Advances in Obstetrics and Gynecology Research, 2025, Volume 3, Issue 2
https://ojs.bbwpublisher.com/index.php/AOGR
Online ISSN: 2981-8060

Podocyte Injury in Preeclampsia: Mechanisms and Therapies

Ying Wang[1], Xiu Wang[2]*

[1]The Second Clinical College of Medicine, Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China;
[2]Xi'an People's Hospital (the Fourth Hospital of Xi'an City), Xi'an 710004, Shaanxi, China

**Author to whom correspondence should be addressed.*

***A*bstract:** Pre-eclampsia is still one of the leading causes of maternal and fetal morbidity and mortality worldwide, affecting multiple organ systems. Despite extensive research, its underlying etiology remains unclear. Proteinuria is a hallmark of a diagnosis of preeclampsia and is usually accompanied by podocyte damage, which is changes in the structure and function of the podocytes. Recent technological advances have identified a critical role for podocytes in the loss of renal filtration function in preeclampsia. However, the molecular mechanisms leading to proteinuria and podocyte damage in preeclampsia are unknown, which leads to a lack of targeted therapy. Recent years have witnessed challenges the traditional view, that kidney damage in preeclampsia is caused only by glomerular endothelial cell injury. Similarly, podocytes were identified as key players in the pathogenesis of proteinuria in preeclampsia. In this review, we review the mechanisms of renal injury (especially podocytes) in preeclampsia to elucidate the relevance of podocyte injury to proteinuria and suggest specific therapeutic strategies for proteinuria in preeclampsia.

Keywords: Pre-eclampsia; Podocytes; Pathogenesis; Proteinuria

Online publication: July 8, 2025

1. Introduction

Pre-eclampsia is a common syndrome usually presenting after the 20th week of gestation with an overall prevalence of approximately 2–5 percent [1]. Pre-eclampsia pathology is characterized by impaired trophoblastic invasion and abnormal remodeling of the uterine spiral arteries, resulting in placental ischemia and the subsequent secretion of soluble factors that activate immune cells and induce endothelial cell [2]. This clinical stage of generalized ischemia is characteristic of preeclampsia. Although most patients have a favorable obstetric outcome, some patients develop adverse and serious complications. Without timely intervention, these complications may lead to intrauterine growth restriction, placental abruption, or even death [3]. Mothers with preeclampsia are at risk of developing serious complications, such as eclampsia, HELLP syndrome, and multisystem organ dysfunction, all of which pose a serious threat to maternal and fetal health (**Figure 1**). Proteinuria is a key diagnostic marker

for preeclampsia, since the kidneys are particularly susceptible to the soluble factors secreted by the placenta. Proteinuria occurs due to damage to the glomerular filtration barrier, of which podocytes are a crucial component. Proteinuria in preeclampsia is closely associated with changes in podocytes, providing a new perspective for understanding preeclampsia nephropathy. In this review, we provide an update and overview of the pathogenesis of proteinuria in preeclampsia, focusing on the involvement of podocytes.

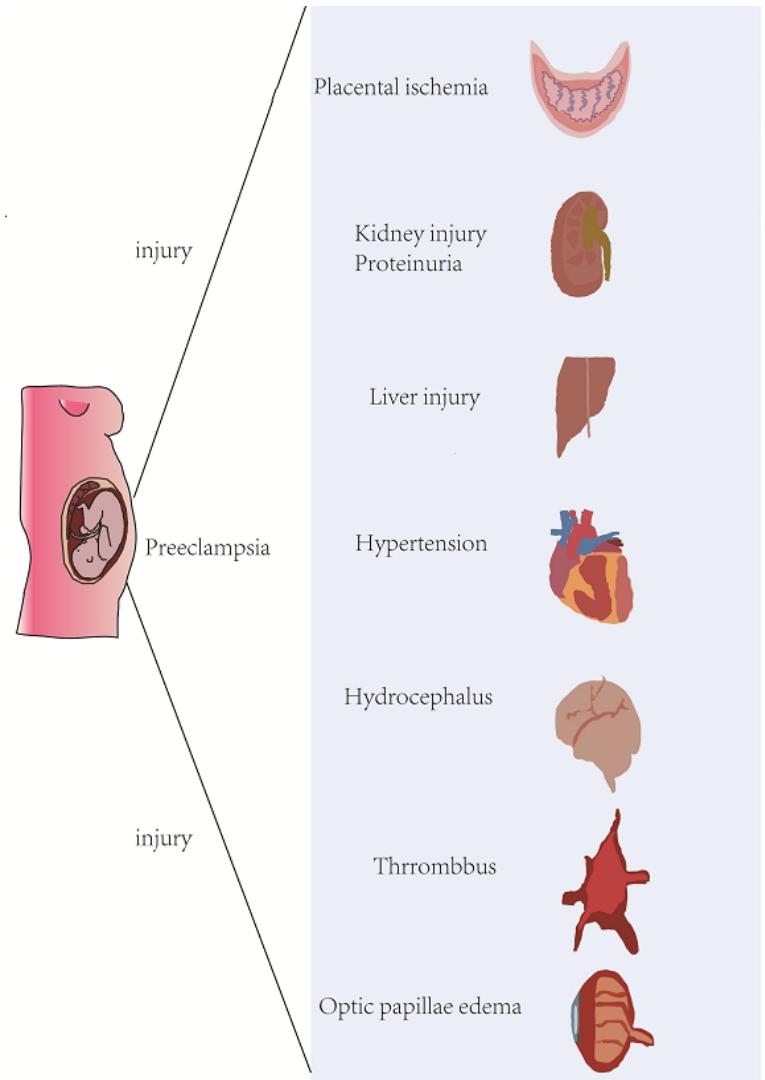

Figure 1. Features of preeclampsia.

2. The molecular and cellular basis of proteinuria in preeclampsia: focusing on the podocyte

Preeclampsia is a pregnancy-specific disorder characterized by the onset of hypertension and proteinuria after 20 weeks of pregnancy [4]. The proteinuria associated with preeclampsia is unknown, which poses a great challenge for targeted therapy. Preeclampsia is thought to be caused by endothelial cell dysfunction [5]. This lesion is also seen in hypertensive patients of pregnancy without proteinuria. This suggests that endothelial cell injury alone is not sufficient to explain the loss of filtration function. Recent studies have highlighted the critical role of podocytes in the

glomerular filtration barrier, providing new insights into the pathophysiology of proteinuria in preeclampsia [6].

3. Mechanisms of podocyte injury in preeclampsia

3.1. The role of the signaling pathway of the WNT

In normal placentas, tight junctions are composed of the peripheral protein ZO-1, the integral protein occludin, and the claudins 1, 3, and 5. However, in patients with preeclampsia, the expression of claudins 1, 3, and 5 is significantly decreased, while the expression of ZO-1 and occludin remains unchanged. This decrease in claudins leads to an increase in the permeability of the tight junctions in placental endothelial cells, resulting in decreased placental perfusion and endothelial dysfunction [7]. The loss of claudin 5 downregulates the expression of the peripheral protein ZO-1, induces the nuclear translocation of ZONAB, and subsequently suppresses the expression of WNT inhibitory factor-1 (WIF1), thereby activating the WNT signaling pathway [8]. Specifically, knockout of claudin 5 or WIF1 in podocytes in mice recapitulates the manifestations of podocyte injury and proteinuria, highlighting the critical role of claudin 5 in suppressing WNT activity in the kidney [9].

3.2. The role of the β-catenin signaling pathway

C-X-C chemokine receptor type 4 (CXCR4), a G protein-coupled receptor (GPCR), is a critical regulator of podocyte injury and proteinuria, especially in the context of oxidative stress [10]. Recent studies have shown that CXCR4 expression is significantly upregulated in the placenta and peripheral blood of patients with preeclampsia. This upregulation is associated with increased inflammatory responses, vascular damage, and altered immune cell regulation, suggesting that CXCR4 may contribute to the pathogenesis of preeclampsia by regulating these processes [11]. When CXCR4 is bound to CXCL12, it undergoes conformational changes that activate its associated G proteins and phosphorylate serine/threonine residues. This phosphorylation creates binding sites for β-arrestin-1, which activates the Src family kinases, forming a CXCR4/β-arrestin-1/Src signaling complex. Activation of this complex triggers the phosphorylation of Src, which in turn induces transactivation of the epidermal growth factor receptor (EGFR) and subsequent phosphorylation of extracellular signal-regulated kinases 1 and 2 (ERK1/2), thereby propagating downstream signaling cascades [12,13]. These events activate β-arrestin, which regulates podocyte cytoskeletal rearrangement and expression of adhesion molecules, thereby compromising the integrity of the filtration barrier [14]. Additionally, β-arrestin promotes podocyte apoptosis, resulting in podocyte loss and dysfunction of the filtration barrier [15].

3.3. The activation of the NLRP3 inflammasome

The NLRP3 inflammasome, a multiprotein complex, drives the secretion of IL-1 and IL-18 through caspase-1 activation and also facilitates the release of high-mobility group box 1 (HMGB1) [16]. In patients with preeclampsia, the expression of the NLRP3 inflammasome is significantly upregulated in the placentas [17], which is associated with an excessive inflammatory state. Inflammation of the NLRP3 inflammasome induces the release of inflammatory cytokines and abnormal expression of structural proteins, leading to podocyte injury and proteinuria [18]. Oxidative stress is a key factor in the activation of the NLRP3 inflammasome [19], with superoxide anion ($\cdot O_2^-$) and hydrogen peroxide (H_2O_2) being involved in this process [20]. Reduced levels of reactive oxygen species (ROS) can inhibit the activation of the NLRP3 inflammasome, thereby protecting podocyte morphology. Additionally, fatty acid-binding protein 4 (FABP4) promotes inflammasome activation through a positive feedback loop with IL-17.

3.4. Reactive oxygen species (ROS)

Hypoxia during pregnancy is associated with a high level of reactive oxygen species (ROS) in the placenta, which leads to oxidative stress. Mitochondria are a major source of ROS, and hypoxia significantly affects mitochondrial structure, alters electron transport chain function [21], and increases ROS production [22]. In preeclampsia, placental tissues are highly stressed, driving disease progression [23]. Mitochondrial dysfunction is closely linked to podocyte injury, characterized by decreased mitochondrial membrane potential and increased levels of cytochrome C [24]. ROS levels excessively high can damage cellular macromolecules, resulting in structural and functional impairments [25]. ROS can damage and kill cells by activating various biochemical pathways, such as the polyol pathway, advanced glycation end-products pathway, protein kinase C pathway, and hexosamine pathway [26]. In preeclampsia, levels of advanced oxidation protein products (AOPPs) are significantly elevated, closely linked to the state of oxidative stress [27]. AOPPs interact with the receptor for advanced glycation end-products (RAGE) on podocyte surfaces, activating NADPH oxidase complexes (such as Nox2 and p47phox) and increasing ROS production. ROS further activates nuclear factor-κB (NF-κB), promoting the expression of Wnt ligands (such as Wnt1 and Wnt7a) and activating the Wnt/β-catenin signaling pathway. This results in podocyte dedifferentiation and mesenchymal transition, which is characterized by the loss of podocyte-specific markers (such as nephrin and podocalyxin) and the increase of injury markers (such as fibronectin), resulting in podocyte dysfunction and proteinuria [28].

3.5. VEGF and podocyte damage

Podocytes are the principal source of vascular endothelial growth factor (VEGF) within the glomerulus, and they play a crucial role in maintaining glomerular function. Mice with podocyte-specific knockout of VEGF display severe glomerular injury, underscoring the critical role of VEGF in regulating glomerular function. In preeclampsia, elevated levels of soluble fms-like tyrosine kinase 1 (sFlt-1) decrease the availability of VEGF within the glomerulus [29]. sFlt-1 exerts its effects on podocytes through two mechanisms: First, it indirectly inhibits the transfer of VEGF from podocytes to endothelial cells, resulting in endothelial cell damage and the release of toxic endothelin-1, which subsequently injures podocytes and induces proteinuria. Second, sFlt-1 directly disrupts the VEGF autocrine loop in podocytes [30].

Podocytes and glomerular endothelial cells are key components of the glomerular filtration barrier, and their functions depend on an appropriate concentration of VEGF within the glomerulus [31]. sFlt-1 interferes with the communication between podocytes and glomerular endothelial cells, ultimately affecting both cell types. Podocyte injury may result from the disruption of the VEGF autocrine loop or from toxic mediators released by damaged endothelial cells. This may provide a plausible explanation for the occurrence of proteinuria in patients with preeclampsia [32].

4. Therapy strategies for podocyte injury

Podocyte injury is a central pathological characteristic of proteinuric nephropathies and holds significant implications for renal function and disease progression. As our understanding of the molecular mechanisms underlying podocyte dysfunction grows, therapeutic strategies targeting podocyte injury are emerging, aiming to preserve the integrity and function of podocytes.

4.1. Glucocorticoids (GCs): The cornerstone of therapy

Glucocorticoids have long been a mainstay in the treatment of podocyte-related proteinuric nephropathies [33].

Their therapeutic effectiveness is attributed to multiple mechanisms, including stabilizing the actin cytoskeleton, upregulating nephrin expression, reducing IL-6 levels, and inhibiting podocyte apoptosis [34]. These effects are mediated by the glucocorticoid receptor present on podocytes [35]. In addition to their anti-inflammatory effects, glucocorticoids modulate the expression of key proteins [36], thereby influencing the structure and function of podocytes. Glucocorticoids enhance the integrity of the glomerular filtration barrier by activating the promoter of the podocyte slit diaphragm protein nephrin, thereby promoting its glycosylation and phosphorylation [37]. These modifications strengthen the interaction between nephrin and the actin cytoskeleton [38]. Glucocorticoids directly act on podocytes to prevent them from detaching from the glomerular basement membrane (GBM), stabilize actin filaments, and prolong podocyte survival. Their anti-inflammatory actions further alleviate glomerular inflammation by inhibiting the secretion of pro-inflammatory cytokines, such as interleukin, transforming growth factor-β (TGF-β), and tumor necrosis factor (TNF).

4.2. Emerging therapeutic strategies

With a greater understanding of the molecular mechanisms underlying podocyte injury, novel therapeutic strategies are constantly emerging. Monoclonal antibodies targeting the angiopoietin-like protein 3 (ANGPTL3) represent a promising therapeutic approach [39]. ANGPTL3 is a secretory glycoprotein whose C-terminal fibrinogen-like domain (FLD) plays a critical role in podocyte injury. Anti-ANGPTL3-FLD antibodies reduce the activation of integrin αvβ3 and downstream Rac1, thus decreasing reactive oxygen species (ROS) production within podocytes. This intervention relieves mitochondrial damage and apoptosis, establishing ANGPTL3 as a potential target for treating proteinuria [40]. Other emerging therapies include the mycophenolate mofetil (MMF), which restores the integrity of the podocyte actin cytoskeleton, and ofatumumab [41], a human-mouse chimeric CD20 monoclonal antibody that protects podocytes by preventing actin cytoskeleton remodeling and podocyte detachment. In preeclampsia, the excessive production of soluble Fms-like tyrosine kinase 1 disrupts the glomerular filtration barrier by inhibiting the VEGF signaling pathway. Strategies to reduce sFLT1-mediated injury include using siRNA to inhibit sFLT1 production and employing dextran sulfate plasma exchange to clear sFLT1 from circulation. These approaches have shown promise in animal models and clinical settings, extending gestation and improving proteinuria.

5. Conclusion

In this review, we have focused on the biology of podocytes, investigating their associated signaling pathways and regulatory factors. This approach not only has deepened our understanding of the unique structural and functional characteristics of podocytes but also provides new perspectives for future research directions. Despite significant advances in identifying the molecular composition of podocytes, many critical questions remain unanswered.

In future research on how renal disease progresses in preeclampsia, the development and use of appropriate animal models will be important. Podocyte injury triggers a complex biological response that is essential for maintaining the integrity of the glomerular structure. while some studies have provided valuable insights into the molecular links between “damaged” podocytes and proteinuria, the challenge lies in identifying the most promising therapeutic targets from a multitude of molecular events. The critical role of the glomerular three-layer structure, comprising endothelial cells, the glomerular basement membrane, and podocytes, in maintaining filtration barrier integrity is well established. The central involvement of podocytes in proteinuria has positioned

them as the most promising therapeutic target for proteinuria-related diseases.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Tersigni C, Maulucci G, Castellani R, et al., 2022, Enoxaparin Increases D6 Receptor Expression and Restores Cytoskeleton Organization in Trophoblast Cells from Preeclampsia. Cells, 11(13): 2036.

[2] Kornacki J, Olejniczak O, Sibiak R, et al., 2023, Pathophysiology of Pre-Eclampsia—Two Theories of the Development of the Disease. International Journal of Molecular Sciences, 25(1): 307.

[3] Cormick G, Betran A, Ciapponi A, et al., 2016, Inter-Pregnancy Interval and Risk of Recurrent Pre-Eclampsia: Systematic Review and Meta-Analysis. Reproductive Health, 13: 1–10.

[4] Program N, 2000, Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. American Journal of Obstetrics and Gynecology, 183(1): S1–S22.

[5] Assady S, Wanner N, Skorecki K, et al., 2017, New Insights into Podocyte Biology in Glomerular Health and Disease. Journal of the American Society of Nephrology, 28(6): 1707–1715.

[6] Embarazo A, Saleem M, Bueno J, et al., 2007, A Novel Renal Perspective of Preeclampsia: A Look from the Podocyte. Nephrol Dial Transplant, 22(5): 1477–1490.

[7] Liévano S, Alarcón L, Chávez–Munguía B, et al., 2006, Endothelia of Term Human Placentae Display Diminished Expression of Tight Junction Proteins During Preeclampsia. Cell and Tissue Research, 324(3): 433–448.

[8] Sun H, Li H, Yan J, et al., 2022, Loss of CLDN5 in Podocytes Deregulates WIF1 to Activate WNT Signaling and Contributes to Kidney Disease. Nature Communications, 13(1): 1600.

[9] Balkawade R, Chen C, Crowley M, et al., 2019, Podocyte-Specific Expression of Cre Recombinase Promotes Glomerular Basement Membrane Thickening. American Journal of Physiology–Renal Physiology, 316(5): F1026–F1040.

[10] Mo H, Wu Q, Miao J, et al., 2017, CXC Chemokine Receptor Type 4 Plays a Crucial Role in Mediating Oxidative Stress-Induced Podocyte Injury. Antioxidants & Redox Signaling, 27(6): 345–362.

[11] Zheng Z, Chen H, Zhu S, et al., 2021, CXCR4/CXCR7 Protein Expression Levels in Placentas of Patients with Preeclampsia. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 27: e931192–1.

[12] Georgopoulos N, Kirkwood L, Southgate J, 2014, A Novel Bidirectional Positive-Feedback Loop Between Wnt–β-Catenin and EGFR–ERK Plays a Role in Context-Specific Modulation of Epithelial Tissue Regeneration. Journal of Cell Science, 127(13): 2967–2982.

[13] MacLaine N, Wood M, Holder J, et al., 2008, Sensitivity of Normal, Paramalignant, and Malignant Human Urothelial Cells to Inhibitors of the Epidermal Growth Factor Receptor Signaling Pathway. Molecular Cancer Research, 6(1): 53–63.

[14] Pawig L, Klasen C, Weber C, et al., 2015, Diversity and Inter-Connections in the CXCR4 Chemokine Receptor/Ligand Family: Molecular Perspectives. Frontiers in Immunology, 6: 156039.

[15] Chen Q, Yin Y, Wei J, et al., 2016, Increased Expression of High Mobility Group Box 1 (HMGB1) in the Cytoplasm of Placental Syncytiotrophoblast from Preeclamptic Placentae. Cytokine, 85: 30–36.

[16] Weel I, Romão-Veiga M, Matias M, et al., 2017, Increased Expression of NLRP3 Inflammasome in Placentas from Pregnant Women with Severe Preeclampsia. Journal of Reproductive Immunology, 123: 40–47.

[17] Sánchez-Aranguren L, Prada C, Riaño-Medina C, et al., 2014, Endothelial Dysfunction and Preeclampsia: Role of Oxidative Stress. Frontiers in Physiology, 5: 99092.

[18] Abais J, Xia M, Li G, et al., 2014, Contribution of Endogenously Produced Reactive Oxygen Species to the Activation of Podocyte NLRP3 Inflammasomes in Hyperhomocysteinemia. Free Radical Biology and Medicine, 67: 211–220.

[19] Yan J, Li Y, Yang H, et al., 2018, Interleukin-17A Participates in Podocyte Injury by Inducing IL-1β Secretion Through ROS-NLRP3 Inflammasome-Caspase-1 Pathway. Scandinavian Journal of Immunology, 87(4): e12645.

[20] Chang G, Yang X, Liu W, et al., 2021, RETRACTED: FABP4 Facilitates Inflammasome Activation to Induce the Treg/Th17 Imbalance in Preeclampsia via Forming a Positive Feedback with IL-17A. Molecular Therapy-Nucleic Acids, 24: 743–754.

[21] Schoots M, Gordijn S, Scherjon S, et al., 2018, Oxidative Stress in Placental Pathology. Placenta, 69: 153–161.

[22] Silvestro S, Calcaterra V, Pelizzo G, et al., 2020, Prenatal Hypoxia and Placental Oxidative Stress: Insights from Animal Models to Clinical Evidences. Antioxidants, 9(5): 414.

[23] Myatt L, Cui X, 2004, Oxidative Stress in the Placenta. Histochemistry and Cell Biology, 122: 369–382.

[24] Wen Y, Liu L, Xu Q, et al., 2018, Knocking Down Cabin1 Induces Glomerular Podocyte Injury. International Urology and Nephrology, 50: 983–991.

[25] Circu M, Aw T, 2010, Reactive Oxygen Species, Cellular Redox Systems, and Apoptosis. Free Radical Biology and Medicine, 48(6): 749–762.

[26] Sachse A, Wolf G, 2007, Angiotensin II–Induced Reactive Oxygen Species and the Kidney. Journal of the American Society of Nephrology, 18(9): 2439–2446.

[27] Zhou L, Cao W, Xie C, et al., 2012, The Receptor of Advanced Glycation End Products Plays a Central Role in Advanced Oxidation Protein Products-Induced Podocyte Apoptosis. Kidney International, 82(7): 759–770.

[28] Zhou L, Chen X, Lu M, et al., 2019, Wnt/β-Catenin Links Oxidative Stress to Podocyte Injury and Proteinuria. Kidney International, 95(4): 830–845.

[29] Eremina V, Jefferson J, Kowalewska J, et al., 2008, VEGF Inhibition and Renal Thrombotic Microangiopathy. New England Journal of Medicine, 358(11): 1129–1136.

[30] Harper S, Xing C, Whittle C, et al., 2001, Expression of Neuropilin-1 by Human Glomerular Epithelial Cells In Vitro and In Vivo. Clinical Science, 101(4): 439–446.

[31] Henao D, Cadavid Á, Saleem M, 2013, Exogenous Vascular Endothelial Growth Factor Supplementation Can Restore the Podocyte Barrier-Forming Capacity Disrupted by Sera of Preeclamptic Women. Journal of Obstetrics and Gynaecology Research, 39(1): 46–52.

[32] Foster R, Hole R, Anderson K, et al., 2003, Functional Evidence That Vascular Endothelial Growth Factor May Act as an Autocrine Factor on Human Podocytes. American Journal of Physiology-Renal Physiology, 284(6): F1263–F1273.

[33] Müller-Deile J, Schenk H, Schiffer M, 2019, Minimal Change Disease and Focal Segmental Glomerulosclerosis. Der Internist, 60: 450–457.

[34] Cruz-Topete D, Cidlowski J, 2014, One Hormone, Two Actions: Anti- and Pro-Inflammatory Effects of Glucocorticoids. Neuroimmunomodulation, 22(1–2): 20–32.

[35] Li X, Chuang P, D'Agati V, et al., 2015, Nephrin Preserves Podocyte Viability and Glomerular Structure and

Function in Adult Kidneys. Journal of the American Society of Nephrology, 26(10): 2361–2377.

[36] Broek M, Smeets B, Schreuder M, et al., 2022, The Podocyte as a Direct Target of Glucocorticoids in Nephrotic Syndrome. Nephrology Dialysis Transplantation, 37(10): 1808–1815.

[37] Zhao X, Khurana S, Charkraborty S, et al., 2017, α Actinin 4 (ACTN4) Regulates Glucocorticoid Receptor-Mediated Transactivation and Transrepression in Podocytes. Journal of Biological Chemistry, 292(5): 1637–1647.

[38] Agrawal S, Chanley M, Westbrook D, et al., 2016, Pioglitazone Enhances the Beneficial Effects of Glucocorticoids in Experimental Nephrotic Syndrome. Scientific Reports, 6(1): 24392.

[39] Liu J, Gao X, Zhai Y, et al., 2015, A Novel Role of Angiopoietin-Like-3 Associated with Podocyte Injury. Pediatric Research, 77(6): 732–739.

[40] Lv Q, Han X, Ni J, et al., 2022, Anti-ANGPTL3-FLD Monoclonal Antibody Treatment Ameliorates Podocyte Lesions Through Attenuating Mitochondrial Damage. Cell Death & Disease, 13(10): 867.

[41] Hackl A, Nüsken E, Voggel J, et al., 2023, The Effect of Mycophenolate Mofetil on Podocytes in Nephrotoxic Serum Nephritis. Scientific Reports, 13(1): 14167.