monocyte subtypes differ between preterm and term neonates. Specifically, CD14++CD16+ (intermediate) monocytes were more frequently present in term infants, whereas elevated levels of non-classical monocytes (CD14+CD16++) were characteristic of preterm infants developing BPD. Both monocyte subtypes were the main source of intracellular TNF-α expression. Multifactorial modeling of protein profiles identified FGF2, sIL-2Rα, MCP-1, MIP-1a, and TNF-α as predictors of BPD. It has been confirmed that TNF-α, IL-6, and IFN-α are the most highly activated cytokines in severe BPD [40].

L.C. Eldredge et al. identified a predominance of CD14+CD16+ and CD14+CD16– monocytes in tracheal aspirates from ventilated patients with a gestational age of less than 29 weeks and aged less than 30 days. Moreover, the mRNA expression of IL-1A, IL-1B, and IL-1 receptor antagonist genes was elevated in monocytes obtained from tracheal aspirates on days 7, 14, and 28 of life compared with monocytes obtained on day 3 of life. This study confirms that early alterations in monocyte-specific pathways of the IL-1 cytokine family — a potent pro-inflammatory cytokine — may be associated with the development of BPD [41]. In contrast, low production of anti-inflammatory cytokines, particularly IL-10, is observed in the setting of BPD [42]. Comparable cytokine profiles can also be observed in animals (mice, sheep) receiving mechanical ventilation (hyperoxia).

It has been demonstrated that the development of BPD is associated with an increase in intermediate monocytes and the persistence of high levels of non-classical monocytes, as well as with high expression of TNF-α, IL-6, IL-8, MCP-1, MIP-1a, IL-1Rα, sIL-2Rα, EGF, and FGF2. The described signature (a unique molecular profile) is associated with monocyte activation, proliferation, chemotaxis, and myeloid cell

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

recruitment [40]. These findings are consistent with transcriptome analysis, which revealed that TNF-α, IL-2, IL-6, IL-10, and interferons are the most highly activated cytokines in patients with moderate and severe BPD. With regard to the functional significance for BPD development, TNF-α and IFN-γ signaling are known to drive polarization of the pro-inflammatory monocyte and macrophage phenotype, enhancing the extravasation of these cells and the accumulation of AMs. Moreover, these cytokines exhibit considerable pro-fibrotic potential [43].

The picture of monocyte and granulocyte activation revealed by protein and transcriptome analyses is further illustrated by the activation network of genes involved in immune cell regulation, cell-matrix interactions, and remodeling (IL-6, TNF-α, CXCL9, LGALS3, MMP7, TLR3, IL-10, TCR, LAT) in BPD. The differential expression of genes involved in leukocyte chemotaxis and eosinophil accumulation (*CAT, CDH13, IL-10, LGALS3, TNFRSF1A, BID, TF, ZFP36)* was regulated by TNF-α [39]. Mild BPD manifestations were associated with the involvement of the Wnt1 pathway and increased IL-5 expression [44].

The predominance of non-classical and intermediate monocyte subtypes, confirmed by a characteristic transcriptome and protein signature, reflects processes critical for BPD development. The identification of distinct developmental pathways from circulating monocytes to lung macrophages highlights the potential of specific monocyte subtypes to make differential contributions to the populations of alveolar, interstitial, and pulmonary intravascular macrophages [45]. Whereas non-classical blood monocytes give rise to intravascular macrophages in the lungs, classical monocytes have been associated with interstitial and alveolar macrophages. Intermediate CD14+ monocytes expressing macrophage markers represent transitional stages of monocyte-to-macrophage differentiation. The role of macrophages, including their influence on growth factor production and their association with a pro-fibrotic phenotype, underscores their potential as critical regulators of BPD development [46].

INTERCELLULAR INTERACTIONS BETWEEN MACROPHAGES, ALVEOLAR EPITHELIAL CELLS, AND ENDOTHELIAL CELLS IN BRONCHOPULMONARY DYSPLASIA

Y. He et al. assessed intercellular communication and found that, among signal-sending cells, alveolar epithelial type I cells (AT1) exhibited the greatest number and strength of interactions with other cell types. In contrast, among signal-receiving cells, CAR4+ endothelial cells displayed the greatest interaction strength. It is known that pulmonary endothelial cells (ECs) are essential participants in gas exchange. Despite this, the extent and function of EC heterogeneity in the lungs remain incompletely understood. To date, several EC populations have been identified, including macrovascular endothelium (maEC), microvascular endothelium (miEC), and a novel population of Car4-high ECs. Car4-high ECs express a unique gene signature, and ligand–receptor analysis indicates that they are poised to receive reparative signals from AT1 cells. Following acute injury, they are predominantly localized to regenerating regions of the alveoli [24].

A close relationship exists between macrophages and alveolar epithelial cells. Macrophages participate in the following signaling pathways as signal-receiving cells.

- SEMA3 (the semaphorin-plexin signaling pathway, Sema3/Plexin) represents a series of molecular interactions initiated by the binding of semaphorin receptors (including plexins and neuropilins) to their ligands. This pathway plays a key role in the development of the nervous system, in particular by guiding axonal growth and contributing to the formation of neural connections. Beyond nervous system development, the semaphorin-plexin pathway is involved in the regulation of cell migration and angiogenesis, as well as in immune responses. For example, Sema3A, a member of the semaphorin family, has been studied for its effects on thymocyte (thymus cell) functions, including proliferation, migration, and adhesion.
- MIF (macrophage migration inhibitory factor) activates various signaling pathways that influence cell growth, survival, and the immune response. Key signaling pathways engaged by MIF include MAPK (ERK1/2) and NF-κB, as well as interactions with Toll-like receptor 4 (TLR4) and chemokine receptors. MIF can activate MAPK pathways such as ERK1/2, thereby promoting cell proliferation, including that of tumor cells. MIF activates the NF-κB pathway, leading to increased production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8. MIF upregulates TLR4 expres-

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

sion, which enhances the immune response to Gram-negative bacteria. MIF can interact with chemokine receptors (e.g., CXCR2 and CXCR4), thereby influencing cell migration. MIF can inhibit apoptosis (programmed cell death), which is important for maintaining cell survival under conditions of inflammation and tumor growth.

- GALECTINS (galectins) are a family of carbohydrate-binding proteins involved in various cellular processes, including adhesion, migration, proliferation, and apoptosis. Galectin signaling pathways, such as galectin-3/SMAD and galectin-9/Tim-3, play an important role in the development of diseases, including fibrosis and the immune response. *Galectin-3* and *the TGF-β/SMAD* signaling pathway — galectin-3 can activate this pathway, leading to fibrosis and scar tissue formation, and also promotes the translocation of transcription factors into the nucleus for collagen synthesis. The galectin-9/Tim-3 signaling pathway is an important regulatory mechanism for immune cells such as natural killer (NK) cells. Galectins, including galectin-1, galectin-3, galectin-9, and galectin-12, are involved in the development of leukemia by influencing the growth, differentiation, and survival of cancer cells.
- CXCL (chemokine (C-X-C motif) ligand) is a family of chemokines, proteins involved in the recruitment and activation of leukocytes (immune cells). They play an important role in inflammation, the immune response, the development of lymphoid organs, and other biological processes.
- CCL (C-C motif ligand, chemokines with a C-C motif) represents a subfamily of chemokines. The CCL subfamily, in particular, plays an important role in inflammatory processes, during infection, organ and tissue injury, and in lymphocyte migration. The CCL subfamily is characterized by the presence of two adjacent cysteines (without an intervening amino acid) in the amino acid sequence of the chemokines. CCL chemokines primarily attract monocytes, macrophages, eosinophils, and lymphocytes, thereby regulating the immune response to various pathological processes.

At the same time, macrophages act as signal senders, participating in GRN (Gene Regulatory Network) signaling pathways. These pathways represent a cascade of intracellular reactions initiated by the binding of a growth factor to its receptor on the cell surface. This pathway plays a key role in the regulation of cell growth, differentiation, survival, and many other cellular processes, as well as in CCL signaling.

MIF is a pleiotropic cytokine and one of the key factors in intercellular communication. MIF is antagonistic to glucocorticoids and prolongs the survival of inflammatory cells [47]. It should be noted that adequate MIF levels are required for lung development, since both MIF deficiency and overexpression in neonatal mice have been shown to cause alveolar and vascular abnormalities. It has been established that MIF signaling involves two pathways. MIF signaling between AT2 cells and endothelial cells may be required for alveolarization and angiogenesis, whereas the involvement of macrophages in MIF signaling following hyperoxia may promote inflammation and impair lung maturation [24].

In the control group, among all pro-inflammatory macrophages (CD86+), the Cybb protein was expressed in 60.1% of cells, whereas in patients with BPD it was expressed in only 4.6% ($p < 0.05$). Thus, Cybb expression in M1 macrophages is significantly reduced in BPD.

It was also established that in the control group, 86.5% of all Cybb-expressing cells simultaneously co-expressed the pro-inflammatory macrophage marker CD86. In BPD, this proportion was only 7.3% ($p < 0.05$). This indicates that the co-expression of Cybb and CD86, a marker of pro-inflammatory macrophages, is impaired in BPD [24].

It has been shown that alveolar epithelial cells actively interacted with macrophages via MIF-(CD74+CD44) signaling pathways. Macrophages were more active and engaged in more extensive interactions with alveolar epithelial cells in mice with BPD through MIF-(CD74+CD44) signaling. It should be noted that M1 macrophages play an important role in the development of lung injury in BPD. This role correlates with a specific reduction in Cybb gene expression and its end product in macrophages, as well as with the potential activation of MIF signaling pathways.

FEATURES OF THE GENETIC REGULATION OF INTERCELLULAR INTERACTIONS

It has been established that differentially expressed genes in mice with BPD are enriched for leukocyte migration and M1 macrophage infil-

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

tration of the lungs. The influence of hub genes (*Cybb, Papss2, F7, Fpr2*) has been confirmed at the single-cell level. Specifically, reduced *Cybb* expression is associated with M1 macrophage infiltration. In an experimental study, Yi He et al. from China identified 16 hub genes associated with immune system function. Subsequently, single-cell identification analysis was performed using data from 65,733 cells (38,223 cells from the BPD group and 27,510 cells from the control group). It was shown that, of the 65,733 single cells, 2,492 were classified as alveolar macrophages and 5,447 as other macrophage types. Cell source analysis revealed that the *Cybb, Fpr2,* and *F7* genes were highly expressed in macrophages in both the BPD group and the control group. Among the total number of single cells, 12,615 cells expressed the *Cybb* gene (19.19%), representing the highest percentage among the three genes. At the next stage, to assess the functional role of the identified genes, the researchers evaluated hub gene expression between the BPD group and the control group using scRNA-seq data and demonstrated that *Cybb* gene expression was reduced in the BPD mouse group. Comparison of *Cybb* gene expression at the single-cell level between BPD mice and wild-type mice also showed that this reduction was primarily attributable to lower mean expression and a lower percentage of *Cybb*-positive cells in macrophages in BPD mice compared with wild-type mice. These results indicate that *Cybb* expression was predominantly reduced in macrophages under hyperoxic conditions [24]. It should be noted that hub genes are genes that play a key role in metabolic pathways, possess a large number of connections with other genes, and exert a significant influence on cell function. Alterations in the expression or activity of hub genes may be associated with specific diseases and conditions, making them useful for the diagnosis and monitoring of various diseases.

The CYBB protein, also known as NOX2 or gp91phox, is a transmembrane subunit of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, also referred to as cytochrome b-245 [48]. CYBB is a key component of NADPH oxidase, an enzyme complex that generates superoxide, a reactive oxygen species. CYBB is a transmembrane protein composed of two subunits: alpha and beta. Mutations in the *CYBB* gene lead to chronic granulomatous disease, since a deficiency of functional CYBB protein impairs the ability of immune cells to effectively combat infections. The CYBB protein is localized to cellular membranes, primarily within phagosomes (intracellular compartments where pathogen degradation takes place).

Cybb is a gene associated with enhanced inflammatory infiltration of lung tissue by macrophages. It encodes gp91phox (NOX2), a component of the phagocytic NADPH oxidase (NOX) family, which primarily generates ROS. *Cybb* is required not only for microbial killing and host defense but also for immune and inflammatory regulation. Studies have demonstrated an important role for *Cybb* in LPS-induced lung injury [24, 48, 49]. In particular, *Cybb* expression in macrophages appears to play a protective role in the aseptic inflammatory response. Germ-free *Cybb*-deficient mice developed spontaneous lung inflammation independently of the microbiota composition. Moreover, *Cybb*-deficient alveolar macrophages tended toward pro-inflammatory responses with an enhanced cytokine response and gave rise to an immunoactivated CD11bhigh subpopulation following sterile stimulation, such as with Toll-like receptor agonists [49]. In a mouse model of zymosan-induced systemic inflammatory response syndrome, *Cybb* deficiency in mice was associated with elevated chemokine levels, neutrophil infiltration, platelet activation, and thrombosis, suggesting an anti-inflammatory role for *Cybb*, particularly alveolar macrophage-derived *Cybb* [50]. Furthermore, *Cybb*-deficient macrophages exhibited enhanced transcriptional priming of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. In addition, they triggered post-translational activation of NLRP3 through increased K^+ efflux and mitochondrial damage [51]. In a study by Y. He et al., a specific reduction in *Cybb* expression was detected in lung macrophages under hyperoxic conditions [24]. Such an abnormal pattern of *Cybb* expression under hyperoxia may adversely affect lung development and homeostasis. Interestingly, the *Cybb* gene, which is located on the X chromosome, may be responsible for sex-dependent BPD phenotypes.

INFLUENCE OF SEX ON THE TRANSCRIPTOME, DIFFERENTIATION, AND FUNCTIONS OF MACROPHAGES

Sex-dependent differences in macrophage diversity and function have been identified in many

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

diseases [37, 52, 53]. In an experimental study, C. Leek et al. detected sex-specific differences in the differential gene expression (DGE) of macrophages. In female mice, 132 DEGs were identified (71 upregulated, 61 downregulated) compared with the normoxic control. In contrast, in male AMs, 58 DEGs were identified (26 upregulated, 32 downregulated) [37]. One of the highly expressed genes in hyperoxia-exposed AMs was the gene encoding extracellular matrix protein 1 (*ECM1*), which plays an important role in macrophage polarization. *ECM1* is actively expressed in macrophages, particularly in those infiltrating tissues under inflammatory conditions. Macrophage-specific knockout of *ECM1* increases the expression of arginase 1 (ARG1) and impairs polarization toward the M1 macrophage phenotype. Macrophage-specific knockout of *ECM1* ameliorates pathological changes in a mouse model of inflammatory bowel disease, highlighting the importance of *ECM1* in M1 macrophage polarization. The expression of the *Fcna* gene (Ficolin A) is also increased in hyperoxia-exposed AMs; it mediates complement activation and enhances pro-inflammatory responses in the lungs [37].

The gene encoding fatty acid-binding protein 4 (Fabp4) is an adipokine and one of the most strongly suppressed genes; it regulates inflammation and angiogenesis. Interestingly, Fabp4 expression was increased in peribronchial vessels of neonates with BPD and enhanced angiogenesis [54]. The gene encoding pyruvate dehydrogenase kinase 4 (Pdk4) was also suppressed in hyperoxia-exposed AMs. Pdk4 plays an important role in the metabolic reprogramming of macrophages [55, 56]. The DEGs identified in the study by C. Leek et al. were associated with the cell cycle, DNA integrity and apoptosis, myeloid cell differentiation, leukocyte migration, and interferon-beta production. Macrophages play a key role in interferon signaling owing to their dual function: they serve as important producers of interferon and exhibit high sensitivity to it [37].

In the study by C. Leek et al., one of the unique genes with increased expression in female AMs was the prolactin receptor gene *Prlr* (prolactin receptor), which is expressed in macrophages and modulates local inflammatory responses, angiogenesis, phagocytosis of apoptotic cells, and cytokine production [37]. Prolactin has been shown to increase heme oxygenase-1 expression and vascular endothelial growth factor production in human macrophages, indicating its potential role in angiogenesis. In males, AMs exhibited increased expression of the gene encoding secreted phosphoprotein 1 (*Spp1*). *Spp1*, or osteopontin, is an arginine-glycine-aspartate-containing adhesive glycoprotein produced by AMs [57]. *Spp1* plays an important role in the recruitment and accumulation of myeloid cells at sites of injury. *Spp1* in lung macrophages stimulates fibrotic processes and macrophage polarization toward a pro-fibrotic phenotype [57].

In the study by C. Leek et al., it was found that pathways associated with DNA damage and IFN-β, glucose and carbohydrate metabolism, ossification, and aging were positively enriched in AMs from female mice. In contrast, oxidative phosphorylation and the tricarboxylic acid cycle were negatively enriched in AMs from male mice [37]. Loss of Klf4 increased macrophage polarization similarly to that observed with LPS or IFN-γ stimulation, and hyperoxia reduced Klf4 expression in macrophages *in vitro*. Interferon regulatory factors play a crucial role in macrophage function and differentiation. *Irf1* plays an important role in enhancing the myeloid cell response to IFN-γ and in myeloid cell development. *Irf2* inhibits the expression of glycolytic genes and pro-inflammatory responses. *Irf4* is critically important for the synergistic macrophage response induced by IL-4. Runx2, a transcription factor known primarily for its role in bone metabolism, also substantially influences macrophage function, particularly during inflammation and tissue remodeling. The expression levels of these transcription factors in male and female AMs did not differ according to sex or treatment, suggesting that transcription factors may bind differently to chromatin in male and female AMs under hyperoxic conditions.

Furthermore, C. Leek et al. assessed the influence of sex on AM gene activity across all developmental periods. They found that three genes exhibited high expression in hyperoxia-exposed females: integrin subunit alpha M (*ITGAM*, the gene encoding CD11b protein), C-type lectin domain family 5 member A (Clec5a), and guanylate binding protein 3 (*Gbp3)* [37]. *ITGAM* and CD11b play an important role in macrophage functions, including adhesion, migration, and phagocytosis. Guanylate binding protein 3 (Gbp3) is a member of the guanylate binding protein (GBP) family, a group of intracellular guanosine triphosphatases

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

induced by IFN-γ. It also plays a role in macrophage activation and the immune response [58]. *Clec5a* modulates macrophage function and contributes to the pathophysiology of chronic lung diseases, including chronic obstructive pulmonary disease [59, 60]. No differentially expressed genes were detected in male AMs in response to hyperoxia.

Chromatin remodeling was more pronounced in female prenatal myeloid cells, whereas the Wnt signaling pathway was more pronounced in males. Postnatal female myeloid cells were enriched for pathways associated with leukocyte migration, whereas male cells were enriched for pathways associated with the cellular response to TGF-β [37].

Furthermore, the expression of sex-specific genes was higher in pro-inflammatory CD14+CD16– monocytes (279 genes) than in double-positive non-classical (or patrolling) CD14+CD16+ monocytes (33 genes). Male CD14+CD16– monocytes were enriched for inflammatory pathways associated with IL-1, TNF, and neutrophil degranulation. Female monocytes were enriched for genes related to oxidative stress-induced senescence, chromatin remodeling, oxidative phosphorylation, and the response to IFN-α in both monocyte classes. Metabolic pathways differed markedly according to sex in both CD14+CD16– and CD14+CD16+ monocytes. Carbohydrate metabolism and glycolysis were enriched in male cells, whereas oxidative phosphorylation and associated pathways were enriched in female cells [37]. D. Sahoo et al. showed that apoptosis and cell death were more pronounced in female AMs. Male AMs were positively enriched for pro-inflammatory pathways, nitric oxide generation, and T-cell activation, and negatively enriched for the aerobic electron transport chain and oxidative phosphorylation [61].

Thus, sex influences AM function and polarization. The balance between the pro-inflammatory and anti-inflammatory roles of macrophages is critically important in the progression of lung injury. *In vitro*, classically activated macrophages (M1) secrete pro-inflammatory mediators such as TNF-α and ROS in the acute phase, whereas alternatively activated macrophages (M2) participate in the resolution of inflammation and tissue repair at a later phase. Studies have shown that alveolar macrophages from female mice express higher levels of M2 genes, indicating sex-dependent differences in macrophage polarization.

CONCLUSION

Elucidating the patterns of immune cell infiltration of the pulmonary parenchyma and the key immunomodulators involved may facilitate targeted therapeutic interventions directed at inflammation, which is of vital importance for improving the treatment of BPD. The study of immune signatures represents a promising avenue toward the development of anti-inflammatory therapeutic approaches.

Based on the results of published studies, distinct immune and gene signatures have been successfully identified in monocyte and macrophage samples from preterm infants with BPD at various time points after birth, complemented by comprehensive protein and transcriptome profiling. The immune response identified in preterm infants with BPD holds immense potential for the development of diagnostic and therapeutic strategies. However, future studies with larger patient cohorts are required to determine the differential impact of prenatal complications and genetic background on disease characteristics.

Thus, the diversity of pathophysiological mechanisms leading to the development and progression of bronchopulmonary dysplasia warrants in-depth investigation in experimental and clinical studies. With each passing year, our understanding of the pathogenesis of this chronic lung disease, which manifests in infancy, continues to expand. This will ultimately enable the delineation of the phenotypic heterogeneity of the disease and the implementation of a personalized approach to the prevention and treatment of bronchopulmonary dysplasia.

ADDITIONAL INFORMATION

Authors' contribution. E.V. Loshkova — scientific concept of the publication, structure, research and data analysis, writing, discussion of the manuscript and verification of the content, final approval of the manuscript for publication; T.S. Liulka — research and data analysis, structure, writing, technical editing; I.V. Doroshenko — research and data analysis, structure, writing, drawing preparation, technical editing; A.V. Budkin, Yu.S. Rafikova A.A. Terentieva, G.N. Yankina, E.V. Mikhalev, M.V. Rebrienko, A.D. Popova — discussion of the manuscript; V.A. Zhelev — control of deadlines; M.V. Fedosova — discussion

ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

of the manuscript, stylistic editing of text and technical editing.

All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Е.В. Лошкова — научная концепция публикации, структурирование материала, поиск и анализ источников литературы, написание статьи, обсуждение рукописи и проверка содержания, окончательное утверждение рукописи для публикации; Т.С. Люлька — поиск и анализ литературы, структурирование материала, написание статьи, техническое редактирование; И.В. Дорошенко — поиск и анализ литературы, структурирование материала, написание статьи, подготовка рисунков, техническое редактирование; А.В. Будкин, Ю.С. Рафикова, А.А. Терентьева, Г.Н. Янкина, Е.В. Михалев, М.В. Ребриенко, А.Д. Попова — обсуждение рукописи; В.А. Желев — контроль сроков выполнения; М.В. Федосова — обсуждение рукописи, стилистическое редактирование текста и техническое редактирование.

Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)

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ISSN 3034-6312 (Print) ISSN 3034-6320 (Online)