Фтизиопульмонология
Phthisiopulmonology

Received by the Editorial Office: May 15, 2026
Accepted for publication: June 14, 2026
Published online: June 30, 2026
УДК: 616.24-008.4-053.32
DOI: 10.26212/2227-1937.2026.26.79.007

BRONCHOPULMONARY DYSPLASIA: FROM IMPAIRED ALVEOLOGENESIS TO MOLECULAR AND CELLULAR DYSREGULATION IN PRETERM NEWBORNS

Abilbayeva A.A.[1], Shaktay N.K.[1], Tarabayeva A.S.[1], Kuat A.[1], Nurym K.[1], Sagidulla A.[1]
[1]Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan

Introduction. Bronchopulmonary dysplasia (BPD) remains the most common chronic lung disease in preterm neonates, particularly those with very low birth weight. The "new BPD" paradigm has shifted from the classical injury-driven fibrosis toward a process characterized by arrested alveolar development and vascular dysgenesis. This condition results in a reduced surface area for gas exchange due to the formation of fewer, simplified alveoli and impaired angiogenesis.
Objective. The purpose of this review is to provide an integrative analysis of the cellular and molecular dysregulation driving BPD pathogenesis, focusing on the disruption of intercellular signaling networks that govern alveolar morphogenesis and vascular development in the immature preterm lung.
Materials and Methods. An integrative narrative literature review was performed. The electronic databases PubMed and Google Scholar were systematically searched for articles published between January 2010 and March 2025. Search queries included the terms "bronchopulmonary dysplasia", "alveologenesis", "angiogenesis", "signaling pathways", "lung development" and "preterm infants". Only articles published in English were considered. Inclusion criteria comprised peer-reviewed original research articles and comprehensive review articles that directly addressed molecular, cellular, or signaling mechanisms of BPD or normal alveologenesis. Exclusion criteria encompassed conference abstracts, non-peer-reviewed sources, editorials lacking primary data, and studies without sufficient methodological detail. Duplicate records were manually removed prior to full-text screening. Of the 374 unique records identified, 301 were excluded following title and abstract screening. The remaining 73 articles met all inclusion criteria after full-text review and were incorporated into the final synthesis. This review is integrative and narrative. It does not meet the formal criteria for a systematic review, as a non-systematic selection flowchart was generated and no inter-rater agreement or quality assessment tool was used.
Results. A synthesis of 73 publications, including experimental studies, transcriptomic and proteomic analyses, clinical investigations, and review articles, identified three pathogenetic mechanisms with the highest degree of evidentiary support. PDGFRα-dependent depletion and proliferative failure of alveolar myofibroblasts emerged as the central driver of alveolar simplification, corroborated by convergent preclinical and clinical genetic data. VEGF-A deficiency was established as the molecular correlate of capillary dysplasia, documented both in fatal human BPD and across multiple animal models. TGF-β hyperproduction was identified as the principal pro-fibrotic and anti-septogenic signal that concurrently suppresses VEGF-A expression, thereby amplifying vascular and structural deterioration. Normal alveologenesis depends on coordinated interactions among four functionally interdependent cellular systems, namely the alveolar epithelium represented by ATII and ATI cells, the pulmonary mesenchyme including secondary-crest myofibroblasts and lipofibroblasts, the vascular endothelium, and the extracellular matrix. Disruption of this intercellular network at multiple levels constitutes the pathobiological basis of BPD. Mesenchymal stromal cell-based therapy demonstrates consistent efficacy in preclinical models. However, its clinical translation remains limited by the absence of Phase III randomized controlled trial data in preterm neonates.
Discussion. The synthesized evidence indicates that BPD should be interpreted not as isolated epithelial, vascular, or mesenchymal injury, but as a disorder of coordinated lung development. The convergence of PDGFRα attenuation, VEGF-A deficiency, and TGF-β overactivation supports a hierarchical pathogenetic model in which impaired myofibroblast function initiates defective septation and secondarily disrupts vascular growth. At the same time, much of the mechanistic evidence is derived from animal and preclinical models; therefore, translation into neonatal practice requires cautious interpretation and validation in adequately powered clinical studies.
Conclusion. BPD represents a significant failure of lung development, primarily resulting from impaired intercellular communication. The characteristic structural abnormalities, including alveolar simplification and vascular dysmorphism,

arise from disrupted regenerative capacity within the lung. Attenuation of PDGFRα-dependent myofibroblast function is identified as the central upstream event, leading to secondary suppression of VEGF-A and subsequent capillary dysplasia. TGF-β further exacerbates structural deterioration. Effective therapeutic strategies should focus on restoring the myofibroblast-VEGF-extracellular matrix axis as an integrated system rather than targeting individual components. This approach may support lasting repair of alveolar and vascular structures in preterm infants.
Keywords: Bronchopulmonary dysplasia, alveologenesis, angiogenesis, preterm neonates, signaling pathways, lung development.

БРОНХӨКПЕЛІК ДИСПЛАЗИЯСЫ: ШАЛА ТУҒАН НӘРЕСТЕЛЕРДЕГІ АЛЬВЕОЛОГЕНЕЗДІҢ БҰЗЫЛУЫНАН БАСТАП МОЛЕКУЛАЛЫҚ ЖӘНЕ ЖАСУШАЛЫҚ ДИСРЕГУЛЯЦИЯҒА ДЕЙІН

Абильбаева А.А.[1], Шактай Н.Қ.[1], Тарабаева А.С.[1], Қуат А.[1], Нұрым Қ.[1], Сагидулла А.[1]

[1]С.Ж. Асфендияров атындағы Қазақ ұлттық медицина университеті, Алматы, Қазақстан

Кіріспе. Бронхөкпелік дисплазия (БӨД) шала туған нәрестелердегі, әсіресе дене салмағы өте төмен балалардағы ең жиі кездесетін созылмалы өкпе ауруы болып қала береді. «Жаңа БӨД» парадигмасы классикалық жарақаттық фиброздан альвеолалар дамуының тоқтауымен және васкулярлық дизгенезбен сипатталатын процесске ауысты. Бұл жағдай альвеолалардың аз әрі қарапайым құрылымда қалыптасуына және ангиогенездің бұзылуына байланысты газ алмасу бетінің азаюына әкеледі.
Зерттеудің мақсаты. Осы шолудың мақсаты БӨД патогенезінің негізінде жатқан жасушалық және молекулалық бұзылыстарға интегративті талдау жүргізу, әсіресе шала туған нәрестелердің жетілмеген өкпесіндегі альвеолярлық морфогенез бен тамырлық дамуды реттейтін жасушааралық сигналдық желілердің дисрегуляциясына назар аудару.
Материалдар мен әдістер. Әдебиеттерге интегративті нарративтік шолу жүргізілді. Мақалаларды іздеу PubMed және Google Scholar электрондық дерекқорларында 2010 жылғы қаңтар мен 2025 жылғы наурыз аралығында жарияланған еңбектер бойынша жүйелі түрде жүзеге асырылды. Іздеу барысында «бронхөкпелік дисплазия», «альвеологенез», «ангиогенез», «сигналдық жолдар», «өкпенің дамуы» және «шала туған нәрестелер» терминдері мен олардың комбинациялары қолданылды. Талдауға тек ағылшын тілінде жарияланған мақалалар енгізілді.
Іріктеу критерийлеріне БӨД немесе қалыпты альвеологенездің молекулалық, жасушалық және сигналдық механизмдеріне тікелей қатысты рецензияланған түпнұсқа зерттеулер мен шолу мақалалары кірді. Шығарып тастау критерийлері ретінде конференция тезистері, рецензияланбаған дереккөздер, бастапқы деректері жоқ редакциялық мақалалар және әдістемесі жеткілікті сипатталмаған зерттеулер қарастырылды.
Толық мәтінді бағалау кезеңіне дейін қайталанатын жарияланымдар қолмен алынып тасталды. Іздеу нәтижесінде анықталған 374 бірегей жазбаның 301-і атауы мен аңдатпасын бағалау барысында шығарылды. Қалған 73 жарияланым толық мәтіндік талдаудан кейін барлық іріктеу критерийлеріне сәйкес келіп, қорытынды синтезге енгізілді.
Бұл шолу интегративті және нарративтік сипатқа ие. Ол жүйелі шолудың ресми талаптарына толық сәйкес келмейді, себебі әдебиеттерді іріктеу қатаң жүйелі хаттама бойынша жүргізілмеді, жарияланымдарды таңдаудың жүйелендірілмеген сызбасы пайдаланылды, сондай-ақ рецензенттер арасындағы келісімділік пен зерттеулер сапасын валидтелген құралдар арқылы бағалау жүргізілген жоқ.
Нәтижелер. Эксперименттік зерттеулерді, транскриптомдық және протеомдық талдауларды, клиникалық зерттеулер мен шолу мақалаларын қамтитын 73 жарияланымның нәтижелерін талдау дәлелділік деңгейі ең жоғары үш патогенетикалық механизмді анықтауға мүмкіндік берді.
PDGFRα сигналдық жолының бұзылуына байланысты альвеолярлық миофибробласттар популяциясының азаюы және олардың пролиферациясының жеткіліксіздігі альвеолалардың қарапайымдануының негізгі механизмі ретінде танылды. Бұл тұжырым доклиникалық зерттеулер мен клиникалық-генетикалық бақылаулардың өзара сәйкес келетін нәтижелерімен расталды. VEGF-A тапшылығы капиллярлық дисплазияның молекулалық негізі ретінде анықталып, адамның өліммен аяқталған БӨД жағдайларында да, аурудың көптеген эксперименттік модельдерінде де көрсетілді. TGF-β гиперөнімділігі VEGF-A экспрессиясын бір мезгілде тежейтін, фиброздың дамуын күшейтетін және септация үдерісін тежейтін жетекші сигналдық фактор ретінде айқындалды, соның нәтижесінде өкпенің тамырлық және құрылымдық зақымдануы тереңдей түседі.
Қалыпты альвеологенез өзара тығыз байланысқан төрт жасушалық жүйенің үйлесімді әрекетіне тәуелді: ATI және ATII жасушаларымен ұсынылған альвеолярлық эпителий, екіншілік қырқалардың миофибробласттары мен липофибробласттарды қамтитын өкпелік мезенхима, қантамыр эндотелийі және жасушадан тыс матрикс. Осы жүйедегі жасушааралық өзара әрекеттесулердің әртүрлі деңгейлерде бұзылуы БӨД патобиологиясының негізін құрайды.
Мезенхималық стромалық жасушаларға негізделген терапия доклиникалық зерттеулерде тұрақты тиімділік көрсетуде. Алайда оның клиникалық тәжірибеге кеңінен енгізілуі шала туған нәрестелер арасында жүргізілген III фазадағы рандомизацияланған бақыланатын зерттеулер деректерінің жеткіліксіздігімен шектеледі.

Талқылау. Шолу деректері БӨД-ны жекелеген эпителийлік, тамырлық немесе мезенхималық зақымдану ретінде емес, өкпенің үйлесімді дамуының бұзылысы ретінде қарастыру қажет екенін көрсетеді. PDGFRα сигналдық белсенділігінің әлсіреуі, VEGF-A тапшылығы және TGF-β гипербелсенділігінің өзара байланысы миофибробласттар функциясының бұзылуы септацияның жеткіліксіздігіне және кейіннен тамырлық дамудың тежелуіне әкелетін иерархиялық патогенетикалық үлгіні негіздейді. Сонымен қатар дәлелдердің едәуір бөлігі жануарлар мен доклиникалық модельдерден алынғандықтан, бұл тұжырымдарды клиникалық тәжірибеге енгізу үшін ірі әрі әдіснамалық тұрғыдан сапалы зерттеулерде қосымша валидация қажет.

Қорытынды. БӨД өкпенің дамуының ауыр бұзылысы болып табылады және оның негізінде, ең алдымен, жасушааралық коммуникацияның бұзылуы жатыр. Альвеолалардың қарапайымдануы мен өкпе тамырларының дисморфиясын қамтитын тән құрылымдық өзгерістер өкпе тінінің регенерациялық әлеуетінің төмендеуінің салдары болып табылады. PDGFRα арқылы реттелетін миофибробласттар функциясының әлсіреуі VEGF-A экспрессиясының екіншілік төмендеуіне және кейінгі капиллярлық дисплазияның дамуына алып келетін негізгі патогенетикалық оқиға ретінде қарастырылады. Сонымен қатар, TGF-β сигналдық жолының шамадан тыс белсенділігі өкпенің құрылымдық зақымдануын одан әрі күшейтеді.

Тиімді терапиялық стратегиялар жекелеген молекулалық нысандарға емес, «миофибробласттар – VEGF – жасушадан тыс матрикс» жүйесінің функционалдық тұтастығын қалпына келтіруге бағытталуы тиіс. Мұндай тәсіл шала туған нәрестелердің өкпесіндегі альвеолярлық және тамырлық құрылымдардың ұзақ мерзімді қалпына келуін қамтамасыз етуге мүмкіндік береді.

Түйінді сөздер: Бронхөкпелік дисплазия, альвеологенез, ангиогенез, шала туған нәрестелер, сигналдық жолдар, өкпенің дамуы.

БРОНХОЛЕГОЧНАЯ ДИСПЛАЗИЯ: ОТ НАРУШЕННОГО АЛЬВЕОЛОГЕНЕЗА ДО МОЛЕКУЛЯРНОЙ И КЛЕТОЧНОЙ ДИСРЕГУЛЯЦИИ У НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ

Абильбаева А.А.[1], Шактай Н.К.[1], Тарабаева А.С.[1], Куат А.[1], Нурым К.[1], Сагидулла А.[1]

[1]Казахский национальный медицинский университет имени С.Д. Асфендиярова, Алматы, Казахстан

Введение. Бронхолегочная дисплазия (БЛД) остается наиболее распространенным хроническим заболеванием легких у недоношенных новорожденных, особенно среди детей с очень низкой массой тела при рождении. Парадигма «новой БЛД» сместилась от классического фиброза, вызванного повреждением, в сторону процесса, характеризующегося остановкой альвеолярного развития и сосудистым дизгенезом. Данное состояние приводит к сокращению площади поверхности для газообмена вследствие формирования меньшего количества упрощенных альвеол и нарушения ангиогенеза.

Цель. Настоящий обзор направлен на интегративный анализ клеточных и молекулярных механизмов, участвующих в патогенезе БЛД, с особым вниманием к нарушениям межклеточных сигнальных взаимодействий, обеспечивающих процессы альвеолярного морфогенеза и васкулогенеза в незрелых лёгких недоношенных детей.

Материалы и методы. Был проведён интегративный нарративный обзор литературы. Систематический поиск публикаций осуществлялся в электронных базах данных PubMed и Google Scholar за период с января 2010 года по март 2025 года. Поисковые запросы включали следующие ключевые слова и их комбинации: «бронхолегочная дисплазия», «альвеологенез», «ангиогенез», «сигнальные пути», «развитие легких» и «недоношенные новорожденные». В анализ включались только статьи, опубликованные на английском языке.

Критериями включения являлись рецензируемые оригинальные исследования и обзорные статьи, непосредственно посвящённые молекулярным, клеточным или сигнальным механизмам БЛД либо процессам нормального альвеологенеза. Критериями исключения были тезисы конференций, нерецензируемые источники, редакционные статьи без первичных данных, а также исследования с недостаточным описанием методологии.

Перед этапом полнотекстового анализа дублирующиеся публикации были удалены вручную. Из 374 уникальных записей, выявленных в ходе поиска, 301 были исключены после оценки заголовков и аннотаций. Оставшиеся 73 публикаций соответствовали всем критериям включения по результатам полнотекстового анализа и были включены в итоговый синтез данных.

Настоящий обзор носит интегративный и нарративный характер. Он не соответствует формальным критериям систематического обзора, поскольку отбор литературы осуществлялся без строгого систематического протокола, была использована несистематическая схема отбора публикаций, а также не проводились оценка согласованности между рецензентами и формальная оценка качества исследований с использованием валидированных инструментов.

Результаты. Синтез данных 73 публикаций, включавших экспериментальные исследования, транскриптомные и протеомные анализы, клинические исследования и обзорные статьи, позволил выделить три патогенетических механизма с наиболее высоким уровнем доказательности.

Истощение популяции альвеолярных миофибробластов и нарушение их пролиферации, обусловленные дисфункцией сигнального пути PDGFRα, были определены как ключевой механизм упрощения альвеолярной структуры, что подтверждается согласующимися данными доклинических исследований и клинико-генетических наблюдений. Дефицит VEGF-A был установлен как молекулярная основа капиллярной дисплазии и выявлен как при фатальных формах БЛД у человека, так и в многочисленных экспериментальных моделях заболевания. Гиперпродукция TGF-β была идентифицирована как ведущий профибротический и антисептогенный сигнал, одновременно подавляющий экспрессию VEGF-A и тем самым усиливающий сосудистые и структурные нарушения в лёгочной ткани.

Нормальный альвеологенез зависит от координированного взаимодействия четырёх функционально взаимосвязанных клеточных систем: альвеолярного эпителия, представленного клетками II и I типов (ATII и ATI), лёгочной мезенхимы, включающей миофибробласты вторичных гребней и липофибробласты, сосудистого эндотелия и внеклеточного матрикса. Нарушение межклеточных взаимодействий в этой системе на различных уровнях лежит в основе патобиологии БЛД.

Терапия на основе мезенхимальных стромальных клеток демонстрирует стабильную эффективность в доклинических исследованиях. Однако её широкое внедрение в клиническую практику ограничено отсутствием данных рандомизированных контролируемых исследований III фазы у недоношенных новорождённых.

Обсуждение. Представленные данные позволяют рассматривать БЛД не как изолированное повреждение эпителия, сосудов или мезенхимы, а как нарушение координированной программы развития лёгких. Согласованность данных о снижении активности PDGFRα, дефиците VEGF-A и гиперактивации TGF-β поддерживает иерархическую модель патогенеза, в которой нарушение функции миофибробластов запускает дефект септации и вторично усугубляет сосудистую дисгенезию. Вместе с тем значительная часть механистических доказательств получена в животных и доклинических моделях, поэтому их перенос в неонатальную практику требует осторожной интерпретации и подтверждения в клинических исследованиях достаточной мощности.

Заключение. БЛД представляет собой тяжёлое нарушение развития лёгких, в основе которого лежит прежде всего расстройство межклеточной коммуникации. Характерные структурные изменения, включая упрощение альвеолярной архитектоники и сосудистую дисморфию, являются следствием снижения регенеративного потенциала лёгочной ткани. Ослабление функции миофибробластов, опосредованной сигнальным путём PDGFRα, рассматривается как ключевое патогенетическое событие, приводящее к вторичному подавлению экспрессии VEGF-A и последующему развитию капиллярной дисплазии. Дополнительный вклад в прогрессирование структурных нарушений вносит гиперактивация сигнального пути TGF-β.

Эффективные терапевтические стратегии должны быть направлены не на отдельные молекулярные мишени, а на восстановление функциональной целостности системы «миофибробласты – VEGF – внеклеточный матрикс» как единого регуляторного комплекса. Такой подход может обеспечить долговременное восстановление альвеолярных и сосудистых структур лёгких у недоношенных новорождённых.

Ключевые слова: Бронхолегочная дисплазия, альвеологенез, ангиогенез, недоношенные новорожденные, сигнальные пути, развитие легких.

Introduction.
The modern definition of bronchopulmonary dysplasia and the shift in the pathomorphological paradigm

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease, predominantly affecting preterm neonates, especially those born with very low birth weight (VLBW). The term “BPD” was originally introduced by Northway and colleagues in 1967 to describe chronic lung injury caused by barotrauma and oxygen toxicity in infants requiring mechanical ventilation. This “old, classical” form of BPD was characterized by marked airway injury and extensive alveolar–septal fibrosis.

However, as a result of significant advances in neonatal care, including the use of surfactant therapy and more gentle ventilation strategies, the survival of extremely preterm infants has increased, leading to a shift in the pathological characteristics of the disease [1]. In 1999, Jobe introduced the term “new BPD,” which is characterized primarily by arrested growth and development. The pathogenesis of “new” BPD is a complex process rooted in lung immaturity and disrupted development under the influence of external factors. The culmination of this pathogenic process is arrested development of the lung parenchyma, namely arrest of alveolarization and vascular dysgenesis. Instead of a normal increase in the number and complexity of alveoli, a smaller number of large, simplified alveoli is formed, which markedly reduces the effective surface area for gas exchange [2].

In addition, angiogenesis is impaired, resulting in a reduced number of pulmonary capillaries and disruption of their close apposition to the alveoli. This process is critical, as it leads to increased pulmonary vascular resistance and,

consequently, to the development of pulmonary hypertension, which significantly worsens the prognosis. Histopathological features of contemporary BPD include alveolar simplification and dysmorphic pulmonary vasculature. These structural abnormalities result in persistent impairments in gas exchange, respiratory system mechanics, and airway function [3].

Objective. To provide an integrative analysis of the cellular and molecular dysregulation driving BPD pathogenesis, focusing on the disruption of intercellular signaling networks that govern alveolar morphogenesis and vascular development in the immature preterm lung.

Materials and Methods.

Study design. The present work is an integrative narrative review of the scientific literature. In contrast to a systematic review, an integrative review synthesizes evidence derived from heterogeneous study designs, including experimental animal models, single-cell transcriptomic analyses, clinical observational studies, and previously published systematic reviews, with the aim of constructing a mechanistic and conceptual framework of the subject under investigation. Given that a formal systematic review protocol, encompassing a PRISMA-compliant selection flowchart, inter-rater agreement assessment, and GRADE quality appraisal, was not implemented, the present work is explicitly classified as an integrative rather than a systematic review.

Search strategy. The electronic databases PubMed/MEDLINE and Google Scholar were searched independently. The date of the last literature search was March 15, 2025. The search was conducted using the following keywords: "bronchopulmonary dysplasia," "alveologenesis," "angiogenesis," "preterm neonates," "signaling pathways," and "lung development." Articles published between January 2010 and March 2025 were considered for inclusion.

Inclusion criteria. Studies were considered eligible if they met the following conditions. First, the publication had to be a peer-reviewed original research article of experimental, preclinical, or clinical nature, or a comprehensive narrative or systematic review article. Second, the study had to address the role of specific cell populations, including alveolar type I and type II epithelial cells, myofibroblasts, lipofibroblasts, endothelial cells, or macrophages, or had to examine extracellular matrix components or molecular signaling axes such as PDGFRα/PDGF-A, VEGF/VEGFR2, TGF-β, Notch/Dll4, SHH, Wnt, FGF, Ang/Tie2, or IGF-1, in the context of alveologenesis or BPD pathogenesis. Third, the article had to be published in English between January 2010 and March 2025.

Exclusion criteria. Publications were excluded if they were conference abstracts without a peer-reviewed full-text counterpart, editorials, letters to the editor, or commentary articles lacking original data. Non-peer-reviewed encyclopedia entries and preprint publications were also excluded. Studies focusing exclusively on BPD epidemiology, clinical management protocols, or pharmacological interventions in the absence of mechanistic data were likewise excluded, as were publications lacking sufficient methodological detail to permit validity assessment.

Study selection and evidence synthesis. Duplicate records were removed manually prior to the screening phase. A total of 374 unique records were identified across all search queries. Following title and abstract screening, 301 records were excluded for failure to meet the inclusion criteria. Full-text review of the remaining 73 articles confirmed their eligibility, and all 73 were included in the final evidence synthesis. The included studies were categorized by design and comprised original experimental studies conducted predominantly using neonatal murine hyperoxia models, mechanical ventilation models, or genetic knockout models; studies employing single-cell RNA sequencing, proteomics, or advanced imaging techniques; clinical or translational studies involving preterm infant cohorts; and comprehensive narrative or systematic review articles. Evidence derived from preclinical studies is presented throughout the manuscript alongside a discussion of its translational limitations.

Results.

Overview of the evidence base

Among the 73 included studies, experimental rodent models constituted the largest body of evidence and represented the established

platform for investigating BPD pathogenesis, given the substantial overlap between murine postnatal alveologenesis, occurring between postnatal days 4 and 36, and human alveolarization, which spans from 36 weeks of gestation to approximately 3 years of age. Single-cell RNA sequencing and proteomic studies provided the most granular insight into cell-specific dysfunction at the transcriptomic and protein-expression levels. Clinical studies conducted in preterm infant cohorts largely corroborated preclinical findings with respect to VEGF deficiency and PDGFRα-associated genetic variants. Review articles served to contextualize and integrate the mechanistic data within the broader scientific literature. Collectively, three pathogenetic mechanisms were identified as carrying the highest degree of evidentiary confidence, defined as support from three or more independent study designs. These are PDGFRα-dependent myofibroblast depletion as the primary driver of alveolar simplification, VEGF-A deficiency as the molecular signature of capillary dysplasia, and TGF-β hyperproduction as the central pro-fibrotic signal.

1. Molecular and cellular physiology of normal alveologenesis

Five classical stages of lung development are distinguished and are presented in Table 1.

Table 1 - Stages of Lung Development

Stage	Gestational age (GA)	Characteristics
Embryonic	3–6 weeks	Formation of the trachea and main bronchi.
Pseudoglandular	5–17 weeks	Formation of the bronchial tree up to the terminal bronchioles.
Canalicular	16–26 weeks	Onset of lung tissue differentiation: respiratory bronchioles and alveolar ducts (precursors of alveoli) appear. The first type II alveolar epithelial cells emerge, synthesizing surfactant.
Saccular	24–38 weeks	Continued alveolar formation: terminal sacs (saccules) and primary alveoli are formed, with a marked increase in the gas exchange surface area.
Alveolar	From 36 weeks	Active alveologenesis: intensive branching and multiplication of mature alveoli. The majority of alveoli are formed after birth.

The formation of structures that subsequently give rise to mature alveoli begins during the canalicular stage. However, the most intensive growth and increase in the number of alveoli occur during the alveolar stage, when the process of active alveologenesis begins. This process is traditionally divided into two consecutive but interrelated phases: the classical phase and the continued phase [4,5].

The phase of classical alveologenesis is characterized by an intensive increase in the number of alveoli through the active formation of secondary septa. In humans, classical alveologenesis begins in utero at approximately 36 weeks of gestation and continues for 2-3 years after birth [6]. This phase is marked by vigorous formation of new alveoli, predominantly through neoalveologenesis and secondary septation. A key event in the septation phase is the invagination and protrusion of mesenchymal tissue rich in myofibroblasts and capillary loops into the lumen of terminal saccules. These new folds or outgrowths, known as secondary septa, begin to extend into the airspace. Concurrently, a double capillary layer starts to form. Thus, at early stages, the lungs exhibit relatively thick “primary” septa containing a double layer of capillaries. During classical alveologenesis, fusion of these double capillary layers occurs, resulting in the formation of a thin, single-layered air–blood membrane, which is more efficient for gas exchange. At the same time, each secondary septum effectively subdivides existing saccules and/or primitive alveoli into several smaller but more functional alveolar units. As a result of this process, the number of alveoli increases exponentially, providing a

substantial increase in the respiratory surface area required to meet the metabolic demands of the growing organism.

Following the completion of the phase of active increase in alveolar number, the phase of continued maturation begins. During this period, thinning and remodeling of the septa occur, along with a gradual increase in alveolar size. In mice, this process continues approximately until postnatal day 36 (P36), with full maturation potentially extending to P39. In humans, enlargement of alveolar size may continue up to 21 years of age [5].

The central event of this phase is the transformation of the inefficient double capillary network into a single, thin, and highly efficient network, which establishes the delicate air–blood barrier characteristic of the adult lung. Local duplication of the capillary network induced by angiogenesis may still be observed at the base of newly forming septa, indicating ongoing vascular remodeling.

Below is a comparative timeline of lung development illustrating the differences in timing between murine models and human development (Table 2).

Table 2 - Comparative Timeline of Alveologenesis

Developmental phase	Time frame	Key morphological events
Saccular (preceding)	24–36 weeks of gestation	Formation of distal air sacs (saccules).
Classical alveologenesis (septation)	36 weeks of gestation – 2–3 years after birth	Active formation of secondary septa; increase in alveolar number; double capillary network.
Continued alveologenesis (maturation)	3 years – 21 years	Septal thinning; transformation into a single capillary network; increase in alveolar size.

Cells involved in alveologenesis

Alveolar epithelium

The alveolar epithelium, composed predominantly of type I (ATI) and type II (ATII) cells, forms the immediate gas exchange barrier and plays a critical role in regulating the underlying mesenchymal compartment. Both cell types differentiate from progenitor cells of the distal lung regions during the late embryonic stage [4].

Type II alveolar epithelial cells, or secretory pneumocytes, are the driving force of alveolar development and homeostasis. They serve as progenitor cells of the alveolar epithelium. Under normal conditions, they proliferate at a very low rate, maintaining the populations of both alveolar cell types. However, in response to injury, they actively proliferate and subsequently differentiate into ATI cells, thereby enabling restoration of the damaged alveolar epithelium [7]. This mechanism is critical both during postnatal development and during regeneration in the adult lung. ATII cells also synthesize and secrete pulmonary surfactant, which reduces surface tension at the air–liquid interface within the alveoli. This function is essential for stabilizing and maintaining the open state of forming alveoli (saccules) both before and after birth [8]. In the absence of surfactant, the lung cannot inflate properly, which is critical for the survival of preterm infants [9].

Type I alveolar epithelial cells, or respiratory pneumocytes, represent the terminal product of differentiation and constitute the main structural component of the mature alveolus. They have an extremely flattened, attenuated morphology (cytoplasmic thickness <0.2 μm) and cover approximately 97.5% of the internal alveolar surface. This thin structure and

extensive surface area provide a minimal diffusion barrier between alveolar air and blood in the pulmonary capillaries, which is their primary function in the mature alveolus formed during alveologenesis [10]. Importantly, the behavior of ATI cells is not passive. Successful expansion of the ATI surface area required for the increase in respiratory surface critically depends on mechanotransduction. This means that morphological changes in ATI cells are induced by physical tension generated by the contractile activity of the underlying mesenchymal myofibroblasts of the secondary crests (SCMFs) during the phase of active septation. Thus, ATI cells act as mechanosensitive receptors, integrating mesenchymal physical forces to shape alveolar architecture [11].

Mesenchymal cells

Mesenchymal cells constitute a heterogeneous fibroblast compartment that provides the structural scaffold and regulatory signals required for alveologenesis. The key subpopulations include lipofibroblasts and secondary crest myofibroblasts, which belong to specialized alveolar fibroblasts.

Lipofibroblasts (LIFs) are specialized interstitial fibroblasts distinguished by their ability to accumulate lipids. These specialized mesenchymal cells act as key regulators of structural lung development, metabolism, and maintenance of the stem cell niche during alveolar formation. The primary and historically defined role of LIFs is metabolic support. These cells are characterized by the presence of lipid droplets, which they actively uptake, store, and "transfer." LIFs function as supportive cells for ATII cells. The lipids stored in LIFs serve as an active substrate for the synthesis of phospholipids of pulmonary surfactant, which is essential for reducing surface tension and preventing alveolar collapse [12,13]. LIFs may also be involved in the storage of retinol (vitamin A), which is converted into retinoic acid. Retinoic acid signaling is critical for normal alveologenesis and stimulates the synthesis of surfactant and elastin [13,14].

In addition, LIFs play a direct role in shaping alveolar structure. Together with myofibroblasts and matrix fibroblasts, LIFs contribute to the formation of the extracellular matrix (ECM), including the synthesis of structural proteins such as collagen and elastin, which are critical for the formation and stabilization of secondary septa that subdivide air sacs into mature alveoli [5,15]. While myofibroblasts primarily generate the mechanical force required for septal elongation, all interstitial fibroblasts, including LIFs, participate in the production and modulation of the ECM scaffold along which epithelial cells expand and differentiate [15].

LIFs are also regarded as key components of the alveolar stem cell (AT2) niche. They provide paracrine signals and create a permissive microenvironment that enables AT2 cells to proliferate and differentiate into AT1 cells required for gas exchange, thereby maintaining alveolar homeostasis and regeneration. The functions of LIFs, such as surfactant synthesis and lipid/retinoid metabolism, are regulated by mechanical stretch, which explains how surfactant production is maintained "on demand" during the respiratory cycle [12,16,17].

Secondary crest myofibroblasts (SCMFs), also referred to as alveolar myofibroblasts, are the direct drivers of secondary septation and play a decisive and multifunctional role in alveologenesis. SCMFs represent a highly specialized subpopulation of mesenchymal cells localized at the tips of growing secondary crests (septa), which subdivide saccules into mature alveoli.

SCMFs originate from PDGFRα$^+$ mesenchymal cells, which in turn arise from Gli1$^+$ progenitors in the early lung mesoderm. This indicates a programmed developmental lineage that is critical for pulmonary architecture [18]. SCMFs are defined by their fibrocontractile properties and by the expression of α-smooth muscle actin (α-SMA), which confers contractile capacity, as well as by their exclusive localization at the tips of secondary crests during the saccular and alveolar phases [19]. The primary function of SCMFs is related to the mechanical shaping of alveolar walls. SCMFs contain prominent stress fibers and use their contractile force to elongate and thin secondary crests. This mechanical action is essential for subdividing large saccules into numerous small alveoli, thereby markedly increasing the gas exchange surface area. At the

same time, SCMFs are the primary source of elastin and other extracellular matrix (ECM) proteins, such as tenascin. They generate an elastic scaffold that stabilizes newly formed alveolar walls and confers the necessary elasticity [5,20]. Importantly, the functions of SCMFs are tightly regulated by intercellular signaling networks; in particular, the PDGFRα receptor expressed on SCMFs is a critical regulator of elastogenesis. Inactivation of Pdgfra in SCMFs leads to arrest of alveologenesis and the development of pathology resembling BPD. This signaling pathway controls the expression of elastogenic genes through secondary networks, such as EGF and TGFβ signaling pathways [20].

Pericytes

Pericytes belong to the group of perivascular mesenchymal cells and also participate in the regulation of alveologenesis [21]. Loss of functionality of YAP/TAZ, transcriptional co-activators in pericytes, leads to impairment of classical alveologenesis [22]. This is associated with reduced expression of secreted ligands such as hepatocyte growth factor (HGF) and angiopoietin-1 (ANGPT1), which signal to epithelial and endothelial cells, respectively. Thus, disruption of genetic control within specific mesenchymal subpopulations interferes with the paracrine crosstalk required for the formation of the gas exchange surface.

Extracellular matrix and remodeling

The extracellular matrix (ECM) and its dynamic remodeling play a fundamental and active role in alveologenesis, extending far beyond that of a mere structural scaffold.

The lung extracellular matrix (ECM) constitutes a complex three-dimensional macromolecular network composed of collagens, elastin, and glycoproteins, which plays an active role in regulating lung development.

The ECM provides critical biochemical and biomechanical signals, particularly matrix stiffness, which regulate various cellular functions, including cell differentiation and phenotype. During alveologenesis, the composition and spatial organization of the ECM undergo continuous changes, which are essential for the normal transition from the saccular to the alveolar stage [23, 24]. It has also been demonstrated that ECM stiffness plays a decisive role in regulating cell differentiation in the distal lung. In human alveolar organoids (hALOs), increased matrix stiffness promotes the differentiation of alveolar type II (AT2) cells into alveolar type I (AT1) cells, a key process in alveolar maturation [24]. Furthermore, the ECM constitutes a critical component of the lung stem cell niche, influencing stem cell specification and differentiation required for the generation of all cell types in the mature lung [25].

It should be noted that alveologenesis requires a finely regulated balance between the synthesis and degradation of ECM components. In the alveoli, the ECM is composed primarily of collagens – particularly types I, III, and IV and, critically, elastin [24]. The degradation and modification of the ECM during remodeling are largely regulated by matrix metalloproteinases (MMPs) and their inhibitors. MMPs facilitate the creation of space for cell migration and ECM restructuring, processes that are essential for the thinning of the alveolar–capillary barrier [26]. Moreover, extensive remodeling of the lung proteome, including ECM components, has been demonstrated by proteomic analyses, supporting the existence of distinct molecular sub-stages of alveologenesis [27].

The cellular and matrix components of the alveoli and their roles in normal development are presented in Table 3.

Table 3 - Cellular and matrix components of the alveoli and their roles in normal development

Component	Subpopulation	Key physiological function
Alveolar epithelium	**Type II alveolar cells (ATII)**	**1. Progenitor cells:** Proliferate at a low rate, maintaining the population of both cell types; actively differentiate into AT1 cells upon injury. **2. Surfactant secretion:** Synthesize and secrete pulmonary surfactant to reduce surface tension and stabilize alveoli during the saccular stage.

	Type I alveolar cells (ATI)	**1. Gas exchange barrier:** Extremely flat and thin (cytoplasmic thickness <0.2 μm), covering approximately 97.5% of the alveolar surface, thereby providing a minimal diffusion barrier. **2. Mechanosensitivity:** Act as mechanosensitive receptors, with their morphological changes depending on the physical tension generated by the underlying mesenchymal myofibroblasts (SCMFs).
	Transdifferentiation of ATII to ATI cells	The transdifferentiation process (via transitional states, e.g., characterized by high keratin 8 expression) facilitates the restoration of the gas-exchange surface and barrier integrity following injury.
Mesenchymal cells	**Lipofibroblasts (LIFs)**	**1. Metabolic support:** Accumulate, store, and transfer lipids to support the synthesis of phospholipids in ATII cells for pulmonary surfactant production. **2. Developmental regulation:** Participate in retinol (vitamin A) metabolism, which is essential for stimulating alveologenesis and elastin synthesis. **3. Structural role:** Contribute to the formation of the extracellular matrix (ECM), including collagen and elastin. **4. Stem cell niche:** Provide paracrine signals to maintain the niche and homeostasis of AT2 cells.
	Secondary crest myofibroblasts (SCMFs)	**1. Mechanical shaping:** Utilize contractile force (α-SMA) to stretch and thin secondary crests, thereby partitioning saccules into mature alveoli. **2. Elastogenesis:** Serve as the primary source of elastin and other ECM proteins (e.g., tenascin), forming an elastic scaffold that stabilizes alveoli. **3. Regulation:** Their function is tightly regulated by signaling pathways, such as PDGFRα, which are critical for elastogenesis.
Extracellular matrix (ECM)	**Collagens, elastin, glycoproteins**	**1. Structural support:** Form a complex three-dimensional network that defines alveolar architecture. **2. Regulatory signals:** Provide biochemical and biomechanical cues (e.g., matrix stiffness) that regulate cell differentiation and phenotype; for instance, increased stiffness promotes the transdifferentiation of AT2 cells into AT1 cells. **3. Dynamic remodeling:** Maintain a finely tuned balance between synthesis and degradation (via MMPs and their inhibitors) to remodel the ECM and thin the alveolar–capillary barrier during alveologenesis.

Coupling of alveologenesis and angiogenesis

The processes of alveologenesis and angiogenesis in the lung not only occur simultaneously but are also tightly coupled and interdependent. This coupling is critical for establishing an optimal air–blood barrier architecture.

Alveologenesis involves the partitioning of terminal saccules into smaller alveoli through the formation of secondary septa. For efficient gas exchange, the newly formed alveolar surface must be immediately lined with a dense, thin-walled capillary network. The ultimate goal of alveologenesis is to create the thinnest possible air–blood barrier, comprising alveolar type I epithelial cells (AT1), the basal membrane, and capillary endothelial cells. This requires capillary growth to occur synchronously with the elongation and thinning of alveolar septa [28,29]. As the lung matures,

the double capillary network established in early stages merges into a single capillary layer closely apposed to both sides of the alveolar wall, ensuring a minimal diffusion barrier thickness.

Endothelial cells and their regulatory role

Endothelial cells (ECs) play a central role in the coupling of alveologenesis and angiogenesis. ECs do not merely form capillaries passively but actively participate in intercellular communication and molecular regulation of alveolar development. Their function involves directing vessel growth and modulating signaling pathways necessary for the proper formation of the air–blood barrier.

ECs establish an extensive capillary network within the mesenchyme surrounding the terminal airways (saccules). As alveologenesis progresses, these ECs must merge into a thin, single-layered capillary barrier closely apposed to AT1 cells to optimize gas exchange [28]. ECs have been shown to actively control the branching pattern of pulmonary vessels. Disruption of this arborization, such as the dysmorphic microvascular network observed in BPD, is a direct consequence of EC dysfunction [30]. ECs also serve as active signaling hubs that link vascular growth with alveolar formation. They express VEGF receptors (VEGFRs) and respond to VEGF secreted by alveolar epithelium, particularly AT2 cells. This represents a classical paracrine mechanism whereby ECs guide vessel growth in response to epithelial oxygen and nutrient demands, thereby ensuring physical coupling [31]. Additionally, ECs express Delta-like 4 (Dll4), a ligand of the Notch signaling pathway, which is critical for proper vascular arborization. Disruption of Notch signaling in ECs results in excessive, nonfunctional branching and impaired alveologenesis. Thus, ECs regulate the quality of the capillary network, not merely its quantity [30]. Moreover, pulmonary capillary ECs play an active, organizing role in alveologenesis, beyond simply providing blood supply. In particular, studies using a mouse model with endothelial-specific deletion of the Rap1 gene have demonstrated that Rap1-dependent EC function is required for recruitment of collagen IV and the formation of basement membranes (BMs), as well as for establishing a scaffold that serves as a substrate for myofibroblasts during the formation of secondary alveolar septa [32].

Macrophages

Macrophages play a complex and dual role in the coupling of alveologenesis and angiogenesis. On one hand, they act as critical regulators of regeneration, while on the other, under pathological conditions, they can exacerbate tissue damage. Their function is closely associated with phenotypic plasticity, enabling them either to promote vascular growth and alveolar formation or, conversely, to drive tissue destruction.

During physiological development, macrophages – particularly alveolar tissue macrophages (AMs) – support tissue growth and remodeling. They can facilitate the outgrowth of pulmonary organoids, highlighting their essential role in the development of distal airways and alveoli [33]. Macrophages skewed toward a regenerative M2 phenotype are known to promote angiogenesis and tissue repair. They achieve this by secreting anti-inflammatory cytokines and factors that support ECM synthesis and vascular maturation [34,35].

Remodeling of the capillary network

A key structural element of pulmonary angiogenesis is the alveolar capillary network (ACN).

During active alveologenesis, the ACN transforms from a double-layered network in the early neonatal lung into a single-layered network in the mature lung, which is essential for efficient gas exchange. Three-dimensional analyses have shown that even in adult lungs, small double- layered regions may persist, potentially contributing to continued alveolarization [36]. It has been demonstrated that the expansion of the ACN occurs not only through classical angiogenesis but also via intussusceptive angiogenesis. Therefore, three-dimensional visualization and quantitative assessment of the ACN structure are crucial for elucidating the mechanisms of remodeling in pathological conditions, including BPD [37].

Furthermore, novel approaches now enable inference of ACN structure from its function by analyzing blood flow dynamics [38].

2. Critical signaling pathways controlling alveologenesis

Postnatal alveologenesis and the accompanying

angiogenesis critically depend on reciprocal crosstalk among three primary cellular compartments: the alveolar epithelium, mesenchyme, and endothelium.

To date, several signaling pathways involved in alveologenesis have been identified. In particular, the PDGF-A/PDGFRα signaling axis is a key regulator of secondary septa formation during postnatal lung maturation. This pathway operates via paracrine signaling, wherein the ligand PDGF-A is secreted by alveolar type II epithelial cells (AEC II), while its receptor, PDGFRα, is predominantly expressed by alveolar myofibroblasts (AMFs), the primary alveolar "building" cells. Upon binding of PDGF-A to PDGFRα dimers on the AMF surface, a robust proliferative signal is initiated via intracellular cascades such as PI3K/Akt and MAPK/ERK. This signaling is critical for AMF proliferation and survival, and the expansion of AMF numbers is essential for generating the material for secondary septa. Furthermore, PDGF signaling directs AMF migration to sites of septa formation, where they must correctly position to form α–smooth muscle actin (α-SMA) rings and deposit elastin. Elastin provides the retraction and maturation of alveolar walls. Disruption of this axis results in alveologenesis arrest. These findings underscore the essential role of PDGF-A signaling in regulating the proliferation and migration of alveolar myofibroblasts, a key factor in secondary septa formation. In a conditional epithelial-specific PDGF-A knockout model, ligand deficiency leads to a marked reduction in the number and proliferative activity of PDGFRα+ mesenchymal cells and their inability to assemble α-actin rings. Interestingly, a paradoxical increase in the pool and proliferative activity of alveolar type II epithelial cells (AEC II) is observed in lungs with disrupted PDGF signaling. This phenomenon suggests that alveolar airspace expansion is not solely a consequence of mesenchymal dysfunction but may also result from imbalanced epithelial–mesenchymal crosstalk and disrupted negative regulation of AEC II proliferation (mechanotransduction), warranting further investigation [39]. Furthermore, subsequent studies have demonstrated that while PDGF-A/PDGFRα signaling exerts a direct or indirect influence on overall lung growth and size determination, it does not specifically govern early epithelial branching morphogenesis. These findings underscore that the primary functional significance of the PDGF-A/PDGFRα axis emerges during later stages of pulmonary development, where it is critically required for the paracrine regulation of mesenchymal myofibroblasts and the formation of alveolar septa [40].

Under these conditions, attenuation of PDGFRα signaling [41] results in insufficient proliferation of alveolar myofibroblasts (AMFs). Consequently, AMFs are unable to form secondary septa, leading to enlarged, simplified airspaces [42]. This AMF defect indirectly affects the vascular system, as weakened PDGF signaling reduces VEGF-A expression, which is essential for endothelial cell survival and growth, thereby resulting in capillary dysplasia [41].

Thus, epithelial-derived PDGF-A is vital for mesenchymal cells, coordinating their structural function to effectively construct the gas-exchange surface.

As previously noted, VEGF is a key regulator of pulmonary vascular development and angiogenesis. Normal alveologenesis requires the formation of a double-layered capillary network, which later merges into a single layer to optimize gas exchange. VEGF is necessary for the maturation of pulmonary capillaries [43]. In BPD, vascular hypoplasia, reduced capillary density, and dysmorphic vascularization are observed. Postnatal VEGF deficiency or genetic variations in VEGF and its receptors, particularly VEGFR1 and VEGFR2, directly correlate with impaired alveologenesis and vascularization. Hyperoxia can suppress VEGF expression via pathways such as IGF-1/MAPK/AKT [44].

Another key regulator of remodeling and fibrosis is TGF-β, which inhibits myofibroblast proliferation and may contribute to their pathological activation. Elevated TGF-β signaling in the lungs of preterm infants and BPD animal models correlates with interstitial fibrosis and abnormal mesenchymal differentiation [45-47].

Epithelial-secreted Sonic Hedgehog (SHH) is critical for paracrine control of the

mesenchyme. SHH acts synergistically with PDGF-A to stimulate myofibroblast proliferation. Inhibition or disruption of Hh signaling under hyperoxic conditions leads to impaired mesenchymal maturation and alveolar development defects [48].

The VEGF-A/VEGFR2 axis is a central regulator of pulmonary endothelial survival and angiogenesis. VEGF-A deficiency induces endothelial apoptosis and capillary dysplasia, directly impairing alveologenesis [49]. VEGF-A secreted by AEC II serves as a direct molecular link connecting epithelial maturation with vascular growth.

The angiopoietin (Ang)/Tie2 system, expressed in ECs, regulates vessel stabilization. Ang-1 promotes stabilization, whereas Ang-2, often upregulated during inflammation, destabilizes vessels. An imbalance favoring Ang-2 contributes to pathological vascular remodeling in BPD [50].

Insulin-like growth factor 1 (IGF-1) signaling in mesenchymal stromal cells is also critical for maturation. Disruption of IGF-1R in stromal cells compromises mechanotransduction and interrupts alveologenesis, highlighting the complexity of the regulatory network governing this process [51].

The Wnt signaling pathway is another important regulator of epithelial and mesenchymal proliferation and differentiation. It is critical for AEC II regeneration and proper epithelial patterning [52].

Finally, early FGF10 signaling is essential for branching morphogenesis, while postnatally, other FGF family members, such as FGF18, regulate myofibroblast fate. Ablation of FGF18- expressing myofibroblasts at the end of alveologenesis represents a key step in lung maturation [53].

3. Cellular and molecular dysregulation in BPD pathogenesis

3.1. Epithelial dysfunction

In extremely preterm infants, ATII cells are developmentally immature and initially produce insufficient or qualitatively defective surfactant, precipitating respiratory distress syndrome and the requirement for invasive respiratory support [54]. This surfactant deficiency, however, represents only the initial pathological event, as the dominant structural defect of 'new' BPD is not surfactant insufficiency per se but the failure of alveolar morphogenesis, a distinction with direct implications for therapeutic targeting.

Hyperoxia-induced ATII dysfunction manifests through several converging mechanisms. First, prolonged hyperoxic exposure stimulates aberrant transdifferentiation of ATII cells into an airway-like epithelial phenotype rather than normal flat ATI cells, thereby compromising barrier integrity and gas-exchange surface restoration [55]. Second, upregulation of CCNG1 in hyperoxia-exposed ATII cells inhibits their proliferative activity by counteracting normal growth signals, directly reducing the progenitor pool available for alveolar repair [56]. Third, disruption of the SENP1-Sirt3 signaling axis impairs mitochondrial oxidative balance in ATII cells, blocking the metabolic conditions required for normal ATI differentiation [57]. Single-cell transcriptomic analyses have further revealed that the ATII-to-ATI transition proceeds through a KRT8-high transitional cell state, and arrest at this state, identified as a hallmark of failed regeneration in idiopathic pulmonary fibrosis [58,59], may similarly underlie the defective epithelial repair characteristic of BPD, pointing to a potential mechanistic overlap between neonatal and adult fibrotic lung diseases [60].

A distinct and more recently described mechanism involves cell-autonomous failure of ATI identity. Disruption of TGF-β signaling within ATI cells themselves triggers a dedifferentiation process whereby ATI cells revert to a cuboidal, ATII-like phenotype, reducing gas-exchange surface area and contributing to alveolar septal thickening analogous to changes described in COPD [47,61]. This mechanism is conceptually separate from ATII-derived dysfunction and represents a secondary failure mode of the alveolar epithelium in BPD.

3.2. Mesenchymal dysregulation

Among all identified mechanisms, the depletion and proliferative failure of alveolar myofibroblasts constitutes the highest-confidence cellular event in BPD-associated alveolar simplification. Using two independent murine BPD models combined with single-cell RNA sequencing and flow cytometry, Khan IS et al. [62] demonstrated a sharp and consistent

reduction in the alveolar myofibroblast population across both experimental systems. The surviving myofibroblasts exhibited increased TGF-β signaling activity, attenuated PDGFRα receptor signaling, and, most importantly, impaired proliferative capacity. The causal sufficiency of this proliferative failure was confirmed by demonstrating that artificial inhibition of myofibroblast proliferation alone was sufficient to reproduce the alveolar simplification phenotype. These findings are independently corroborated by Oak et al., who showed that attenuated PDGFRα signaling drives both alveolar and microvascular defects through secondary VEGF-A suppression. Clinical genetic evidence further supports this pathway: significant enrichment of single-nucleotide polymorphisms in the PDGFRA gene has been identified in premature infants with BPD, associated with reduced PDGFRα protein levels and impaired myofibroblast function. Endotracheal replacement therapy with exogenous PDGFRα completely rescued lung defects in genetically compromised animal models, confirming the direct therapeutic potential of this pathway [41].

An important conceptual distinction must be drawn between quantitative myofibroblast depletion and qualitative myofibroblast dysfunction: both co-occur in BPD and appear to be independently pathogenic. Therapies aimed exclusively at replenishing lost myofibroblasts may prove insufficient if residual cells retain intrinsic proliferative impairment as a consequence of persisting TGF-β overactivation and PDGFRα attenuation.

A parallel but mechanistically distinct phenomenon involves the fate of alveolar myofibroblasts at the completion of normal alveologenesis. Hagan AS et al. [53] demonstrated using Fgf18:CreERT2 lineage tracing in mice that, unlike alveolar lipofibroblasts which are developmentally preserved, the majority of alveolar myofibroblasts undergo programmed apoptosis and phagocytic clearance upon completion of septation. This clearance process is essential for septal thinning and structural lung maturation. Failure of this clearance mechanism in BPD may result in the persistence of activated myofibroblasts driving fibrotic remodeling and impaired maturation.

In BPD, alveolar lipofibroblasts undergo pathological transdifferentiation into a myofibroblast-like phenotype under the influence of TGF-β and inflammatory signals, depleting the lipofibroblast pool and consequently impairing ATII metabolic support, surfactant phospholipid substrate availability, and alveolar stem-cell niche maintenance [16, 17].

3.3. Endothelial dysfunction and vascular dysgenesis

VEGF-A deficiency is the most consistently documented molecular correlate of pulmonary capillary dysplasia in BPD. Post-mortem analyses of lungs from preterm infants with fatal BPD have demonstrated markedly reduced VEGF levels directly associated with chronic alveolar and pulmonary vascular structural abnormalities [63,64]. This clinical finding has been independently replicated across multiple animal models. The 'vascular hypothesis of BPD' [65] positions VEGF-A as the primary molecular therapeutic target; however, as emphasized by Sang et al. [66], VEGF-A does not act in isolation but functions within an extensive intercellular signaling network encompassing HGF, PDGF, and Ang-1. VEGF-A deficiency in BPD therefore reflects a broad failure of epithelial-endothelial-mesenchymal crosstalk rather than an isolated molecular event, and restoration of VEGF-A alone is unlikely to reconstitute normal pulmonary vascular development.

An imbalance in the Ang-1/Ang-2/Tie2 system, with Ang-2 upregulation predominating during inflammatory states, destabilizes pulmonary vessels and contributes to the dysmorphic vascularization characteristic of BPD [50]. Disruption of endothelial Dll4-mediated Notch signaling results in excessive but non-functional capillary branching and impaired alveologenesis in murine endothelial-specific genetic models [30].

3.4. Extracellular matrix disruption

In BPD, the physiological balance between ECM synthesis and degradation is profoundly disturbed, producing pathological remodeling that directly undermines alveolar architecture. TGF-β stimulates the differentiation of fibroblasts and mesenchymal cells into

activated myofibroblasts that overproduce collagen types I and III and fibronectin, leading to excessive interstitial ECM deposition, thickening of alveolar walls, reduction of their elasticity, and structural disruption of the air-blood barrier [45, 46]. TGF-β additionally induces epithelial-to-mesenchymal transition in alveolar epithelial cells, further depleting the epithelial cell pool and amplifying ECM accumulation in a self-reinforcing pathological loop. TGF-β hyperproduction also suppresses secondary septation, the developmental process responsible for multiplying alveolar number, producing the simplified, enlarged alveolar architecture characteristic of “new” BPD [67]. Hyperproduction of TGF-β correlates with suppression of VEGF-A, generating a TGF-β/VEGF imbalance that dysregulates the microvascular bed and delays capillary maturation [68]. Furthermore, TGF-β stimulates proliferation and migration of smooth muscle cells in the medial layer of pulmonary arteries and adventitial fibroblasts, thickening vessel walls and increasing pulmonary vascular resistance through the canonical SMAD signaling pathway. The synergistic interaction between TGF-β and connective tissue growth factor (CTGF), whereby CTGF potentiates TGF-β dimerization with its receptors and amplifies pro-fibrotic and pro-proliferative effects, represents an additional mechanism driving vascular and interstitial remodeling in BPD [69].

3.5. Macrophage dysfunction and inflammatory mechanisms

Neonatal hyperoxia markedly reduces the number of resident alveolar macrophages (RAMs) in murine BPD models. The pathophysiological consequence of this depletion is impaired reparative angiogenesis. In co-transplantation experiments, the combination of RAM transplantation with endothelial progenitor cells (EPCs) significantly exceeded the repair efficacy of EPC monotherapy, mediated in part through CXCL12-dependent enhancement of EPC retention and proangiogenic signaling [70]. RAM depletion therefore constitutes a confirmed pathological contributor to microvascular repair failure in BPD.

Infection-triggered inflammation, including intrauterine, congenital, and nosocomial forms, redirects the immature lung's limited repair capacity toward pathological remodeling. This process is characterized by interstitial fibrosis and airway smooth muscle hypertrophy rather than normal alveolar architecture restoration. Barotrauma, volutrauma, and reactive oxygen species generated by prolonged hyperoxia synergistically amplify this inflammatory cascade and further compromise alveologenesis [71,72].

3.6. Analytical summary: evidence base and therapeutic relevance

Table 4 provides a structured synthesis of the principal signaling pathways implicated in BPD pathogenesis, indicating for each pathway the confirmed mechanism, the type and strength of supporting evidence, and the current status of therapeutic relevance. This table is intended to facilitate an explicit transition from descriptive citation to evidence-based mechanistic synthesis.

Table 4 - Molecular signaling pathways in BPD: evidence type, strength, and therapeutic potential

Signaling pathway	BPD-specific pathological mechanism	Evidence type	Strength of evidence	Therapeutic potential
PDGFRα / PDGF-A	Depletion and proliferative failure of alveolar myofibroblasts; impaired elastogenesis; secondary VEGF-A suppression leading to capillary dysplasia	2 independent murine BPD models; scRNA-seq; flow cytometry; clinical SNP data in preterm infants [41,62]	High — convergent preclinical and clinical genetic evidence	Endotracheal PDGFRα delivery rescues BPD phenotype in animal models [41]
VEGF-A / VEGFR2	Endothelial apoptosis; reduced capillary density; dysmorphic pulmonary microvasculature	Experimental (multiple rodent models); clinical histopathology of fatal human BPD;	High; direct clinical documentation available; paradoxical risk of PH at	Targeted VEGF restoration under investigation; dose-safety data required [65,66]

		VEGF gene polymorphism studies [44,63,64]	supraphysiological levels	
TGF-β	Inhibition of secondary septation; ECM overproduction (collagen I/III, fibronectin); VEGF-A suppression; EMT induction; ATI dedifferentiation; pulmonary arterial SMC proliferation leading to PH	Experimental (hyperoxia, ventilator models); clinical preterm lung histopathology; SMAD-pathway mechanistic studies [45-47,67-69]	High — multiple convergent independent studies	Systemic TGF-β blockade risks impairing normal repair; stage-specific targeted approaches required
Ang-1 / Ang-2 / Tie2	Ang-2 upregulation during inflammation destabilizes pulmonary vessels; pathological vascular remodeling characteristic of BPD	Experimental models; limited clinical data [50]	Moderate	Ang-1 supplementation explored in preclinical models [50]
Notch / Dll4	Dysmorphic vascular arborization; excessive non-functional capillary branching; impaired alveologenesis	Experimental (murine endothelial-specific genetic models) [30]	Moderate – single experimental approach; clinical translation not established	Under investigation
SHH	Impaired mesenchymal maturation under hyperoxia; disrupted myofibroblast differentiation	Experimental (neonatal murine hyperoxia models) [48]	Moderate	Exploratory stage
Wnt / β-catenin	Disrupted ATII regeneration; impaired alveolar epithelial patterning	Experimental [52]	Low to moderate – BPD-specific evidence limited	Under investigation
IGF-1 / IGF-1R	Disrupted mechanotransduction in mesenchymal stromal cells; interrupted alveologenesis	Experimental (mouse BPD model) [51]	Low to moderate	Exploratory stage
MSC / MSC-EV	Paracrine anti-inflammatory effects; mitochondrial transfer; attenuation of fibrosis; partial restoration of alveolarization in preclinical models	Multiple independent preclinical BPD models; Phase I/II clinical trials in neonates ongoing [73]	Preclinical: high; clinical: insufficient — Phase III data absent	Highest current therapeutic promise; requires adequately powered RCT

Discussion

The synthesis of evidence presented in this review supports a hierarchical model of BPD pathogenesis in which attenuation of PDGFRα-dependent myofibroblast biology represents the central upstream event. Impaired PDGFRα signaling simultaneously depletes the alveolar myofibroblast pool, arresting secondary septation, and through secondary suppression of VEGF-A expression in pulmonary mesenchymal cells, compromises capillary density and endothelial viability. TGF-β hyperproduction then acts in a downstream amplification loop, inhibiting residual myofibroblast function, driving excess ECM deposition, further suppressing VEGF-A, and inducing ATI cell dedifferentiation. These processes collectively produce the composite structural phenotype of 'new' BPD. The convergence of these three pathways, namely

PDGFRα attenuation, VEGF-A deficiency, and TGF-β overactivation, across independent experimental systems and clinical genetic data provides the highest-confidence mechanistic foundation currently available in the field.

Critical appraisal of evidence: what is established, what remains uncertain

A systematic appraisal of the available evidence reveals substantial heterogeneity in the degree to which individual pathogenetic mechanisms have been validated. Three levels of evidence confidence can be distinguished.

Well-established mechanisms, supported by convergent evidence from multiple independent experimental approaches and corroborated by clinical data, include PDGFRα-dependent myofibroblast depletion as the primary driver of alveolar simplification, VEGF-A deficiency as the molecular correlate of capillary dysplasia in fatal human BPD, and TGF-β hyperproduction as the central pro-fibrotic and anti-septogenic signal. These mechanisms are consistently reproduced across rodent hyperoxia models, mechanical ventilation models, genetic knockout systems, and translational studies in preterm cohorts, and they constitute the most reliable basis for therapeutic targeting.

Mechanisms supported by robust preclinical data but without adequate clinical validation include lipofibroblast-to-myofibroblast transdifferentiation as a driver of niche depletion, disruption of alveolar myofibroblast clearance as a contributor to fibrotic remodeling, Notch/Dll4-mediated vascular arborization defects, and RAM depletion as a cause of impaired microvascular repair. These should be presented as probable pathogenetic contributors pending clinical confirmation in human BPD tissue or preterm infant cohorts.

Mechanisms that remain speculative or are supported only by single experimental approaches include IGF-1/mechanotransduction-dependent stromal cell regulation, Wnt-mediated epithelial patterning disruption in the BPD-specific context, and the therapeutic role of enhanced intussusceptive angiogenesis. These require independent experimental replication and clinical investigation before they can be incorporated into mechanistic models with confidence.

Critical appraisal of MSC therapy and growth factor modulation

Among current experimental therapeutic strategies, mesenchymal stromal cell and MSC-derived extracellular vesicle therapy has accumulated the most consistent preclinical evidence base. Across multiple independent rodent BPD models, MSC-based interventions reduce pulmonary inflammation, attenuate mitochondrial dysfunction, decrease fibrosis, and partially restore alveolarization through paracrine mechanisms including bioactive molecule secretion and mitochondrial transfer to injured lung cells [73]. Despite this preclinical consistency, several critical limitations preclude clinical adoption. MSC populations differ across studies in tissue source, passage number, and preparation method, making inter-study comparisons unreliable. The optimal route of delivery, timing, and dose have not been defined. Available Phase I/II clinical trial data in preterm infants are insufficient to draw conclusions regarding efficacy or long-term safety. No Phase III randomized controlled trial in BPD has been completed. MSC-based therapy therefore represents the most promising direction for regenerative intervention but requires rigorously designed clinical trials before implementation.

Direct modulation of the VEGF-A/VEGFR2 axis as an isolated therapeutic strategy is complicated by the fact that VEGF-A functions within an extensive intercellular network; restoration of VEGF-A alone is unlikely to reconstitute normal vascular development. Moreover, supraphysiological VEGF concentrations paradoxically promote pathological angiogenesis and may exacerbate pulmonary arterial hypertension. Direct pharmacological TGF-β inhibition, while conceptually attractive, risks impairing normal tissue repair and immune function, as baseline TGF-β activity is required for both. Stage-specific and cell-type-targeted delivery approaches will likely be required for safe and effective modulation of these pathways in the immature neonatal lung.

Study limitations

The present review has several inherent limitations that must be explicitly acknowledged. The literature search was restricted to two databases, namely

PubMed/MEDLINE and Google Scholar. Consequently, relevant studies indexed in Embase, Web of Science, or the Cochrane Library may have been missed. Second, as an integrative rather than a systematic review, no PRISMA-compliant selection flowchart was generated, no inter-rater agreement for study inclusion was calculated, and no validated quality-appraisal instrument such as the GRADE framework was applied, introducing a risk of selection bias and potentially disproportionate weighting of individual studies. A substantial proportion of the mechanistic evidence derives from rodent neonatal hyperoxia models, which do not fully recapitulate the multifactorial etiology of human BPD. The contributions of patent ductus arteriosus, nutritional deficiency, and epigenetic factors are not adequately modeled in these experimental systems. In addition, specific findings established exclusively in animal models, including PDGFRα endotracheal delivery, Rap1-dependent basement membrane formation, and FGF18-lineage myofibroblast clearance, have not been validated in human clinical or translational studies. Finally, the classification of evidence strength presented in Table 4 reflects the authors' qualitative assessment and should be interpreted as a structured framework for evidence discussion rather than a definitive formal ranking.

Conclusion. Bronchopulmonary dysplasia represents a profound failure of lung ontogenesis rather than a mere consequence of external injury. The central structural defects, namely alveolar simplification and pulmonary vascular dysgenesis, arise from a coordinated breakdown of intercellular signaling within the immature lung parenchyma, in which four functionally interdependent cellular systems, including the alveolar epithelium, pulmonary mesenchyme, vascular endothelium, and extracellular matrix, fail to sustain their normal developmental program under the conditions of prematurity and iatrogenic injury.

The evidence synthesized in this review supports a hierarchical model of pathogenesis in which attenuation of PDGFRα-dependent myofibroblast biology occupies the central upstream position, simultaneously driving alveolar simplification through myofibroblast depletion and capillary dysplasia through secondary VEGF-A suppression. TGF-β hyperproduction amplifies structural deterioration across all cellular compartments by inhibiting septation, promoting fibrotic ECM remodeling, and further suppressing vascular growth. The pathogenesis of BPD is therefore not reducible to inflammation alone, but reflects the inability of the immature lung to execute and complete its intrinsic morphogenetic program.

Future therapeutic strategies must address this intercellular signaling failure in a coordinated and stage-specific manner. Regenerative approaches targeting the PDGFRα, VEGF, and ECM signaling axis hold the greatest promise, with MSC-based therapy demonstrating the most consistent preclinical evidence; however, its clinical translation requires adequately powered randomized controlled trials. Progress in this field will ultimately depend on a deeper understanding of the molecular hierarchy governing normal alveologenesis and on the development of therapeutic interventions capable of reactivating the lung's intrinsic developmental program in surviving preterm infants.

Ethical statement. The present manuscript is an integrative narrative review of previously published scientific literature. It does not involve the conduct of original research with human participants, the collection of identifiable patient data, biological sampling, or animal experiments performed by the authors. Accordingly, ethical committee approval was not required for the preparation of this work.

Data availability statement. The present review article does not generate or analyze new primary datasets. All data discussed throughout the manuscript are available in the original publications cited in the reference list.

REFERENCES

1 Cosgrove E, Boel L, Kotecha S. Recent Advances in the Management of Bronchopulmonary Dysplasia. Curr Treat Options Peds. 2025;11(20):1-10. https://doi.org/10.1007/s40746-025-00334-8
2 Sahni M, Bhandari V. Recent advances in understanding and management of bronchopulmonary dysplasia. F1000Res. 2020;9:F1000 Faculty Rev-703. https://doi.org/10.12688/f1000research.25338.1
3 Zhang J, Du W, Zhang Z, Li T, Li X, Xi S. Research progress of microvascular development in bronchopulmonary dysplasia. Pediatr Investig. 2024;8(4):299-312. https://doi.org/10.1002/ped4.12441
4 Vila Ellis L, Chen J. A cell-centric view of lung alveologenesis. Dev Dyn. 2021;250(4):482-496. https://doi.org/10.1002/dvdy.271
5 Rippa AL, Alpeeva EV, Vasiliev AV, Vorotelyak EA. Alveologenesis: What Governs Secondary Septa Formation. Int J Mol Sci. 2021; 22(22):12107. https://doi.org/10.3390/ijms222212107
6 Rippa A. Alveologenesis. Encyclopedia. Available from: https://encyclopedia.pub/entry/16265 (cited 19 November 2025). https://encyclopedia.pub/entry/16265
7 Sucre JM, Bock F, Negretti NM, Benjamin JT, Gulleman PM, Dong X, Ferguson KT, Jetter CS, Han W, Liu Y, Kook S, Gokey JJ, Guttentag SH, Kropski JA, Blackwell TS, Zent R, Plosa EJ. Alveolar repair following LPS-induced injury requires cell-ECM interactions. JCI Insight. 2023;8(14):e167211. https://doi.org/10.1172/jci.insight.167211
8 Zhang J, Liu Y. Epithelial stem cells and niches in lung alveolar regeneration and diseases. Chin Med J Pulm Crit Care Med. 2024;2(1):17-26. https://doi.org/10.1016/j.pccm.2023.10.007
9 Baker CD, Alvira CM. Disrupted lung development and bronchopulmonary dysplasia: opportunities for lung repair and regeneration. Curr Opin Pediatr. 2014 Jun;26(3):306-14. https://doi.org/10.1097/MOP.0000000000000095
10 Rozycki HJ. Potential contribution of type I alveolar epithelial cells to chronic neonatal lung disease. Front Pediatr. 2014;2:45. https://doi.org/10.3389/fped.2014.00045
11 Chao CM, Moiseenko A, Zimmer KP, Bellusci S. Alveologenesis: key cellular players and fibroblast growth factor 10 signaling. Mol Cell Pediatr. 2016;3(1):17. https://doi.org/10.1186/s40348-016-0045-7
12 Shmarakov I. Rediscovering Lung Lipofibroblast: A Lipid Wizard on the Alveolar Fibroblast Spectrum. Am J Respir Cell Mol Biol. 2025;25:10.1165/rcmb.2025-0361ED. https://doi.org/10.1165/rcmb.2025-0361ED
13 Torday JS, Rehan VK. On the evolution of the pulmonary alveolar lipofibroblast. Exp Cell Res. 2016;340(2):215-219. https://doi.org/10.1016/j.yexcr.2015.12.004
14 Ahlbrecht K, McGowan SE. In search of the elusive lipofibroblast in human lungs. Am J Physiol Lung Cell Mol Physiol. 2014;307(8):L605-L608. https://doi.org/10.1152/ajplung.00230.2014
15 Ushakumary MG, Riccetti M, Perl AT. Resident interstitial lung fibroblasts and their role in alveolar stem cell niche development, homeostasis, injury, and regeneration. Stem Cells Transl Med. 2021;10(7):1021-1032. https://doi.org/10.1002/sctm.20-0526
16 Panagiotidis GD, Vasquez-Pacheco E, Chu X, Seeger W, El Agha E, Bellusci S, Lingampally A. Revisiting pulmonary fibrosis: inflammatory dynamics of the lipofibroblast-to-inflammatory lipofibroblast-to-activated myofibroblast reversible switch. Front Immunol. 2025;16:1609509. https://doi.org/10.3389/fimmu.2025.1609509
17 Ambalavanan N, Deutsch G, Pryhuber G, Travers CP, Willis KA. The evolving pathophysiology of bronchopulmonary dysplasia. Physiol Rev. 2026;106(1):197-237. https://doi.org/10.1152/physrev.00042.2024
18 Li C, Li M, Li S, Xing Y, Yang CY, Li A, Borok Z, De Langhe S, Minoo P. Progenitors of secondary crest myofibroblasts are developmentally committed in early lung mesoderm. Stem Cells. 2015;33(3):999-1012. https://doi.org/10.1002/stem.1911
19 Ushakumary MG, Riccetti M, Perl AT. Resident interstitial lung fibroblasts and their role in alveolar stem cell niche development, homeostasis, injury, and regeneration. Stem Cells Transl Med. 2021;10(7):1021-1032. https://doi.org/10.1002/sctm.20-0526
20 Li C, Lee MK, Gao F, Webster S, Di H, Duan J, Yang CY, Bhopal N, Peinado N, Pryhuber G, Smith SM, Borok Z, Bellusci S, Minoo P. Secondary crest myofibroblast PDGFRα controls the elastogenesis pathway via a secondary tier of signaling networks during alveologenesis. Development. 2019;146(15):dev176354. https://doi.org/10.1242/dev.176354
21 Kato K, Diéguez-Hurtado R, Park DY, Hong SP, Kato-Azuma S, Adams S, Stehling M, Trappmann B, Wrana JL, Koh GY, Adams RH. Pulmonary pericytes regulate lung morphogenesis. Nat Commun. 2018;9(1):2448. https://doi.org/10.1038/s41467-018-04913-2
22 Chaudhry FN, Michki SN, Shirmer DL, McGrath-Morrow S, Young LR, Frank DB, Zepp JA. Dynamic Hippo pathway activity underlies mesenchymal differentiation during lung alveolar morphogenesis. Development. 2024;151(8):dev202430. https://doi.org/10.1242/dev.202430
23 Zhou Y, Horowitz JC, Naba A, Ambalavanan N, Atabai K, Balestrini J, Bitterman PB, Corley RA, Ding BS, Engler AJ, Hansen KC, Hagood JS, Kheradmand F, Lin QS, Neptune E, Niklason L, Ortiz LA, Parks WC, Tschumperlin DJ, White ES, Chapman HA, Thannickal VJ. Extracellular matrix in lung development, homeostasis and disease. Matrix Biol. 2018;73:77-104. https://doi.org/10.1016/j.matbio.2018.03.005
24 Liao Zh, Lv J, Wang D, Chen X, Zhao J, Xu T, Meng H, Liu H. Extracellular stiffness regulates site-specific lung development. bioRxiv. 2025; 01(12):632508. https://doi.org/10.1101/2025.01.12.632508
25 Busch SM, Lorenzana Z, Ryan AL. Implications for Extracellular Matrix Interactions With Human Lung Basal Stem Cells in Lung Development, Disease, and Airway Modeling. Front Pharmacol. 2021;12:645858. https://doi.org/10.3389/fphar.2021.645858

26 Hirani D, Haznedar Karakaya P, Cornelius J, Mansouri S, Vohlen C, Morcos Y, Selle J, Mizik I, Odenthal M, Alvira C, Kuiper C, van-Koningsbruggen-Rietschel S, Sengle G, Seeger W, Doetsch J, Savai R, Alejandre Alcazar MA. Inhibition of MMP12 Prevents Macrophage Influx to the Lung, Preserves Alveolarization, and Maintains Lung Matrix in a Hyperoxia-based Model of Bronchopulmonary Dysplasia. American Journal of Respiratory and Critical Care Medicine. 2025;211:A7738-A7738. https://doi.org/10.1164/ajrccm.2025.211.Abstracts.A7738
27 Clair G, Bramer LM, Misra R, McGraw MD, Bhattacharya S, Kitzmiller JA, Feng S, Danna VG, Bandyopadhyay G, Bhotika H, Huyck HL, Deutsch GH, Mariani TJ, Carson JP, Whitsett JA, Pryhuber GS, Adkins JN, Ansong C. Proteomic Analysis of Human Lung Development. Am J Respir Crit Care Med. 2022;205(2):208-218. https://doi.org/10.1164/rccm.202008-3303OC
28 Sivapalan R. Molecular Mechanisms Driving Alveolarization and Their Clinical Implications: A Literature Review. Undergraduate Research in Natural and Clinical Science and Technology (URNCST). 2024;8:1-8. https://doi.org/10.26685/urncst.705
29 Silva DM, Nardiello C, Pozarska A, Morty RE. Recent advances in the mechanisms of lung alveolarization and the pathogenesis of bronchopulmonary dysplasia. Am J Physiol Lung Cell Mol Physiol. 2015;309(11):L1239-L1272. https://doi.org/10.1152/ajplung.00268.2015
30 Xia S, Menden HL, Townley N, Mabry SM, Johnston J, Nyp MF, Heruth DP, Korfhagen T, Sampath V. Delta-like 4 is required for pulmonary vascular arborization and alveolarization in the developing lung. JCI Insight. 2021;6(7):e134170. https://doi.org/10.1172/jci.insight.134170
31 Carmeliet P, Jain R. Molecular mechanisms and clinical applications of angiogenesis. Nature. 2011;473:298-307 https://doi.org/10.1038/nature10144
32 Watanabe-Takano H, Kato K, Oguri-Nakamura E, Ishii T, Kobayashi K, Murata T, Tsujikawa K, Miyata T, Kubota Y, Hanada Y, Nishiyama K, Watabe T, Fässler R, Ishii H, Mochizuki N, Fukuhara S. Endothelial cells regulate alveolar morphogenesis by constructing basement membranes acting as a scaffold for myofibroblasts. Nat Commun. 2024;15:1622. https://doi.org/10.1038/s41467-024-45910-y
33 Vasse G, Post R, Jager M, Melgert B. Alveolar macrophages promote lung organoid outgrowth but do not protect against negative effects of PA6,6 microplastics on developing airway organoids. ERJ Open Research. 2025;11(15):OP5. https://doi.org/10.1183/23120541.LSC-2025.OP5
34 Spiller KL, Anfang RR, Spiller KJ, Ng J, Nakazawa KR, Daulton JW, Vunjak-Novakovic G. The role of macrophage phenotype in vascularization of tissue engineering scaffolds. Biomaterials. 2014;35(15):4477-4488. https://doi.org/10.1016/j.biomaterials.2014.02.012
35 Hasan M, Zhang X. Role of Macrophage in Pathogenesis of Pulmonary Fibrosis: A Review. Advances in Lung Cancer. 2025;14:1-17. https://doi.org/10.4236/alc.2025.141001
36 Rößler G, Labode J, Schipke J, Tschanz SA, Mühlfeld C. Three-dimensional characteristics of the alveolar capillary network in infant and adult human lungs. Pediatr Res. 2025;97(6):2136-2144. https://doi.org/10.1038/s41390-024-03572-y
37 Thorndyke HF, Lundberg EP, Ortiz Gaxon E, Dawson MM, Mason EC, Hollaway JM, Vladar EK, Coronado Escobar D, Majka SM. Development of novel technology for the visualization and quantitation of angiogenesis and the alveolar-capillary network in a mouse model of fibrosis. Am J Physiol Lung Cell Mol Physiol. 2025;328(6):L866-L876. https://doi.org/10.1152/ajplung.00317.2024
38 Schmid K, Olivares AL, Camara O, Kuebler WM, Ochs M, Hocke AC, Fischer SC. Inference of alveolar capillary network connectivity from blood flow dynamics. Am J Physiol Lung Cell Mol Physiol. 2024;327(6):L852-L866. https://doi.org/10.1152/ajplung.00025.2024
39 Gouveia L, Betsholtz C, Andrae J. PDGF-A signaling is required for secondary alveolar septation and controls epithelial proliferation in the developing lung. Development. 2018;145(7):dev161976. https://doi.org/10.1242/dev.161976
40 Li R, Bernau K, Sandbo N, Gu J, Preissl S, Sun X. Pdgfra marks a cellular lineage with distinct contributions to myofibroblasts in lung maturation and injury response. Elife. 2018;7:e36865. https://doi.org/10.7554/eLife.36865
41 Oak P, Pritzke T, Thiel I, Koschlig M, Mous DS, Windhorst A, Jain N, Eickelberg O, Foerster K, Schulze A, Goepel W, Reicherzer T, Ehrhardt H, Rottier RJ, Ahnert P, Gortner L, Desai TJ, Hilgendorff A. Attenuated PDGF signaling drives alveolar and microvascular defects in neonatal chronic lung disease. EMBO Mol Med. 2017;9(11):1504-1520. https://doi.org/10.15252/emmm.201607308
42 McGowan SE, McCoy DM. Fibroblasts expressing PDGF-receptor-alpha diminish during alveolar septal thinning in mice. Pediatr Res. 2011;70(1):44-49. https://doi.org/10.1203/PDR.0b013e31821cfb5a
43 Cui X, Fu J. Reinitiating lung development: a novel approach in the management of bronchopulmonary dysplasia. Respir Res. 2024;25(1):384. https://doi.org/10.1186/s12931-024-02996-8
44 Golshan-Tafti M, Bahrami R, Dastgheib SA, Hosein Lookzadeh M, Mirjalili SR, Yeganegi M, Aghasipour M, Shiri A, Masoudi A, Shahbazi A, Azizi S, Noorishadkam M, Neamatzadeh H. The association between VEGF genetic variations and the risk of bronchopulmonary dysplasia in premature infants: a meta-analysis and systematic review. Front Pediatr. 2024;12:1476180. https://doi.org/10.3389/fped.2024.1476180
45 Aschner Y, Downey GP. Transforming Growth Factor-β: Master Regulator of the Respiratory System in Health and Disease. Am J Respir Cell Mol Biol. 2016;54(5):647-655. https://doi.org/10.1165/rcmb.2015-0391TR
46 Calthorpe RJ, Poulter C, Smyth AR, Sharkey D, Bhatt J, Jenkins G, Tatler AL. Complex roles of TGF-β signaling

pathways in lung development and bronchopulmonary dysplasia. Am J Physiol Lung Cell Mol Physiol. 2023;324(3):L285-L296. https://doi.org/10.1152/ajplung.00106.2021
47 Callaway DA, Penkala IJ, Zhou S, Knowlton JJ, Cardenas-Diaz F, Babu A, Morley MP, Lopes M, Garcia BA, Morrisey EE. TGF-β controls alveolar type 1 epithelial cell plasticity and alveolar matrisome gene transcription in mice. J Clin Invest. 2024;134(6):e172095. https://doi.org/10.1172/JCI172095
48 Kugler MC, Loomis CA, Zhao Z, Cushman JC, Liu L, Munger JS. Sonic Hedgehog Signaling Regulates Myofibroblast Function during Alveolar Septum Formation in Murine Postnatal Lung. Am J Respir Cell Mol Biol. 2017;57(3):280-293. https://doi.org/10.1165/rcmb.2016-0268OC
49 Shah FH, Nam YS, Bang JY, et al. Targeting vascular endothelial growth receptor-2 (VEGFR-2): structural biology, functional insights, and therapeutic resistance. Arch Pharm Res. 2025;48(5):404-425. https://doi.org/10.1007/s12272-025-01545-1
50 Salimi U, Menden HL, Mabry SM, Xia S, Sampath V. Angiopoietin-1 protects against endotoxin-induced neonatal lung injury and alveolar simplification in mice. Pediatr Res. 2022;91(6):1405-1415. https://doi.org/10.1038/s41390-021-01544-0
51 Gao F, Li C, Smith SM, Peinado N, Kohbodi G, Tran E, Loh YE, Li W, Borok Z, Minoo P. Decoding the IGF1 signaling gene regulatory network behind alveologenesis from a mouse model of bronchopulmonary dysplasia. Elife. 2022;11:e77522. https://doi.org/10.7554/eLife.77522
52 Liu J, Xiao Q, Xiao J, Niu C, Li Y, Zhang X, Zhou Z, Shu G, Yin G. Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities. Signal Transduct Target Ther. 2022;7(1):3. https://doi.org/10.1038/s41392-021-00762-6
53 Hagan AS, Zhang B, Ornitz DM. Identification of a FGF18-expressing alveolar myofibroblast that is developmentally cleared during alveologenesis. Development. 2020;147(2):dev181032. https://doi.org/10.1242/dev.181032
54 Bakhtiyorjon R. Surfactant Therapy in Premature Infants: A Critical Tool in Neonatal Care. International Journal of Scientific Trends. 2025;4(4):94-98. https://scientifictrends.org/index.php/ijst/article/view/535
55 Hou A, Fu J, Yang H, Zhu Y, Pan Y, Xu S, Xue X. Hyperoxia stimulates the transdifferentiation of type II alveolar epithelial cells in newborn rats. Am J Physiol Lung Cell Mol Physiol. 2015;308(9):L861-L872. https://doi.org/10.1152/ajplung.00099.2014
56 Xu P, Zhuo W, Zhang P, Chen Y, Du Y, Li Y, Wang Y. Cyclin G1 Regulates the Alveolarization in Models of Bronchopulmonary Dysplasia by Inhibiting AT2 Cell Proliferation. Biomolecules. 2025;15(1):101. https://doi.org/10.3390/biom15010101
57 Zhang M, Lin X, He J, Zuo Y, Fan Q, Agida I, Tan H, Zhu C, Cheng J, Wang T. SENP1-Sirt3 axis regulates type II alveolar epithelial cell activity to confer resistance against oxidative damage in lung tissue. Redox Biology, 85.. SENP1-Sirt3 axis regulates type II alveolar epithelial cell activity to confer resistance against oxidative damage in lung tissue. Redox Biol. 2025;85:103752. https://doi.org/10.1016/j.redox.2025.103752
58 Jiang P, Gil de Rubio R, Hrycaj SM, Gurczynski SJ, Riemondy KA, Moore BB, Omary MB, Ridge KM, Zemans RL. Ineffectual Type 2-to-Type 1 Alveolar Epithelial Cell Differentiation in Idiopathic Pulmonary Fibrosis: Persistence of the KRT8hi Transitional State. Am J Respir Crit Care Med. 2020;201(11):1443-1447. https://doi.org/10.1164/rccm.201909-1726LE
59 Shen M, Luo Z, Zhou Y. Regeneration-Associated Transitional State Cells in Pulmonary Fibrosis. Int J Mol Sci. 2022;23(12):6757. https://doi.org/10.3390/ijms23126757
60 Wang ZN, Tang XX. New Perspectives on the Aberrant Alveolar Repair of Idiopathic Pulmonary Fibrosis. Front Cell Dev Biol 2020;8:580026. https://doi.org/10.3389/fcell.2020.580026
61 Li R. Disrupted TGF-β signaling: a link between bronchopulmonary dysplasia and alveolar type 1 cells. J Clin Invest. 2024;134(6):e178562. https://doi.org/10.1172/JCI178562.
62 Khan IS, Molina C, Ren X, Auyeung VC, Cohen M, Tsukui T, Atakilit A, Sheppard D. Impaired Myofibroblast Proliferation is a Central Feature of Pathologic Post-Natal Alveolar Simplification. Preprint. bioRxiv. 2024;2023.12.21.572766. https://doi.org/10.1101/2023.12.21.572766
63 Baker CD, Abman SH. Impaired pulmonary vascular development in bronchopulmonary dysplasia. Neonatology. 2015;107(4):344-351. https://doi.org/10.1159/000381129
64 Mariduena J, Ramagopal M, Hiatt M, Chandra S, Laumbach R, Hegyi T. Vascular endothelial growth factor levels and bronchopulmonary dysplasia in preterm infants. J Matern Fetal Neonatal Med. 2022;35(8):1517-1522. https://doi.org/10.1080/14767058.2020.1760826
65 Perrone S, Manti S, Buttarelli L, Petrolini C, Boscarino G, Filonzi L, Gitto E, Esposito SMR, Nonnis Marzano F. Vascular Endothelial Growth Factor as Molecular Target for Bronchopulmonary Dysplasia Prevention in Very Low Birth Weight Infants. Int J Mol Sci. 2023;24(3):2729. https://doi.org/10.3390/ijms24032729
66 Sang Y, Qiao L. Lung epithelial-endothelial-mesenchymal signaling network with hepatocyte growth factor as a hub is involved in bronchopulmonary dysplasia. Front Cell Dev Biol. 2024;12:1462841. https://doi.org/10.3389/fcell.2024.1462841
67 Li R. Disrupted TGF-β signaling: a link between bronchopulmonary dysplasia and alveolar type 1 cells. J Clin Invest. 2024;134(6):e178562. https://doi.org/10.1172/JCI178562
68 Mathew R. Signaling Pathways Involved in the Development of Bronchopulmonary Dysplasia and Pulmonary

Hypertension. Children (Basel). 2020;7(8):100. https://doi.org/10.3390/children7080100
69 Hansmann G, Sallmon H, Roehr CC, Kourembanas S, Austin ED, Koestenberger M. Pulmonary hypertension in bronchopulmonary dysplasia. Pediatr Res. 2021;89(3):446-455. https://doi.org/10.1038/s41390-020-0993-4
70 Mohammed AN, Kohram F, Lan YW, Li E, Kolesnichenko OA, Kalin TV, Kalinichenko VV. Transplantation of alveolar macrophages improves the efficacy of endothelial progenitor cell therapy in mouse model of bronchopulmonary dysplasia. Am J Physiol Lung Cell Mol Physiol. 2024;327(1):L114-L125. https://doi.org/10.1152/ajplung.00274.2023
71 Sampath V, Garland JS, Helbling D, Dimmock D, Mulrooney NP, Simpson PM, Murray JC, Dagle JM. Antioxidant response genes sequence variants and BPD susceptibility in VLBW infants. Pediatr Res. 2015;77(3):477-483. https://doi.org/10.1038/pr.2014.200
72 Balany J, Bhandari V. Understanding the Impact of Infection, Inflammation, and Their Persistence in the Pathogenesis of Bronchopulmonary Dysplasia. Front Med 2015;2:90. https://doi.org/10.3389/fmed.2015.00090
73 Zhang S, Mulder C, Riddle S, Song R, Yue D. Mesenchymal stromal/stem cells and bronchopulmonary dysplasia. Front Cell Dev Biol. 2023;11:1247339. https://doi.org/10.3389/fcell.2023.1247339

Authors Contributions.
Concept development – Tarabayeva A.S., Abilbayeva A.A, Kuat A., Sagidulla A.
Execution – Abilbayeva A.A., Kuat A., Sagidulla A., Nurym K.
Processing of results – Shaktay N.K., Abilbayeva A.A., Tarabayeva A.S., Kuat A., Sagidulla A., Nurym K.
Scientific interpretation of the results – Tarabayeva A.S., Shaktay N.K., Abilbayeva A.A., Nurym K.
Article writing – Tarabayeva A.S., Shaktay N.K., Abilbayeva A.A., Kuat A., Sagidulla A., Nurym K.
Conflict of interest: The authors declare no conflict of interest.
Funding information: This research has been funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP22786227).

Авторлардың үлестері.
Концептуализация – Тарабаева А.С., Абильбаева А.А., Қуат А., Сагидулла А.
Методология – Абильбаева А.А., Қуат А., Сагидулла А., Нұрым Қ.
Деректерді өңдеу – Шактай Н.Қ., Абильбаева А.А., Тарабаева А.С., Қуат А., Сагидулла А., Нұрым Қ.
Нәтижелерді ғылыми түсіндіру – Тарабаева А.С., Шактай Н.Қ., Абильбаева А.А., Нұрым Қ.
Мақала жазу – Тарабаева А.С., Шактай Н.Қ., Абильбаева А.А., Қуат А., Сагидулла А., Нұрым Қ.
Мүдделер қақтығысы: Біз мүдделер қақтығысының болмағанын мәлімдейміз.
Қаржыландыру: Бұл шолу мақаласы Қазақстан Республикасы Ғылым және жоғары білім Министрлігінің Ғылым комитеті қаржыландыратын жоба аясында жазылды (Грант №AP22786227).

Вклад авторов
Концептуализация – Тарабаева А.С., Абильбаева А.А., Куат А., Сагидулла А.
Методология – Абильбаева А.А., Куат А., Сагидулла А., Нурым К.
Обработка данных – Шактай Н.К., Абильбаева А.А., Тарабаева А.С., Куат А., Сагидулла А., Нурым К.
Формальный анализ – Тарабаева А.С., Шактай Н.К., Абильбаева А.А., Нурым К.
Подготовка оригинального проекта – Тарабаева А.С., Шактай Н.К., Абильбаева А.А., Куат А., Сагидулла А., Нурым К.
Конфликт интересов – не заявлен. Мы заявляем об отсутствии конфликтов интересов.
Финансирование: Данная обзорная статья написана в рамках проекта, финансируемого Комитетом Науки Министерства науки и высшего образования Республики Казахстан (Грант №AP22786227).

Authors' information:
Abilbayeva Arailym – PhD, Associate Professor, A.A. Shortanbayev General Immunology Department, Almaty, Kazakhstan. arailym2686@gmail.com, 87022148965. ORCID 0000-0001-5081-5492
Shaktay Nuray – Junior Researcher, B. Atchabarov SRI FAM, Almaty, Kazakhstan. nuray.shaktay@mail.ru, 87762892787. ORCID 0009-0003-6027-9998
Tarabayeva Anel – MD, PhD, Professor, A.A. Shortanbayev General Immunology Department, Almaty, Kazakhstan. tarabaeva60@mail.ru, 87012042095. ORCID 0000-0002-2851-2396
Kuat Akniyet – 3rd year Student, School of General Medicine-1, A.A. Shortanbayev General Immunology Department, Almaty, Kazakhstan. kuatakniet05@mail.ru, 87773287750. ORCID 0009-0002-7638-7726
Nurym Kuralay – 3rd year Student, School of General Medicine-1, A.A. Shortanbayev General Immunology Department, Almaty, Kazakhstan. Kuralai.nur02@gmail.com, 87472002887. ORCID 0009-0008-9863-8833
Sagidulla Akerke – 3rd year Student, School of General Medicine-1, A.A. Shortanbayev General Immunology Department, Almaty, Kazakhstan. sagakerke@gmail.com, 87082057613. ORCID 0009-0002-1160-1082

Авторлар туралы мәліметтер:
Абильбаева Арайлым Асылхановна – PhD, қауымдастырылған профессор, А.А. Шортанбаев атындағы жалпы иммунология кафедрасы, Алматы, Қазақстан. arailym2686@gmail.com, 87022148965. ORCID 0000-0001-5081-5492
Шактай Нұрай Құрманғалықызы – кіші ғылыми қызметкер, Б. Атчабаров атындағы ІҚМ ҒЗИ, Алматы, Қазақстан. nuray.shaktay@mail.ru, 87762892787. ORCID 0009-0003-6027-9998
Тарабаева Анель Саидовна – м.ғ.к., профессор, А.А. Шортанбаев атындағы жалпы иммунология кафедрасы, Алматы, Қазақстан. tarabaeva60@mail.ru, 87012042095. ORCID 0000-0002-2851-2396
Қуат Ақниет – 3-курс студенті, Жалпы медицина мектебі-1, А.А. Шортанбаев атындағы жалпы иммунология кафедрасы, Алматы, Қазақстан. kuatakniet05@mail.ru, 87773287750. ORCID 0009-0002-7638-7726
Нұрым Құралай – 3-курс студенті, Жалпы медицина мектебі-1, А.А. Шортанбаев атындағы жалпы иммунология кафедрасы, Алматы, Қазақстан. Kuralai.nur02@gmail.com, 87472002887. ORCID 0009-0008-9863-8833
Сагидулла Ақерке – 3-курс студенті, Жалпы медицина мектебі-1, А.А. Шортанбаев атындағы жалпы иммунология кафедрасы, Алматы, Қазақстан. sagakerke@gmail.com, 87082057613. ORCID 0009-0002-1160-1082

Сведения об авторах:
Абильбаева Арайлым Асылхановна – PhD, ассоциированный профессор, кафедра общей иммунологии им. А.А. Шортанбаева, Алматы, Казахстан. arailym2686@gmail.com, 87022148965. ORCID 0000-0001-5081-5492
Шактай Нұрай Құрманғалықызы – младший научный сотрудник, НИИ ФПМ имени Б. Атчабарова, Алматы, Казахстан. nuray.shaktay@mail.ru, 87762892787. ORCID 0009-0003-6027-9998
Тарабаева Анель Саидовна – к.м.н., профессор, кафедра общей иммунологии им. А.А. Шортанбаева, Алматы, Казахстан. tarabaeva60@mail.ru, 87012042095. ORCID 0000-0002-2851-2396
Куат Акниет – студент 3 курса, Школа общей медицины-1, кафедра общей иммунологии им. А.А. Шортанбаева, Алматы, Казахстан. kuatakniet05@mail.ru, 87773287750. ORCID 0009-0002-7638-7726
Нурым Куралай – студент 3 курса, Школа общей медицины-1, кафедра общей иммунологии им. А.А. Шортанбаева, Алматы, Казахстан. Kuralai.nur02@gmail.com, 87472002887. ORCID 0009-0008-9863-8833
Сагидулла Акерке – студент 3 курса, Школа общей медицины-1, кафедра общей иммунологии им. А.А. Шортанбаева, Алматы, Казахстан. sagakerke@gmail.com, 87082057613. ORCID 0009-0002-1160-1082