НЕОНАТОЛОГІЯ, ХІРУРГІЯ ТА ПЕРИНАТАЛЬНА МЕДИЦИНА
NEONATOLOGY, SURGERY AND PERINATAL MEDICINE
Т. XVI, №3(61), 2026
VOL. XVI, №3(61), 2026
ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)
KEY TITLE: NEONATOLOGÌÂ, HÌRURGÌÂ TA PERINATAL'NA MEDICINA (ONLINE)
ABBREVIATED KEY TITLE: NEONATOL. HÌR. PERINAT. MED. (ONLINE)

УДК: 616-053.32-018.2-092-078-037-084
DOI: 10.24061/2413-4260.XVI.3.61.2026.34

THE EXTRACELLULAR MATRIX AS AN INTEGRATOR OF MULTISYSTEM ADAPTATION IN PRETERM INFANTS

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Abstract.

Preterm birth remains a leading cause of neonatal morbidity, mortality, and long-term complications. Contemporary understanding of prematurity pathogenesis increasingly centers on the concept of multisystem maladaptation, with the extracellular matrix (ECM) serving as a key mediator. Historically viewed as a structural connective tissue component, the ECM is now recognized as a dynamic signaling system regulating cell proliferation, differentiation, mechanotransduction, intercellular communication, and tissue remodeling.

Aim. *This review aims to synthesize current evidence on the role of the extracellular matrix in multisystem adaptation and compensation in preterm infants and to analyze the main mechanisms of ECM remodeling in the development of neonatal and early childhood pathologies.*

This narrative review incorporated experimental and clinical studies published from 2021 to 2026 across PubMed, Scopus, Web of Science, and the Cochrane Library. Recent studies on matrix biology, mechanobiology, neonatal inflammation, and ECM-associated biomarkers were analyzed. It was established that structural and signaling disturbances in the ECM are associated with the development of bronchopulmonary dysplasia, cerebral damage, vascular dysfunction, necrotizing enterocolitis, and other prematurity-related complications. Oxidative stress, systemic inflammation, hyperoxia, and mechanical ventilation have been identified as key triggers of pathological matrix remodeling. Emerging directions in modern neonatology include ECM-associated biomarkers, proteomic technologies, extracellular vesicles, and ECM-targeted therapy.

The extracellular matrix should be regarded as the central integrator of multisystem adaptation in preterm infants and a promising platform for personalized prediction, prevention, and treatment of prematurity-related complications.

Keywords: *preterm infants; extracellular matrix; multisystem adaptation; extracellular matrix remodeling; mechanotransduction; personalized neonatology.*

Introduction

Preterm birth represents a central challenge in modern neonatology and pediatrics, owing to high risks of neonatal mortality, severe early neonatal complications, and long-term health problems that impair children's quality of life [1].

In Ukraine, the birth rate has decreased by 32% over the past four years, while the proportion of preterm infants has steadily increased. In 2024, 11,148 preterm infants were born, accounting for 6.3% of all newborns [Ministry of Health, 2024]. Notably, 70% of newborns exhibit two or more concurrent perinatal pathologies, which significantly affects the perinatal and early neonatal course and determines clinical severity [2, 3].

Preterm birth occurs during a critical period of active morphogenesis and structural and functional organs maturation, when tissue proliferation, differentiation, and remodeling remain incomplete. Immature adaptive mechanisms are further compromised by oxidative stress, systemic inflammation, hyperoxia, hemodynamic instability, and invasive intensive care procedures, leading to disrupted organ development.

Perinatal complications also vary by age and sex [4]. Boys exhibit higher neonatal mortality and severe morbidity rates than girls, reflecting the biologically based «neonatal disadvantage» of males [5].

Despite numerous studies addressing specific aspects of preterm infant pathology, the ECM's role as an integral mechanism of multisystem adaptation remains insufficiently systematized. A deeper understanding of ECM remodeling in preterm infants advance comprehension of perinatal pathology pathogenesis, facilitate the identification of novel prognostic approaches, and support the development of personalized neonatal care concept.

As of June 1, 2026, a literature search was conducted across PubMed, Scopus, Cochrane Central Register of Controlled Trials (Central), and Web of Science databases.

Aim

This review aims to synthesize current evidence on the role of the extracellular matrix in multisystem adaptation and compensation in preterm infants and to analyze the main mechanisms of ECM remodeling underlying neonatal and early childhood pathologies.

The extracellular matrix (ECM) represents a key structural and functional system supporting tissue adaptation and postnatal maturation. The traditional view of the ECM as a passive mechanical scaffold has shifted considerably in recent years. It is now recognized as a highly organized dynamic signaling system regulating cell proliferation, differentiation, migration, intercellular communication, and tissue repair [6].

Increasing evidence suggests ECM dynamics as a potential marker of healthy longevity [7]. The ECM's main components – collagens, elastin, fibronectin, laminin, proteoglycans, and matrix-associated proteins – form a complex microenvironment determining tissue mechanical properties and modulating growth factor, integrin, and mechanotransduction signaling pathways [8-10].

The ECM is particularly critical during the perinatal period, when intensive organogenesis and tissue remodeling occur. The extracellular matrix mediates alveolarization,

angiogenesis, and elastic airway framework formation; regulates neuronal migration and formation of intercellular interactions; and ensures the structural organization of the vascular wall and adaptation to postnatal hemodynamic changes [11, 12].

Unlike mature tissues, the fetal ECM is characterized by elevated plasticity, high hydration, predominant embryonic isoforms of fibronectin, laminin, tenascin, hyaluronic acid, and immature collagen structures. This composition supports intensive cell proliferation, angiogenesis, and morphogenetic tissue mobility. In preterm infants, this stage of ECM biological immaturity coincides with abrupt changes in oxygenation, hemodynamics, nutritional supply, and mechanical load, inducing significant adaptive stress in the extracellular matrix system [13, 14].

A particularly promising modern concept views the ECM as a central regulator of multisystem adaptation and compensation in preterm infants. Matrix remodeling processes have been demonstrated to concurrently contribute to the development of bronchopulmonary dysplasia, pulmonary hypertension, white matter injury, neurodevelopmental delay, myocardial remodeling, vascular immaturity, retinopathy of prematurity, and intestinal barrier dysfunction. Thus, the ECM may be considered a unified pathogenic platform for multi-organ dysfunction in preterm infants [15-17].

Oxidative stress, systemic inflammation, and mechanical ventilation-associated tissue damage significantly contribute to ECM dysregulation. Activation of pro-inflammatory cytokines and matrix metalloproteinases, alongside disruption of mechanotransduction signaling pathways, may result in degradation of ECM structures, disorganization of collagen and elastin fibers, impaired angiogenesis, and pathological tissue remodeling [18, 19].

Recent literature has increasingly focused on the concept of disruption of extracellular matrix maturation, with preterm birth serving as a model of interrupted matrix development and incomplete structural and functional organ adaptation.

The concept of mechanobiology of the preterm infant warrants particular attention, as mechanical factors after birth directly modify ECM structure and signaling function. Mechanical ventilation, oxygen therapy, changes in lung compliance, and hemodynamic fluctuations activate mechanosensitive integrin-FAK-YAP/TAZ signaling pathways, which alter the synthesis of collagen, elastin, and matrix glycoproteins [20-22].

Excessive mechanical forces from mechanical ventilation have been identified as a primary pathological trigger, activating transcriptional programs associated with fibrosis, chronic inflammation, and collagen production, and initiating molecular cascades that lead to persistent lung tissue remodeling [23]. In preterm infant lungs, this pathological process is associated with impaired alveolarization, elastin fiber fragmentation, and simplified lung architecture characteristic of modern bronchopulmonary dysplasia [24, 25].

The concept of matrix-mediated neuroinflammation is currently under active investigation. In the preterm infant brain, the ECM regulates neuronal migration, oligodendrocyte maturation, and synaptic network formation. Immaturity of the white matter matrix of the brain, imbalance of hyaluronic acid, and activation of matrix metalloproteinases are associated with preoligodendrocyte damage, periventricular leukomalacia, and subsequent cognitive impairments [26,27]. The ECM has been identified as a principal mediator of neuroinflammatory memory in the preterm infant brain, wherein early systemic inflammation programs lasting changes in the neuromatrix and synaptic plasticity.

The concept of extracellular matrix memory, while controversial, represents a promising area of investigation. This model proposes that the ECM stores information regarding prior hypoxic, inflammatory, and oxidative damage through alterations in the spatial organization of collagen, elastin, and proteoglycans, coupled with changes in the mechanical properties of the tissue. Matrix memory is hypothesized to constitute the mechanism underlying the programming of long-term cardiovascular, metabolic, and neurological consequences of prematurity manifesting in adulthood [28,29].

The ECM is increasingly recognized as a central component of biological programming. Antenatal inflammation, chorioamnionitis, placental dysfunction, and fetal hypoxia have been demonstrated to alter the matrix microenvironment prior to birth [30], accompanied by impaired expression of collagens, laminin, fibronectin, and ECM-bound growth factors. A preterm infant is born with a pre-reprogrammed matrix, a condition potentially determining subsequent adaptive capacity.

The extracellular matrix (ECM) is integral to the development of vascular immaturity. The vascular matrix in preterm infants is characterized by deficient elastin structure, incomplete formation of the basement membrane, and heightened sensitivity to oxidative stress [31, 32], contributing to endothelial dysfunction, instability of cerebral blood flow, pulmonary hypertension, and retinopathy of prematurity.

Impaired interaction between the endothelium and the ECM may be a central mechanism of microvascular dysregulation in preterm infants [33, 34].

The rapidly emerging field of immunomatrix biology investigates the interactions between the ECM and the immune system. Matrix components have been demonstrated to act as damage-associated molecular patterns (DAMPs), activating Toll-like receptors and sustaining chronic sterile inflammation. ECM immaturity in preterm infants coexists with innate immune system immaturity, establishing an environment conducive to prolonged subclinical (low-grade) inflammation, a mechanism particularly relevant to the pathogenesis of bronchopulmonary dysplasia, necrotizing enterocolitis, and sepsis-associated multi-organ injury [35,36].

Neonatal matrix biology increasingly incorporates the concept of exposome medicine, recognizing that birth transitions the preterm newborn into a radically different extrauterine environment characterized by elevated oxygen concentrations, pharmacological interventions, artificial feeding, microbiome alterations, and intense mechanical stresses. These exogenous factors modify the extracellular

ISSN 2226-1230 (PRINT) ISSN 2413-4260 (ONLINE)

matrix (ECM) structure via epigenetic mechanisms, oxidative stress, and the activation of matrix proteases, thereby establishing the ECM as a principal sensor of the early neonatal exposome [37,38].

The concept of organ-specific matrix remodeling assumes particular significance in this context, given that the ECM of distinct organs exhibits unique molecular compositions and specific signaling properties, wherein elastin and collagen networks predominate in the lungs, hyaluronic acid and chondroitin sulfate proteoglycans characterize the brain, and fibrillar collagen alongside mechanosensory proteins defines the cardiovascular system [31, 39].

The cumulative effect of these processes is systemic ECM damage in preterm infants, manifesting clinically as multisystem pathology characterized by diverse phenotypes of organ dysfunction. Protection of the matrix from degradation during the early postnatal period may enable simultaneous modification of pathogenic mechanisms underlying pulmonary, cerebral, and cardiovascular pathology associated with prematurity (Figure 1).

A principal focus of contemporary neonatology involves the identification of ECM-targeted biomarkers capable of reflecting the degree of tissue immaturity, the intensity of inflammation, the rate of remodeling, and the risk of multisystem complications. Matrix metalloproteinases (MMP-2, MMP-8, MMP-9), tissue inhibitors of metalloproteinases, and fragments of collagen, elastin, fibronectin, osteopontin, periostin, and other matricellular proteins are under active investigation as potential indicators of the severity of adaptive disorders in preterm infants [40,41].

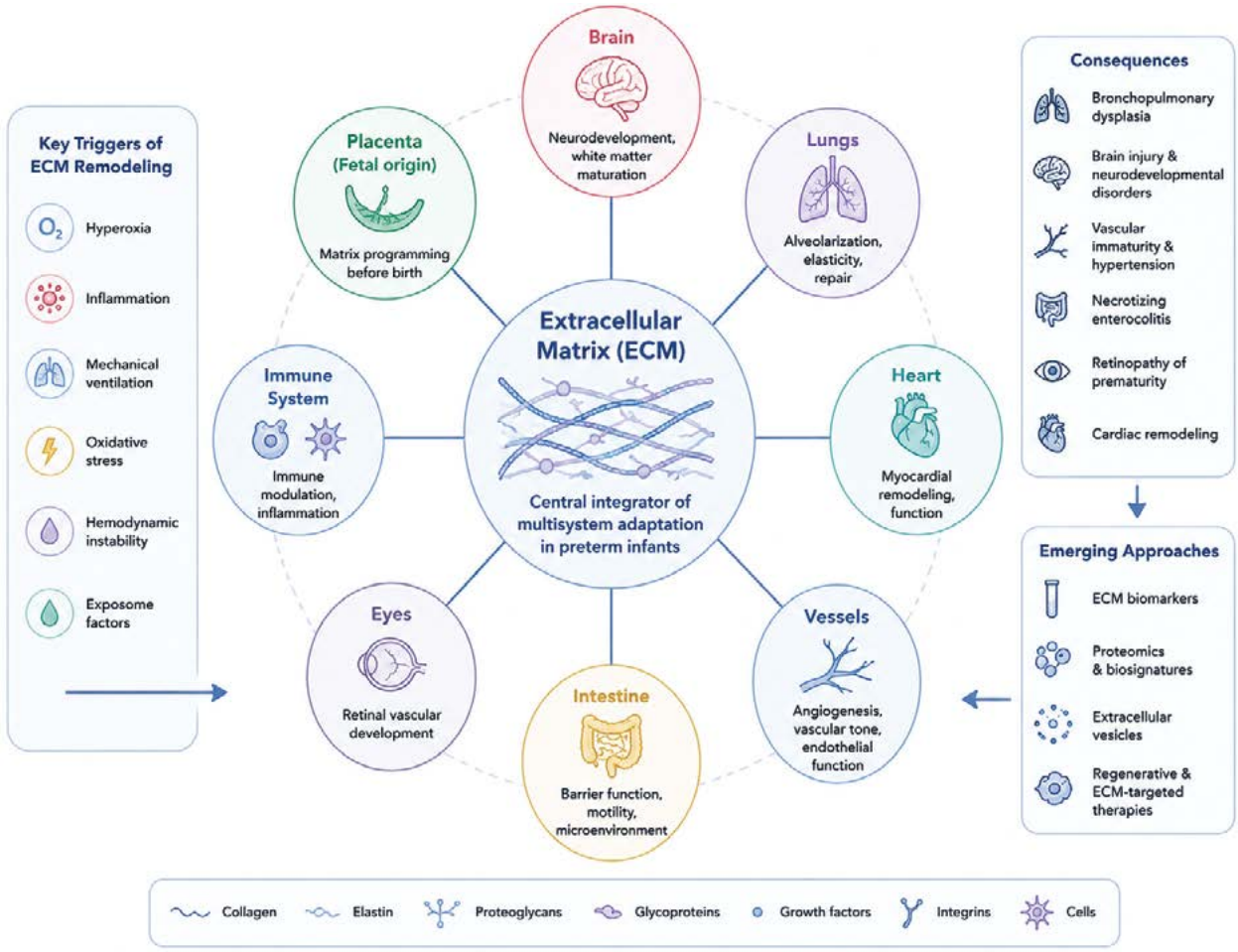


Figure 1. Extracellular Matrix as an Integrator of Multisystem Adaptation in Preterm Infants

Concurrent investigation of ECM-targeted therapeutic approaches includes the use of mesenchymal stem cells, matrix-modulating growth factors, extracellular vesicles, metalloproteinase regulators, and bioengineered matrix constructs [42].

Experimental studies demonstrate that mesenchymal stem cells modulate inflammation through multimodal mechanisms, inhibit fibrosis, stimulate angiogenesis, and normalize lung matrix architecture in bronchopulmonary dysplasia [43]. Extracellular vesicles (EVs) warrant particular consideration as cell-free therapeutic agents that deliver growth factors to tissues, arrest fibrosis, restore matrix integrity, and stimulate lung and brain development in infants [44].

ECM proteomics is anticipated to become a significant future direction. Modern highly sensitive technologies enable analysis of the composition of matrix proteins, peptides, and signaling molecules in minimal volumes of biological material. The concept of comprehensive analysis of the matrix proteome is under active development as a novel tool for neonatal risk stratification. The matrix proteome may be utilized in the future to develop personalized predictive models for bronchopulmonary dysplasia,

retinopathy of prematurity, and neurodevelopmental disorders.

The contemporary understanding of the extracellular matrix in preterm infants extends beyond the traditional conceptualization of the ECM as a structural component of connective tissue. Functioning as an integrative signaling system and a dynamic biological network, the ECM coordinates mechanical, immunological, metabolic, angiogenic, and neuroendocrine processes during postnatal adaptation and compensation. This biological network largely determines the nature of the multisystem response of the preterm infant to interrupted intrauterine maturation, oxidative stress, inflammation, and incomplete organogenesis.

The ECM serves as a target of the pathological process and as a regulator of long-term health programming, determining the trajectory of neurodevelopment, pulmonary maturation, vascular adaptation, and immune response.

The integration of molecular biology, proteomics, systems medicine, and neonatology establishes the foundation for a novel multisystem model of the preterm infant, in which the extracellular matrix constitutes the primary integrator of adaptation, compensation, repair, and the formation of long-term consequences of prematurity, thereby shaping the future development of neonatology in the coming decades.

Conclusions

1. The extracellular matrix in preterm infants functions as an integrative signaling system regulating postnatal adaptation, compensation, organogenesis, inflammation, and repair processes.

2. Preterm birth is characterized by interrupted physiological maturation of the extracellular matrix, contributing to pathological tissue remodeling and multisystem organ dysfunction.

3. Disruptions in matrix architecture and mechanotransduction are implicated in the pathogenesis of major complications of prematurity, including bronchopulmonary dysplasia, white matter injury, retinopathy of prematurity, vascular immaturity, and necrotizing enterocolitis.

4. Contemporary advances in mechanobiology, immunomatrix biology, matrix memory, and exposome medicine have reshaped the understanding of the extracellular matrix as a principal regulator of long-term biological programming in preterm infants.

5. Integration of ECM-oriented biomarkers, proteomics, extracellular vesicles, and regenerative technologies provides a foundation for developing personalized strategies for the prediction, prevention, and treatment of prematurity-associated complications.

Prospects for further research. Further research should focus on validating the role of extracellular matrix-associated biomarkers in large prospective multicenter cohorts of preterm infants, integrating proteomic technologies into neonatal risk stratification, and evaluating the clinical efficacy of ECM-targeted therapeutic strategies for the prevention and treatment of complications of prematurity.

Contribution of co-authors to the preparation of materials for the scientific article:

Tetiana Klymenko: study conception and design, scientific supervision, critical revision of the manuscript for important intellectual content, final approval of the version to be published.

Serhii Matviienko: literature search and analysis, data collection and synthesis, preparation of the manuscript draft, figure preparation, manuscript editing, and final manuscript formatting.

Conflict of interest. The authors declare that there was no actual or potential conflict of interest during the preparation of this article for publication.

Use of Artificial Intelligence. Artificial intelligence (ChatGPT, OpenAI) was used to assist in the preparation of Figure 1. The authors independently verified all scientific content, approved the final version of the figure and the manuscript, and take full responsibility for the accuracy and integrity of the published work.

Sources of funding. This article was published without any financial support.

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ПОЗАКЛІТИННИЙ МАТРИКС ЯК ІНТЕГРАТОР МУЛЬТИСИСТЕМНОЇ АДАПТАЦІЇ У ПЕРЕДЧАСНО НАРОДЖЕНИХ ДІТЕЙ

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Резюме.

Передчасне народження залишається однією з провідних причин неонатальної захворюваності, смертності та формування довготривалих порушень здоров'я. Сучасні уявлення про патогенез недоношеності дедалі більше базуються на концепції мультисистемної дезадаптації, у якій важливу роль відіграє позаклітинний матрикс (extracellular matrix, ECM). Упродовж останніх років ECM перестав розглядатися виключно як структурний компонент сполучної тканини та визначається як динамічна сигнальна система, що регулює процеси клітинної проліферації, диференціації, механотрансдукції, міжклітинної комунікації та тканинного ремоделювання.

Мета огляду – узагальнити сучасні дані щодо ролі позаклітинного матриксу в процесах мультисистемної адаптації передчасно народжених дітей, а також аналіз основних механізмів ремоделювання ECM у формуванні патології неонатального та раннього дитячого віку.

Пошук літератури проведено в базах PubMed, Scopus, Web of Science та Cochrane Library за період 2021-2026 років. Проаналізовано сучасні експериментальні та клінічні дослідження, присвячені матриксній біології, механобіології, неонатальному запаленню, ECM-асоційованим біомаркерам. Встановлено, що порушення структури та сигнальної функції ECM асоціюється з розвитком бронхолегеневої дисплазії, церебральних ушкоджень, судинної дисфункції, некротизуючого ентероколіту та інших ускладнень недоношеності. Оксидативний стрес, системне запалення, гіпероксія та механічна вентиляція легень розглядаються як ключові тригери патологічного матриксного ремоделювання. Перспективними напрямами сучасної неонатології є ECM-орієнтовані біомаркери, протеомні технології, позаклітинні везикули та ECM-таргетна терапія. Позаклітинний матрикс слід розглядати як центральний інтегратор мультисистемної адаптації передчасно народжених дітей та перспективну платформу для персоніфікованого прогнозування, профілактики й терапії ускладнень недоношеності.

Ключові слова: передчасно народжені діти; позаклітинний матрикс; мультисистемна адаптація; ремоделювання тканин; механотрансдукція; персоніфікована неонатологія.

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Отримано: 04 червня 2026 р.
Прийнято до публікації: 24 вересня 2026 р.
Опубліковано: 28 вересня 2026 р.