REVIEW

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PODOCALYXIN AND KIDNEY DISEASES

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Selectivity of blood filtration by the renal glomerulus is largely determined by the presence in its visceral epithelium of the terminally differentiated "octopus-like" cells called podocytes. Podocalyxin (PODXL) is a major transmembrane glycoprotein located on the podocytes' apical surface. Recently, the appearance of PODXL in urine has been considered a marker of nephropathy. The purpose of this review article is to analyze the data of studies on the structural and functional features of podocalyxin and its value in diagnostic, prognostic and potential therapeutic relevance in most common kidney diseases.

K e y w o r d s : podocalyxin, podocyte, renal glomerulus, diabetic nephropathy, kidney diseases.

The renal glomerulus contains terminally developed "octopus-like" cells called podocytes. The glomerulus carries out the initial stage of blood filtration. The glomerulus is a network of vascular tufts enclosed in the Bowman's capsule. It filters the blood and permits selective passage of molecules based on their charge and size, producing primary urine. Selectivity of the glomerulus is based on the typical structure consisting of three primary components: the basement membrane of the glomerulus, the visceral epithelium-podocytes, and the fenestrated vascular endothelium. Each podocyte's pedicels interdigitate with the pedicles of neighboring podocytes, bridging the roughly 200-nm gap among surrounding pedicles, which results in the slit diaphragm acting as a size-selective barrier. Anionic charges prevent anionic proteins from passing over the filter, which is selective according to the electric charge and size of molecules [1]. One specific protein identified in podocytes is called podocalyxin (Fig. 1) [2]. The purpose of this review article is to elaborate on the main structural and functional features of podocalyxin as a podocyte-specific protein, pathomechanisms of podocytopathies that result in podocalyxuria, explore the recent studies, and outline the significant findings regarding the value of podocalyxin in diagnostic, prognostic and potential therapeutic relevance of urinary podocalyxin in most common kidney diseases.

Structure and function of podocalyxin

Podocalyxin (PODXL) is a major transmembrane protein located on the podocytes' apical surface (Fig. 1). Additionally, it can appear on the surface of several tumor cells, hematogenic cells, endothelial cells, and neurons [3]. The podocyte glycocalyx's primary sialoglycoprotein, PODXL, was first discovered in mice and humans. One of the most mucin-dependent deletion deficiencies that science is mindful of is the inability of embryonic podocytes to undergo the proper morphogenesis and produce foot processes. This results in anuria, and mice with germ-line deletion of PODXL die within 24 hours of birth. PODXL is a single-pass transmembrane glycoprotein consisting mainly of O-linked carbohydrates in its extracellular (N-terminal) mucin domain. These carbohydrates are then sialylated and sulfated. Like all mucins, the extracellular domain is negatively charged, providing CD34-family members with at least some of their recognized biological functions. Along with CD34 and endoglycan, PODXL is one of three sialomucins that belong to the CD34 family. At least one extracellular domain of mucins, a broad group of membrane-spanning

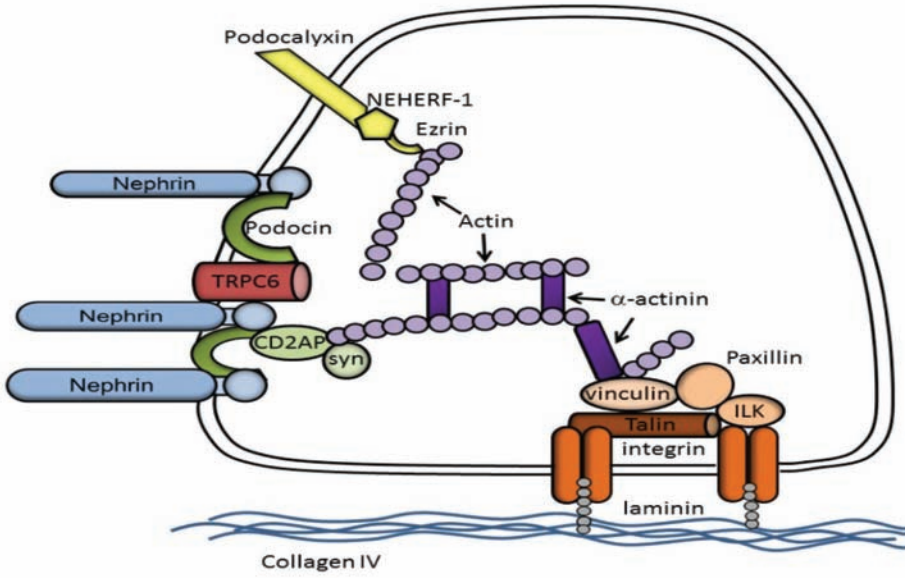

Fig. 1. Diagrammatic representation of a podocyte's lateral-basal region. Podocalyxin is a podocyte transmembrane protein [2]

proteins of type I released, is predicted to contain proline, serine, and threonine residues. The O-linked oligosaccharide post-translational addition (at S/T residues) significantly alters mucin domains, and sulfation and N-linked glycosylation often modify them. Specifically, adding terminal O-linked to the terminal sialic acid sialomucins significantly alters them. The mature human PODXL protein, a 56 kD peptide mass to terminal O-linked sialic a 536-residue glycoprotein, is produced at the cell surface. On the other hand, after glycosylation and other post-translational modifications, a product with an estimated molecular weight of 150–200 kD is created. The extracellular domain is made up of a membrane-proximal stalk domain, a globular domain with a conserved four cysteine (Cys) motif, and a highly O-linked glycosylated, sialated, and sulfated mucin domain of PODXL. Furthermore, the extracellular domain is embellished with N-linked glycosylation at three or four sites, a sterically bulky, highly negatively charged glycoprotein resulting from these modifications. Despite the intracellular domain of PODXL, neither paralogs nor homologs of the CD34 family exhibit a significant degree of conservation in the amino acid sequence of the extracellular domain of PODXL, being significantly conserved across species. While selectin-binding capabilities of sialomucins, particularly PODXL, were shown *in vitro,* it is uncertain whether this function has physiologic implications for most endothelium *in vivo.* Potential target locations require a membrane-proximal ERM (ezrin, radixin, and moesin)-protein interaction domain and serine and threonine (S/T) kinases, such as casein kinases I/II (CKI/II). PKC (protein kinase C) and PTK (protein tyrosine kinases) are found in the intracellular domain of PODXL. Additionally, aspartate-threonine-histidine-leucine (DTHL), the cytoplasmic domain's four C-terminal amino acids, facilitates interactions between proteins with the domain PSD-95/Dlg/ZO-1 (PDZ). Ezrin and NHERF isoforms 1 and 2 (solute carrier family 9 (Na^+/H^+ exchanger), member three regulators-1 and -2) are the best-characterized intracellular binding partners for PODXL-the adaptor proteins NHERF-1/2 and ezrin with various attached partners that may link PODXL to numerous signaling pathways. Similarly, by guiding NHERF-1/2 and ezrin to specific areas of the apical membrane, PODXL could control these complexes' availability, functionality, and localization (Fig. 2) [4]. PODXL is essential to the development of glomeruli, and animals lacking podocalyxin have altered podocyte architecture, as well as the absence of slit diaphragm and foot processes [5]. Because sialomucin has an antiadhesive effect on cells, it keeps the filtration pores open and stops Bowman's capsule's parietal and visceral epithelial layers from clumping together. All these mechanisms are essential for glomerular filtration to remain normal [6]. The preferred protein for immunofluorescent podocyte detection and identification in urine and bioptic

material is PODXL, a crucial indicator of podocyte phenotype.

Pathophysiological mechanisms of podocytes' damage in kidney diseases

The particular form of immune complex glomerulonephritis that results in unique histopathological patterns can cause podocyte injury. For instance, in membranous nephropathy, the subepithelial localization of immune complexes causes massive proteinuria and direct podocyte injury. On the other hand, on biopsy, podocyte damage without immune complex deposits shows clear histopathological lesion patterns. These include focal segmental glomerulosclerosis (FSGS) lesions, which include sclerotic lesions visible in segments of glomeruli, minimal changes (also called minimal change disease), which occurs primarily in children and is named because it appears to have no histopathological abnormalities that can be seen with ultrastructural analysis, diffuse mesangial sclerosis (DMS), which occurs early in life and is characterized by mesangial matrix expansion and podocyte hypertrophy, and collapsing glomerulopathy, which presents as a collapse of the glomerular capillaries and migration of parietal epithelial cells to the tuft, giving the appearance of "pseudocrescents". Patients who have these histological lesions react precisely like these to immunosuppressive treatment. For instance, the majority of patients who respond to steroids and have mild symptoms have favorable outcomes. The data from a kidney biopsy, however, is insufficient for a personalized prognosis and the choice of optimal therapies aimed at the specific etiology of proteinuria in steroid-resistant patients. According to a better understanding of the molecular diagnosis of nephrotic syndrome or the monogenetic causes of proteinuria, the histomorphological lesions of DMS, minimal changes, FSGS, or collapsing glomerulopathy are unspecific lesions that represent various patterns of podocyte injury rather than defining a distinct disease cause or diagnosis that would re-

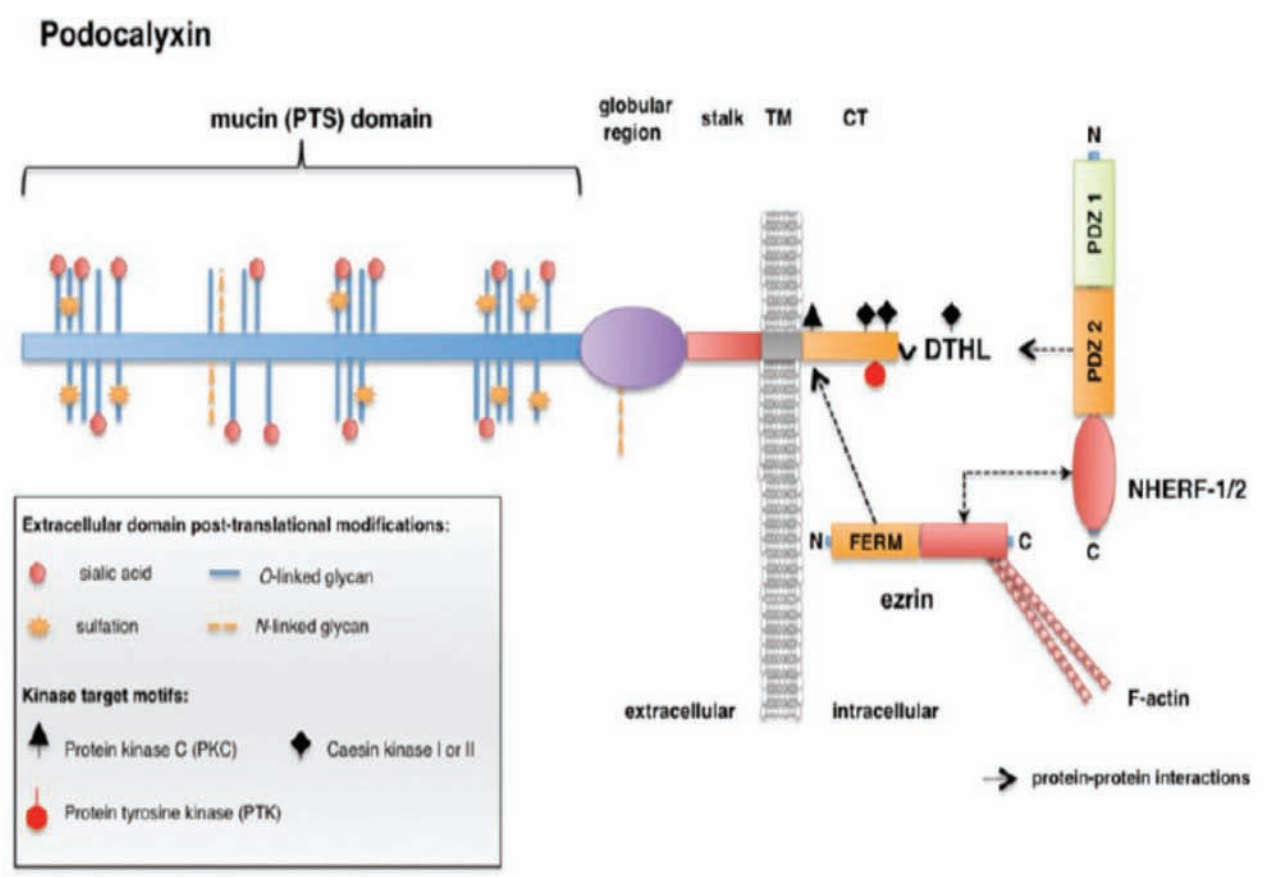

Fig. 2. Podocalyxin nucleates different intracellular signaling complexes in conjunction with NHERF-1/2 and ezrin [4]

quire specific treatment. Several genetic diseases, treatment reactions, or the same genetic disease can all be connected to these pathological patterns. As a result, it is now imperative to rename this group of illnesses as “podocytopathies”, which serve multiple purposes. This classification indicates a cellular target for treatment and identifies the podocyte injury. The classification also helps dispel the old-fashioned idea that DMS, FSGS, collapsing glomerulopathy, and minor changes are “diseases” or diagnoses. This method then starts a diagnostic procedure to determine the causes of podocyte damage and establish a personalized prognosis and treatment strategy. The inflammation is also an important pathological mechanism of podocyte injury [7-10]. Podocytopathies can be diagnosed by morpho-pathological analysis of bioptic kidney material using light and electron microscopy and immunohistochemistry (identifying specific podocyte proteins from the biopsy material). For identification and measurement of blood and urine podocyte-specific proteins like PODXL, the following methods are used: flow cytometry, Western blot, immunofluorescence, mass spectrometry, and reverse transcription polymerase chain reaction are used to detect the mRNA of particular podocyte proteins [2, 10].

Pathophysiological mechanisms of podocytes’ damage and diagnostic relevance of podocalyxuria in secondary nephropathies

Human kidney disease is linked to dominant and recessive podocalyxin mutations. Interestingly, specific PODXL mutations result in anuria, whereas others cause proteinuric kidney disease. Podocalyxin's release into the urine is a common biomarker of several nephrotic illnesses, and PODXL heterozygosity is associated with adult-onset renal disease. The roles of distinct PODXL lesions in the different disease pathologies must be better understood. Pair of mouse stains are made: one that is heterozygous for podocalyxin in all tissues (PODXL+/–) and one that eliminates PODXL from developmentally mature podocytes (PODXL/Pod) [11]. A more recent urine marker for nephropathies is PODXL. High specificity, non-invasive nephropathy diagnosis and monitoring, and the ability to be tested using reasonably easy and sensitive techniques like ELISA are some of these markers’ diagnostic benefits. PODXL is only helpful as an early biomarker in the diagnosis of the following secondary kidney diseases: hypertension, diabetes, lupus nephritis, and preeclampsia. Early diagnosis can enable rapid treatment and prevention from renal replacement therapy, significantly lowering complications and patient mortality.

Diagnostic relevance of podocalyxin in diabetic nephropathy

Podocytopathies greatly influence the structural and functional changes in patients with diabetic nephropathy (DN) [12]. In DN, podocyte density and quantity are lost due to a combination of factors, including GBM thickening, podocyte foot process effacement, and death or detachment of podocyte cells [13]. Pathohistopathology indicates that podocyte hypertrophy and hyperactivity, which harms the slit diaphragm, are the initial signs of DN. Podocyte atrophy, foot process constriction, podocyte fragmentation, and podocyte separation from GBM are characteristics of the advanced stage. All of these alterations cause proteinuria [6]. Therefore, histomorphological studies of diabetic individuals with severe nephropathy and proteinuria show a substantial increase in foot process width [14]. Compared to those with less severe renal impairment, diabetic Pima Indians with clinical nephropathy had fewer glomerular epithelial cells. Furthermore, there is a correlation between the number of podocytes and the severity of proteinuria. According to this study, the best marker of glomerular damage in people with diabetes is the quantity of glomerular podocytes [15]. Glomerular podocytes significantly decreased in another cohort study of type 2 diabetic individuals, even those with normal albuminuria [16]. Podocytes were discovered in the urine of 80% of people with type 2 diabetes with macroalbuminuria and 53% of those with microalbuminuria, according to a Japanese study. During the same assessment, Trandolapril decreased urinary podocytes and urine albumin excretion in DN patients. According to this study, podocyturia can serve as a valuable indicator of disease activity, and trandalopril can be a helpful treatment for DN. Urinary podocalyxin-positive elements (PODXL + EL) levels have also been significantly greater in DN’s early stages than in healthy controls. Additionally, these values showed a substantial correlation with the diagnosis of DN, particularly when normoalbuminuria is present. According to a recent study, urine PODXL was significantly higher in 53.8% of normoalbuminuric, 64.7% of microalbuminuric DN patients, and 66.7% of macroalbuminuric DN patients. Consequently, the

ELISA measuring PODXL in urine can indicate early detection of diabetic nephropathy [17]. Hyperglycemia can directly produce toxicity to cells, leading to podocytes' stress response [18]. According to a recent study, PODXL was found to have higher diagnostic accuracy than microalbumin in cases of DN, and a significant proportion of T2DM normoalbuminuric individuals had elevated PODXL levels. These findings imply that PODXL may be crucial in detecting podocyte damage and DN early. They conclude that PODXL, far more so than microalbuminuria, can potentially be a sensitive and specific marker for the early identification of DN [19]. According to another innovative study, urinary podocalyxin levels can serve as an early biomarker of diabetic nephropathy and may reveal information about glomerular impairment in patients with the disease [20]. Yuxian Xie and colleagues' study showed that the amount of PODXL expressed in urine could serve as a biomarker for podocyte damage in CKD patients at an early stage. Proteinuria may not be as sensitive as urinary PODXL/cr as a measure of glomerular disease damage. In the elderly population, this could make up for the limitations of renal biopsy as a possible non-invasive test with a high diagnostic value for chronic kidney disease [21].

Diagnostic relevance of podocalyxin in preeclampsia

A pregnancy-related condition known as preeclampsia is linked to a high rate of maternal morbidity and death. In preeclampsia, which typically develops after 20 weeks of pregnancy, the primary clinical manifestations are de novo hypertension and proteinuria. Proteinuria, a secondary nephropathy part of preeclampsia, is caused by the death of podocytes at the glomerular level. According to one study, podocyturia may be a predictive indicator for preeclampsia when proteinuria and hypertension were not present in pregnant patients who developed preeclampsia. Furthermore, there was a significant relationship between the severity of proteinuria and the quantity of podocytes, suggesting that the initiation and severity of proteinuria may be correlated with podocyte loss [22]. Podocyturia was shown to have 100% sensitivity and 100% specificity in identifying preeclampsia in a study by Garovic et al. [23]. According to Wang's study, women with preeclampsia had significantly higher urine PODXL levels than women in a typical pregnancy [24]. Regardless of the presence of proteinuria, higher levels of PODXL in urine were detected in pregnant women in Paraguay who had preeclampsia and eclampsia. The amount of podocyte damage was correlated with the PODXL concentration in urine. Regardless of the presence of proteinuria, higher levels of PODXL in urine were detected in pregnant women in Paraguay who had preeclampsia and eclampsia. The level of podocyte damage was correlated with the PODXL concentration in urine [25]. The ELISA technique, a reasonably priced, easy, and helpful way to identify podocyte damage, was used in the same study to quantify urinary PODXL. According to a recent study, women who later developed preeclampsia had significantly higher serum PODXL levels at 11–13 weeks of gestation. When diagnosing delayed preeclampsia early on, serum PODXL may be helpful [24]. Another prospective study found that PODXL is a potential predictor of preeclampsia and that serum PODXL levels rise in preeclampsia [26]. According to Asparuh Nikolov and colleagues' research, a three-fold increased likelihood of developing PE is indicated by elevated PODXL levels [27].

Diagnostic relevance of podocalyxin in hypertensive nephropathy

Due to its association with glomerulosclerosis and progressive podocyte depletion, a key contributor to ESKD is hypertension. Untreated moderate hypertension is linked to ESKD in the elderly. Podocyte sediment mRNA was quantified from kidney donors who had undergone a comprehensive examination, including a routine biopsy at the time of contributions, and had completely normal kidney function and no proteinuria. Kidney donors with entirely normal kidney function and no proteinuria who had undergone a thorough evaluation following a routine biopsy during the transplant procedure had their podocyte sediment mRNA measured. Additionally, the podocyte detachment rate was three times higher in individuals with higher-normal blood pressure than those with mid- and low-normal blood pressure. The age-related ESKD linked to mild hypertension may be explained by this accelerated podocyte detachment, which may result in severe podocyte loss at a later stage. According to these findings, a little increase in podocyte detachment rate, in this case caused by mild hypertension, can have predictable long-term effects that show up later in life [28]. This risk of long-term progression can also be identified non-invasively early on, even before kidney damage is noticeable. Typical focal segmental glomerulo-

sclerosis lesions were found in 13% of adult Africans with hypertension whose bioptic material was examined by a pathologist [29]. In the study, Wang showed that patients with hypertensive nephropathy had decreased intrarenal gene glomerular podocytopenia and the expression of markers linked to podocytes. The extent of kidney fibrosis and renal function were related to these findings, indicating that podocyte loss may be a crucial factor in the etiology of hypertensive nephropathy [30].

Diagnostic relevance of podocalyxin in lupus nephritis

Lupus nephritis (LN) is the most common and severe organ damage associated with systemic lupus erythematosus (SLE). Damage to podocytes and tubular epithelial cells results from glomerular injury, inflammation, cell proliferation, and necrosis, which are characteristics of LN. Urine biomarker assays have shown great potential in monitoring medication response, evaluating disease activity, and diagnosing LN early. This is because they are easy to gather, move, and store independently, allow for routine monitoring, and are non-invasive. Podocyte damage is thought to be a crucial component of LN. Podocyte-derived cellular debris and injury-related urine proteins are possible markers for diagnosing and tracking LN since the degree of proteinuria may be correlated with the type and intensity of podocyte damage. According to recent studies, there are fewer glomerular podocytes in people with lupus glomerulus, proteinuria is associated with fewer podocytes in lupus glomerulus, and patients with lupus nephritis excrete more urine podocytes [31]. Interestingly, it was also discovered that patients with SLE have higher urine levels of podocyte proteins, such as PODXL. As a result, the urine PODXL/creatinine ratio could serve as a non-invasive marker of the kidney damage caused by SLE [32].

Conclusion. A relatively recent marker for podocytopathy detection is PODXL. It may be useful in the early diagnosis of secondary nephropathies because it manifests in urine before microalbuminuria and proteinuria. Reducing the need for renal biopsy is a crucial auxiliary tool for primary nephropathies' diagnosis, differential diagnosis, and prognosis. Since proteinuria is frequently the initial clinical sign of primary nephropathies, the term "early diagnostic marker" only applies to secondary nephropathies. As a marker for the early identification of secondary nephropathies, the most prevalent causes of end-stage kidney disease such as diabetes, lupus, and hypertension, PODXL is crucial. It is also essential for predicting preeclampsia, which is a significant contributor to pregnancy-related problems. Detecting these secondary nephropathies early on will reduce morbidity and mortality and facilitate timely treatment. The benefit of this urinary marker is that it can be measured using straightforward, non-invasive techniques and has excellent sensitivity and specificity for secondary nephropathies. For researchers and clinicians, PODXL holds excellent promise as a diagnostic and prognostic marker; however, additional clinical research is necessary to ascertain its actual diagnostic and predictive value. This marker is indeed a novel therapeutic target for kidney disorders.

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ПОДОКАЛІКСИН ТА ЗАХВОРЮВАННЯ НИРОК

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Селективність фільтрації крові нирковим клубочком значною мірою визначається наявністю в його вісцеральному епітелії диференційованих «щупальцеподібних» клітин – подоцитів. Подокаліксин (PODXL) – це основний трансмембранний глікопротеїн, розташований на апікальній поверхні подоцитів. Віднедавна виявлення PODXL у сечі вважається маркером нефропатії. Метою цього огляду є аналіз результатів досліджень щодо структурно-функціональних особливостей подокаліксину та його значення в діагностиці, прогнозуванні та потенційній терапевтичній значущості при найпоширеніших захворюваннях нирок.

Ключові слова: подокаліксин, подоцит, нирковий клубочок, діабетична нефропатія, захворювання нирок.

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