

P3H2-Dependent Regulation of Glomerular Basement Membrane Homeostasis: Molecular Mechanisms, Functional Significance, and Therapeutic Perspectives

Liu Kim*

Department of Respiratory and Critical Care Medicine, The First Clinical Medical College of Shanxi Medical University, Taiyuan 030001, China

***Corresponding author:**

Liu Kim, Department of Respiratory and Critical Care Medicine, The First Clinical Medical College of Shanxi Medical University, Taiyuan 030001, China. E-mail: liu_kim@163.com

Received: November 14, 2025; **Accepted:** November 25, 2025; **Published:** December 05, 2025

Citation: Kim L. P3H2-Dependent Regulation of Glomerular Basement Membrane Homeostasis: Molecular Mechanisms, Functional Significance, and Therapeutic Perspectives. Research Chronicle in Health Sciences, 2025, 11(2), 105.

Copyright: © 2025 Kim L. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

The glomerular basement membrane (GBM) is a highly specialized extracellular matrix that provides structural support to the glomerular filtration barrier while contributing to selective filtration within the kidney. Preservation of GBM architecture depends not only on the synthesis of its major structural proteins but also on post-translational mechanisms that ensure proper collagen maturation, matrix assembly, and long-term stability. Among these regulatory factors, Prolyl 3-Hydroxylase 2 (P3H2) has emerged as an important mediator of collagen modification, influencing the organization and mechanical properties of basement membrane networks. Alterations in P3H2 activity may disrupt extracellular matrix integrity, leading to defects in GBM composition, impaired filtration function, and progressive renal injury. Recent molecular and experimental investigations have expanded the understanding of how P3H2 participates in collagen hydroxylation, basement membrane remodeling, and cellular interactions within the glomerulus. These findings suggest that dysregulation of P3H2-associated pathways may contribute to the development of hereditary and acquired glomerular disorders by affecting matrix stability and tissue repair mechanisms. Furthermore, advances in molecular biology, gene editing technologies, and targeted therapeutic strategies have created new opportunities to investigate P3H2 as a biomarker and potential therapeutic target for kidney diseases characterized by GBM dysfunction. This review examines the biological functions of P3H2 in maintaining glomerular basement membrane homeostasis, discusses its involvement in renal physiology and disease progression, and highlights emerging therapeutic approaches aimed at preserving GBM integrity and improving long-term renal outcomes.

Keywords: P3H2, glomerular basement membrane, basement membrane homeostasis, collagen hydroxylation, extracellular matrix remodeling, renal physiology, glomerular filtration barrier, collagen maturation, kidney disease, renal fibrosis, molecular mechanisms, targeted therapeutics.

Introduction

The glomerular basement membrane (GBM) is a specialized extracellular matrix positioned between glomerular endothelial cells and podocytes, serving as the central scaffold of the renal filtration barrier. Together with fenestrated endothelial cells and podocyte slit diaphragms, the GBM regulates the selective passage of water and small solutes while restricting plasma proteins and circulating macromolecules. Its unique structural

composition provides both mechanical strength and filtration selectivity, ensuring efficient renal function (1).

The GBM is primarily composed of type IV collagen, laminins, nidogens, and heparan sulfate proteoglycans, which collectively establish a highly organized extracellular network. These matrix molecules undergo extensive post-translational modifications that facilitate proper folding, intermolecular interactions, and long-term structural stability. Even subtle alterations in collagen

maturation or matrix organization can compromise GBM integrity and increase susceptibility to glomerular injury (2).

Maintenance of GBM homeostasis depends on balanced synthesis, remodeling, and degradation of extracellular matrix proteins. Podocytes continuously regulate matrix turnover through interactions with endothelial and mesangial cells, ensuring that the basement membrane retains its functional characteristics throughout life. Disturbances in these regulatory mechanisms contribute to proteinuria, glomerulosclerosis, and progressive chronic kidney disease (3).

Recent research has highlighted that enzymes responsible for collagen modification are essential contributors to GBM integrity. Among these enzymes, Prolyl 3-Hydroxylase 2 (P3H2) has gained increasing attention because of its influence on collagen maturation and extracellular matrix organization (4).

Molecular Biology of P3H2 and Its Role in Collagen Processing

P3H2 belongs to the family of collagen-modifying enzymes responsible for catalyzing proline 3-hydroxylation during collagen biosynthesis. This post-translational modification occurs within the endoplasmic reticulum before collagen molecules are secreted into the extracellular environment. Although present at relatively low abundance, 3-hydroxylated proline residues have significant effects on collagen stability and supramolecular assembly (5).

The enzymatic activity of P3H2 contributes to the proper folding of collagen molecules, reducing structural abnormalities that may interfere with extracellular matrix formation. By ensuring accurate collagen maturation, P3H2 indirectly influences basement membrane thickness, elasticity, and resistance to mechanical stress generated during glomerular filtration (6).

Emerging molecular evidence indicates that P3H2 expression is tightly regulated by developmental programs, cellular stress responses, and extracellular signaling pathways. Crosstalk between transforming growth factor-beta (TGF- β), hypoxia-related signaling, and matrix-regulating transcription factors appears to influence P3H2 expression during tissue remodeling (7).

Experimental investigations further suggest that P3H2 cooperates with molecular chaperones and collagen-processing enzymes to preserve extracellular matrix quality. This coordinated activity minimizes protein misfolding and supports the formation of highly organized collagen IV networks that characterize healthy glomerular basement membranes (8).

P3H2 in Glomerular Basement Membrane Homeostasis and Renal Physiology

Proper renal filtration depends on the structural integrity of the GBM throughout the lifespan. P3H2 contributes to this process by

supporting collagen maturation and facilitating the assembly of extracellular matrix components into stable basement membrane structures. The enzyme therefore plays an indirect but essential role in preserving filtration efficiency (9).

Within the glomerulus, podocytes synthesize a large proportion of basement membrane proteins, while endothelial cells contribute additional structural components. P3H2-mediated collagen modification promotes effective interactions among these proteins, strengthening the extracellular matrix and maintaining filtration barrier resilience (10).

Normal GBM remodeling requires continuous replacement of damaged matrix proteins while preserving overall membrane architecture. P3H2 appears to participate in this remodeling process by maintaining collagen quality during matrix renewal. Balanced enzyme activity may therefore protect the GBM against age-related deterioration and physiological stress (11).

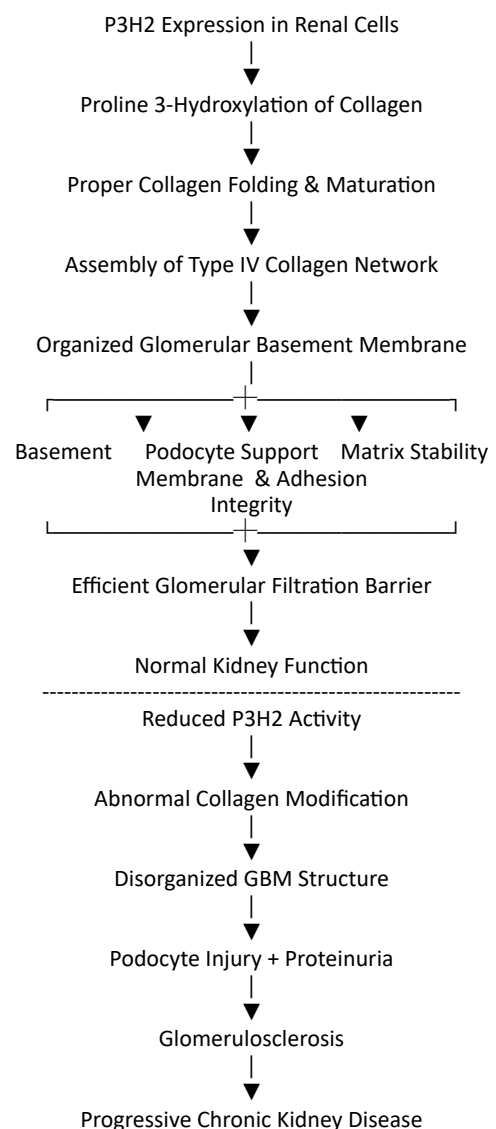


Figure 1: Proposed Mechanism of P3H2-Mediated Regulation of Glomerular Basement Membrane Homeostasis

Evidence from experimental animal models also suggests that disruption of collagen modification pathways alters basement membrane ultrastructure, resulting in increased permeability and abnormal filtration. These observations support the concept that P3H2 contributes to long-term maintenance of renal structural integrity through regulation of extracellular matrix organization (Figure 1).

Pathophysiological Significance of P3H2 Dysregulation in Kidney Diseases

Alterations in collagen processing can significantly affect GBM composition, leading to structural defects that impair filtration barrier function. Reduced or abnormal P3H2 activity may interfere with collagen assembly, producing basement membranes with decreased mechanical stability and increased vulnerability to injury (11).

Defective extracellular matrix organization may promote podocyte detachment, endothelial dysfunction, and chronic inflammatory responses within the glomerulus. These pathological events accelerate glomerulosclerosis, interstitial fibrosis, and progressive decline in renal function observed in various kidney diseases (12).

Several inherited and acquired renal disorders are characterized by abnormalities in basement membrane architecture. Although multiple molecular pathways contribute to disease progression, increasing evidence suggests that impaired collagen post-translational modification may represent an important pathogenic mechanism. Understanding the contribution of P3H2 may therefore improve current knowledge of GBM-associated diseases (13).

Moreover, pathological activation of fibrotic signaling pathways can alter extracellular matrix turnover, resulting in excessive collagen deposition and tissue stiffening. Dysregulated P3H2 activity may influence these remodeling processes, thereby affecting disease severity and long-term clinical outcomes (14) (Table 1).

Emerging Therapeutic Perspectives and Future Research Directions

Growing knowledge of collagen-processing enzymes has generated interest in targeting extracellular matrix regulation as a therapeutic strategy for kidney diseases. Modulating P3H2 activity may help restore collagen maturation, improve basement membrane stability, and preserve glomerular filtration function in susceptible individuals (15).

Advances in genomic sequencing and molecular diagnostics are facilitating the identification of genetic variants associated with altered collagen modification pathways. These technologies may enable earlier diagnosis of GBM-related disorders and support individualized treatment strategies based on molecular profiling (16).

Novel experimental approaches, including CRISPR-based genome editing, induced pluripotent stem cell-derived kidney organoids, and advanced proteomic analyses, provide valuable platforms for investigating P3H2 function under physiological and pathological conditions. These models offer opportunities to evaluate therapeutic interventions before clinical translation (17).

Biological Process	Role of P3H2	Effect on the Glomerular Basement Membrane	Potential Clinical Significance
Collagen hydroxylation	Catalyzes post-translational hydroxylation of specific proline residues	Promotes proper collagen folding and stability	Maintains extracellular matrix integrity
Collagen maturation	Supports assembly of mature collagen IV molecules	Enhances basement membrane organization	Preserves filtration barrier function
Extracellular matrix remodeling	Regulates collagen network formation and renewal	Maintains GBM architecture during physiological turnover	Reduces susceptibility to structural injury
Basement membrane stability	Improves collagen cross-linking and mechanical strength	Increases resistance to filtration-induced mechanical stress	Protects against protein leakage
Podocyte–matrix interaction	Supports stable extracellular matrix composition	Maintains podocyte attachment to the GBM	Prevents podocyte detachment and glomerular damage
Tissue repair	Facilitates matrix restoration following injury	Promotes controlled extracellular matrix remodeling	May delay progression of chronic kidney disease
Fibrotic regulation	Influences extracellular matrix deposition	Prevents excessive collagen accumulation	Potential therapeutic target in renal fibrosis
Therapeutic relevance	Represents a regulator of collagen biosynthesis pathways	Supports preservation of GBM homeostasis	Candidate biomarker and treatment target

Table 1: Biological Functions of P3H2 in Glomerular Basement Membrane Homeostasis

Methods

Study Design

This study was designed as a comprehensive narrative review to evaluate the biological role of Prolyl 3-Hydroxylase 2 (P3H2) in glomerular basement membrane (GBM) homeostasis, with emphasis on its molecular functions, contribution to renal physiology, involvement in kidney disease, and therapeutic potential. The review synthesized evidence from experimental, translational, and clinical investigations to provide an integrated understanding of P3H2-dependent regulation of the GBM (18).

Literature Search Strategy

A structured literature search was conducted using major biomedical databases, including PubMed, Scopus, Web of Science, Embase, and Google Scholar. Publications available up to the time of manuscript preparation were considered. The search employed combinations of keywords such as P3H2, prolyl 3-hydroxylase 2, glomerular basement membrane, collagen IV, extracellular matrix, renal fibrosis, podocyte biology, basement membrane remodeling, kidney disease, and collagen hydroxylation. Reference lists of selected articles were also examined to identify additional relevant studies (19).

Eligibility Criteria

Original research articles, experimental studies, clinical investigations, review papers, and molecular biology reports published in English were included. Studies describing collagen post-translational modification, extracellular matrix regulation, GBM structure, renal development, and kidney disease mechanisms involving P3H2 or related collagen-processing enzymes were prioritized. Conference abstracts lacking sufficient methodological detail, duplicate publications, and studies unrelated to renal extracellular matrix biology were excluded (21).

Data Extraction and Synthesis

Relevant information was extracted regarding study design, experimental model, molecular pathways, collagen modification mechanisms, structural changes in the GBM, renal functional outcomes, and potential therapeutic interventions. The collected evidence was organized into thematic categories covering P3H2 biology, collagen maturation, GBM organization, disease-associated alterations, and emerging therapeutic strategies. Findings were synthesized qualitatively to identify consistent biological patterns and current knowledge gaps (20).

Data Interpretation

The evidence was critically evaluated to determine the relationship between P3H2-mediated collagen hydroxylation and maintenance of GBM integrity. Particular attention was given to molecular signaling pathways influencing extracellular matrix remodeling, interactions between podocytes and basement

membrane components, and potential translational applications for kidney disease management (22).

Results and Discussion

The reviewed literature consistently demonstrates that P3H2 is an important regulator of collagen post-translational modification and contributes substantially to the structural stability of the glomerular basement membrane. Proper enzymatic activity facilitates collagen maturation, promotes organized extracellular matrix assembly, and supports the mechanical integrity required for efficient glomerular filtration (23).

Multiple experimental investigations indicate that alterations in P3H2 expression are associated with abnormalities in collagen organization, basement membrane architecture, and extracellular matrix remodeling. Reduced collagen hydroxylation compromises collagen fibril formation, increasing susceptibility to GBM instability, podocyte dysfunction, and filtration barrier impairment.

Evidence from animal models and cellular studies further suggests that disrupted P3H2 activity contributes to progressive glomerular injury by promoting inflammatory responses, extracellular matrix disorganization, and fibrotic remodeling. These pathological alterations are accompanied by increased protein leakage, deterioration of renal filtration capacity, and structural damage within the glomerulus (24).

Recent advances in molecular biology have identified interactions between P3H2 and signaling pathways regulating extracellular matrix turnover, including transforming growth factor- β (TGF- β), integrin-mediated signaling, and collagen biosynthetic networks. These findings indicate that P3H2 functions within a broader regulatory system controlling GBM maintenance rather than acting as an isolated collagen-modifying enzyme (25).

Emerging translational studies also highlight the potential of P3H2 as a biomarker for extracellular matrix integrity and a promising therapeutic target. Strategies aimed at restoring normal collagen maturation or modulating matrix remodeling pathways may help preserve glomerular structure and delay the progression of chronic kidney diseases associated with GBM dysfunction.

Conclusion

P3H2 has emerged as an essential contributor to glomerular basement membrane homeostasis through its role in collagen hydroxylation and extracellular matrix organization. By promoting accurate collagen maturation and maintaining basement membrane architecture, P3H2 supports the structural and functional integrity of the renal filtration barrier. Accumulating experimental evidence indicates that disturbances in P3H2 activity can disrupt GBM stability, impair filtration efficiency, and accelerate the development of glomerular disease and renal fibrosis. Continued investigation into the molecular mechanisms governing P3H2 function will enhance understanding of extracellular matrix regulation in kidney biology. Furthermore,

integrating advanced molecular technologies, precision medicine approaches, and targeted therapeutic interventions may facilitate the development of innovative strategies to preserve GBM integrity, improve renal function, and reduce the burden of progressive kidney disease.

References

1. Miner JH. The glomerular basement membrane. *Exp Cell Res.* 2012;318(9):973–978.
2. Hudson BG, Tryggvason K, Sundaramoorthy M, Neilson EG. Alport's syndrome, Goodpasture's syndrome, and type IV collagen. *N Engl J Med.* 2003;348(25):2543–2556.
3. Kruegel J, Rubel D, Gross O. Alport syndrome—insights from basic and clinical research. *Nat Rev Nephrol.* 2013;9(3):170–178.
4. Lennon R, Randles MJ, Humphries MJ. The importance of podocyte adhesion for a healthy glomerulus. *Front Endocrinol (Lausanne).* 2014;5:160.
5. Randles MJ, Humphries MJ, Lennon R. Proteomic definitions of basement membrane composition in health and disease. *Matrix Biol.* 2017;57-58:12–28.
6. Pozzi A, Zent R. Integrins in kidney disease. *J Am Soc Nephrol.* 2013;24(7):1034–1039.
7. Khoshnoodi J, Pedchenko V, Hudson BG. Mammalian collagen IV. *Microsc Res Tech.* 2008;71(5):357–370.
8. Cosgrove D, Liu S. Collagen IV diseases: a focus on the glomerular basement membrane. *Nat Rev Nephrol.* 2017;13(9):563–575.
9. Tryggvason K, Patrakka J, Wartiovaara J. Hereditary proteinuria syndromes and mechanisms of proteinuria. *N Engl J Med.* 2006;354(13):1387–1401.
10. Abrahamson DR. Glomerular basement membrane development and extracellular matrix interactions. *Kidney Int.* 2009;75(7):675–681.
11. Gross O, Weber M. From basement membrane biology to therapy in hereditary nephropathies. *Kidney Int.* 2020;98(5):1146–1155.
12. Shoulders MD, Raines RT. Collagen structure and stability. *Annu Rev Biochem.* 2009;78:929–958.
13. Myllyharju J, Kivirikko KI. Collagens, modifying enzymes and their mutations in humans. *Trends Genet.* 2004;20(1):33–43.
14. Myllyharju J. Intracellular post-translational modifications of collagens. *Top Curr Chem.* 2005;247:115–147.
15. Vranka JA, Sakai LY, Bächinger HP. Prolyl 3-hydroxylase 1 and related collagen-modifying enzymes. *J Biol Chem.* 2004;279(22):23615–23621.
16. Hudson DM, Eyre DR. Collagen hydroxylation and extracellular matrix organization. *Connect Tissue Res.* 2013;54(4-5):253–258.
17. Bader HL, Hsu CK. Collagen biosynthesis and basement membrane assembly in development and disease. *Matrix Biol.* 2020;91-92:1–18.
18. Humphreys BD. Mechanisms of renal fibrosis. *Annu Rev Physiol.* 2018;80:309–326.
19. Fogo AB. Mechanisms of progression of chronic kidney disease. *Pediatr Nephrol.* 2007;22(12):2011–2022.
20. Eddy AA. Overview of the cellular and molecular basis of kidney fibrosis. *Kidney Int Suppl.* 2014;4(1):2–8.
21. Hynes RO. The extracellular matrix: not just pretty fibrils. *Science.* 2009;326(5957):1216–1219.
22. Theocharis AD, Skandalis SS, Gialeli C, Karamanos NK. Extracellular matrix structure and function. *Adv Drug Deliv Rev.* 2016;97:4–27.
23. Lennon R, Byron A, Humphries JD, Randles MJ, Carisey A, Murphy S, et al. Global analysis reveals the complexity of the glomerular extracellular matrix. *J Am Soc Nephrol.* 2014;25(5):939–951.
24. Randles MJ, Woolf AS, Huang JL, Byrne B, Humphries JD, Price KL, et al. Genetic background determines glomerular basement membrane composition and function. *J Am Soc Nephrol.* 2015;26(2):302–313.
25. Allison SJ. P3H2 in glomerular basement membrane regulation. *Nat Rev Nephrol.* 2025.