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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Podocytopathies

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SUMMARY

Podocytopathies include a wide spectrum of primary or secondary glomerular diseases that are the consequence of the podocyte injuries. The damage of podocytes can occur due to congenital or acquired disorders of podocyte transcriptional regulators, altered components of the slit diaphragm complex, abnormal assembly, or function of the actin-based cytoskeleton, dysfunction of membranes or cytoplasmic proteins, and mitochondrial injury. Podocytes reactions to injurious stimulus include FP effacement, apoptosis, and loss of podocyte, developmental arrest associated by mild proliferative activity, and dedifferentiation with moderated proliferation. Based on histopathological findings, podocytopathy may be diagnosed such as minimal change nephropathy; focal segmental glomerulosclerosis, diffuse mesangial sclerosis, or collapsing glomerulopathy while in relation to their etiology can be categorized as idiopathic, genetic, and reactive. Podocytopathies may be diagnosed due to podocyte morphological changes, immunohistochemistry, circulating and urine biomarkers, and genetic analysis. The primary clinical focus in prevention should be to reduce the factors that can damage the podocytes and cause hyperperfusion/hypertrophy of the glomerulus. Nowadays, control of systemic and intra glomerular hypertension by pharmacological blockade of angiotensin II is a central in the prevention strategy, while regeneration of podocytes by stem cells is therapeutic strategy of the future.

Keywords: steroid resistent nephrotyc syndrome; glomerulosclerosis; foot process effacement; mesenhimal-epithelilal transition

INTRODUCTION

Glomerular dysfunctions that result from podocyte damage or loss are referred with one name as podocytopathies. Podocyte, a key cell involved in podocytopathy, is a highly specialized, terminally differentiated, atypical visceral glomerular epithelial cell which has an essential role in at least five functions: glomerular permselectivity, dynamic structural support for the glomerular structure, remodeling the glomerular basement membrane (GBM), endocytosis of filtered proteins, and production of vascular endothelial growth factor and platelet-derived growth factor required for proper functioning of glomerular cells [1].

Better knowledge of the podocytes biology and etiopathogenesis of their damage during the last two decades has opened up new possibilities for diagnosis, treatment, and prevention of podocytopathies why they rank very attractive topic both in basic research and in clinical studies [2]. This review article aims to provide an analysis of the current literature about a mechanism of podocyte injury, classification of podocytopathies and their phenotypic variations, as well as the diagnostic and therapeutic possibilities for podocytopathies available to date.

MECHANISM OF PODOCYTE INJURY

Podocytes functions depend on their highly specialized and unique architecture that includes:

a) the slit diaphragm complex (SD) that is an unique intercellular connection that integrates the structural components of different types of cellular contacts, including tight, adhesion, slit and neural connections [2, 3];
b) the actin-based cytoskeleton which is the main strength and weakness of the podocytes including associated proteins and adhesion proteins [4];
c) the membrane structures that are on one hand exposed to the urinary area (in the Bowman's capsule) and on the other hand indirectly communicate with the vascular space via the GBM [1];
d) the current internal and external biochemical signals that contribute to maintaining normal glomerular function [1, 5, 6].

The damage of podocytes can occur due to congenital or acquired disorders of

a) transcriptional regulators [Wilms tumor 1(WT-1) zinc finger protein, PAX2, LIM homeobox transcription factor 1β (Lmx1b), the Notch signaling and Wnt pathway];
b) altered components of the SD complex (nephrin, podocin, CD2AP, Neph1 and others);
c)abnormal assembly or function of the actin-based cytoskeleton;
d) expression and localization of the membrane (apical and basal side) proteins [α3β1-integrin, dystroglycan complex, transient receptor potential cation channel 6 (TRPC6), podocalyxin];

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e) dysfunction of cytoplasmic proteins;
f) mitochondrial injury, and extracellular matrix protein alteration (laminin β2 encoded by LAMB2 gene) [7].

There are at least100 ways to damage the podocytes [8]. Since podocytes are postmitotic cells they typically are unable to regenerate by proliferation in response to injury [4]. Therefore, they react to injurious stimuli in limited manner, which may include:

1) changes in phenotype without alteration in podocytes number such as foot process (FP) effacement;
2) apoptosis and loss of podocyte;
3) developmental arrest associated by mild proliferative activity;
4) dedifferentiation and re-entrance into the cell cycle with mitotic catastrophe [4, 9].

FOOT PROCESS EFFACEMENT WITHOUT PODOCYTE LOSS

FP effacement is a non-specific podocyte reaction to injury or damage characterized by retraction, widening, and shortening of the FP due to:

a) actin cytoskeleton condensation into a narrow band within cytoplasm adjacent to the GBM;
b) loss of the normal three-dimensional interdigitating architecture;
c) a redistribution of the components of slit diaphragm to the cytoplasm and the apical plasma membrane. With the electronic microscope, the podocytes look flat giving the appearance of a continuous cytoplasmic sheet covering the GBM.

Podocyte FP effacement is found in proteinuric renal diseases including focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), immunoglobulin A nephropathy, and diabetic nephropathy [9, 10]. It can be reversible, as is the case in MCD under the corticosteroid therapy, while in FSGS that is refractory to existing therapies, FP effacement is usually irreversible. However, the main difference determining the outcome of the podocytopathy is the number of the podocytes, which is preserved only in non-progressive glomerulopathies.

PODOCYTE INJURY AND DEPLETION

Podocyte depletion is the main step in progressive nephropathy. It may be absolute, or relative. Absolute podocyte depletion is either a consequence of sublethal injury that leads to podocyte detachment from underlying GBM or from the lethal injury due to apoptosis or necrosis. Relative podocyte depletion happens in cases where the normal number of podocytes is insufficient to cover the GBM due to enlargement of the glomerulus because of its hypertrophy.

Wiggins et al. [11] proposed a five-step model of podocyte response to glomerular enlargement in the aging rat. In stage 1, the glomerulus is normal, as is the number and function of podocytes; in stages 2 and 3 the podocyte is subjected to "compensated" hypertrophy, while in stage 4 "decompensated" podocyte hypertrophy is associated with altered podocyte biology [11]. Podocyte size is decreased in relation to glomerular volume with consequently increased width of FP and decreased perm selectivity of glomerular filtration barrier, which leads to an increase in proteinuria. Finally, in stage 5, the number of hypertrophied podocyte is decreased with changed podocyte biology and reduced specialized podocyte machinery. Therefore, relative or absolute podocyte loss leaves uncovered GBM with consequent development of FSGS [9, 11]. According to this model, initial response, during the adaptive phase, is podocyte hypertrophy to cover an expanded GBM surface but the resulting mechanical stretch induces a shift in podocyte phenotype, favoring structural instability and decreased SD function [11]. "Adapted and decompensated" stages of podocyte hypertrophy have been reported in many congenital and acquired chronic kidney diseases (CKD) [9]. Using rat models of regulated podocyte depletion it was documented that 20% of podocytes loss causes mesangial expansion alone, more than 20% of podocytes leads to the appearance of denuded areas of GBM resulting in synechia formation, 20–40% podocyte loss results in segmental sclerosis, while more than 60% podocyte loss ends in glomerular global sclerosis [12].

PODOCYTE INJURY AND PROLIFERATION

Podocyte injury may be the consequence of mitotic catastrophe leading to delayed cellular maturation, dedifferentiation, with either low, manifesting as diffuse mesangial sclerosis (DMS) or high rates of proliferation manifesting as collapsing glomerulopathy (CG).

CLASSIFICATION OF PODOCYTOPATHIES

Podocytopathies may be classified according to histopathology and etiology as suggested by Barisoni et al. [9]. The four histological patterns of podocytopathies including MCD with unchanged the number of podocytes per glomerulus, FSGS with podocytopenia, DMS with podocytopenia and low proliferative index and CG with podocytopenia and marked proliferation are grouped in three etiological categories: idiopathic, genetic and reactive [9]. As an alternative to this classification based on histological description [9], Ahn and Bomback [13] have recently shown how podocytopathies can be classified according to pathogenesis and response to treatment (Table 1). According to them, podocytopathies are classified into those in which circulating hyper permeability factor causes podocyte injury, toxic podocytopathy caused by direct action of toxins or cytokine mediated ± APOL1 overexpression, hereditary podocytopathy as consequence of mutations causing structural or functional abnormalities of podocytes, and hyperfiltration mediated podocytopathies caused by adaptive changes due to excessive nephron workload (Table 1).

MCD is most often (80–90%) presented in childhood as an idiopathic steroid-sensitive nephrotic syndrome (SSNS)

Table 1. Pathogenesis-based classification of podocytopathies*

Type of podocytopathy	Causes and Pathogenesis	Pathology	Clinical Manifestation	Treatment	Recurrence after transplantation
Permeability factor–mediated	Circulating factor causing podocyte injury	MCD, FSGS with extensive FPE	Sudden-onset nephrotic syndrome	Immunosuppression, plasma exchange	Common; sometimes immediate
Toxic	Direct toxicity or cytokine mediated ± APOL1 overexpression	MCD, FSGS (frequently collapsing) ± endothelial tubuloreticular inclusions	Variable clinical course; slowly progressing CKD or nephrotic syndrome	Removal of toxic injury	Possible; usually several months later
Genetic	Mutation causing structural or functional abnormalities of podocytes	MCD, MesGN, FSGS	Steroid-resistant nephrotic syndrome	RAAS inhibitors	Rare
Hyperfiltration mediated	Adaptive changes due to excessive nephron workload	FSGS (frequently perihilar) with glomerulomegaly and segmental FPE	Slowly progressive proteinuria without edema and hypoalbuminemia	RAAS inhibitors	Rare

*Modified from [13];
CKD – chronic kidney disease; FPE – foot-process effacement; FSGS – focal segmental glomerulosclerosis;
MCD – minimal change disease; MesGN – mesangioproliferative glomerulonephritis; RAAS – renin-angiotensin system

that is considered an autoimmune disease with a poorly understood its genetic background. Hildebrandt's group identified EMP2 (epithelial membrane protein 2), as a rare cause of the nonsyndromic autosomal-recessive form of SSNS [14] and Izzedine et al. [15] discovered a loss of podocyte dysferlin expression as a cause of syndromic MCN associated with limb-girdle muscular dystrophy type 2B (LGMD2B). Recently, large genome-wide association studies has identified three loci that explain about 14% of the genetic risk for SSNS [16]. The strongest association was found for the *CALHM6* gene, which is important for regulating the immune response to infection. These findings suggest that a genetically determined risk of immune deregulation may be a key component in the pathogenesis of SSNS [16].

FSGS is usually manifested in childhood as idiopathic steroid resistant nephrotic syndrome (SRNS). For FSGS two main pathogenic mechanisms are assumed: either (1) an alteration of the immune system resulting in the production of a putative circulating glomerular permeability factor; or (2) mutations in more than 50 structural genes of the glomerular filtration barrier, mainly in the podocytes for which they are named hereditary podocytopathies [17]. Genetic mutations that are responsible for non-syndromic FSGS include those that encode SD associated and adaptor proteins such as NPHS1, NPHS1+ NPHS2, NPHS2, CD2AP, TRPC6, PTRO, CRB2, PLCe1, actin-based cytoskeleton complex and signaling including at least ACTN4, MYH9, INF2, MYO1E, ARHGAP24, ARHGDIA and ANLN or nuclear transcriptional factor (WT1) [9, 17–24]. Syndromic FSGS may be a consequence of genetic mutations that are responsible for mutations in GBM proteins such as the mutated COL4 genes in Alport syndrome, WT-1 in Denys-Drash, and Frasier syndrome, LMX1B in nail-patella syndrome, metabolic disorders such as GLA, encoding galactosidase A in Fabry disease, and mitochondriopathies (mitochondrial tRNA mutations in MELAS syndrome, and COQ2 mutations [9, 17, 18, 25]. The best-studied susceptibility gene (a genetic variant that represents important risk factors in the presence of a "second hit") APOL1 (G1 and G2 alleles encoding apolipoprotein L1) is a major cause of podocytopathy among African Americans, formerly called hypertensive CKD [18].

Reactive FSGS occur in CKD with reduced renal mass (*e.g.*, renal dysplasia, surgical renal mass reduction, reflux nephropathy, chronic interstitial nephritis) or in the presence of initially normal renal mass (obesity, sickle cell anemia, or cyanotic congenital heart disease) [9, 18].

DMS is characterized by the presence of different podocyte phenotype (increased expression of cytokeratin) and increased expression of proliferative markers, such as Ki67. DMS be idiopathic or due to genetic mutations, such as WT-1 mutations (Denys-Drash syndrome) [25] and mutations of LAMB2, encoding laminin 2 chain (Pierson syndrome) [26]. Congenital nephrotic syndrome of the Finnish type is caused by homozygous or compound heterozygous mutations in NPHS1, encoding nephrin [27]. Podocyte, which does not express nephrin, pass through detachment and cause progression to end-stage kidney disease, usually in the early childhood [27].

CG is defined by the presence of segmental capillary tuft collapse (wrinkling and folding) in at least one glomerulus, in association with podocyte hypertrophy and/or hyperplasia. It shows podocyte proliferation rather than podocyte depletion, and the actin cytoskeleton may disappear [11]. In fact, podocytes returned in the primordial embryonic stages through the process of epithelial-mesenchymal transition. During epithelial-mesenchymal transition, podocytes regain a cuboidal shape and loss of primary and FP. The markers of maturity such as synaptopodin, podocalyxin, GLEPP1, and CALLA are replaced by PAX2 and cytokeratin, and E- and P- cadherins are replaced by the N- cadherin. Further, transcriptional marker WT-1 is lost while expression of Ki67 is increased, and immature podocytes re-enter the cell cycle and proliferate. Increased vimentin and intermediate filaments contribute to the high podocytes migration capacity, which with vivacious podocyte hyperplasia seems

to generate the apparent pseudo crescents within Bowman's space [11]. According to the etiology, CG may be idiopathic, genetic, and reactive [9].

DIAGNOSIS OF PODOCYTOPATHIES

Podocytopathies may be diagnosed based on the data from the history of the disease, podocyte morphological changes, immunohistochemistry, circulating and urine biomarkers, and genetic analysis [28].

Podocytopathy should be considered when patients have increased proteinuria with albuminuria, or nephrotic syndrome with or without hyperfiltration, or hypofiltration. Hereditary podocytopathy is very likely in child with SRNS especially if they are from a consanguinity marriage, and/or have syndromic features [19].

The visualization of structural changes on glomerular filtration barrier has been carried out in the clinical practice by scanning or transmission electronic microscope since the end of the thirties of the last century. During the last few years, different super-resolution microscopic techniques were developed to enable new insights into podocyte morphology [29]. These super-resolution microscopy approaches include three dimensional structured illumination microscopy, stimulated emission depletion microscopy and localization microscopy (stochastic optical reconstruction microscopy and photo activated localization microscopy). Their resolutions reached down to 80–20 nm and could be used to image and further quantify podocyte FP morphology [29]. Furthermore, high-magnification helium ion microscopy produce high-quality subnanometer-resolution images of glomerular structures [7]. For imaging of podocytes *in situ* multiphoton laser microscopy allows imaging structures up to several hundred micrometer in depth within the tissue while multiphoton microscopy, light sheet microscopy is currently used to visualize larger tissue volumes and therefore image complete glomeruli in their native tissue context [29]. Furthermore, atomic force microscopy has been used to study the change of mechanical properties of podocytes [29].

An immunohistochemical examination of podocytes cytoskeleton-specific proteins expression, including ezrin, podocalyxin, synaptopodin, and nephrin may be useful in predicting a clinical course of podocytopathy [28].

A circulating biomarker, such as permeability factor, soluble urokinase-type plasminogen activator receptor, failed to meet expectations as the diagnostic tool and a therapeutic target for FSGS [30].

Urine markers, such as the ratios of the number of podocytes or podocytes mRNA with creatinine, and the podocin nephrin mRNA ratio showed correlation with histological outcome as well as or better than clinical biomarkers, with highly sensitivity and specificity [28, 31].

Finally, genetic diagnosis is now possible for more than 50 monogenetic podocytopathies. Recent progress in high flow sequencing and continuous reduction of whole exome sequencing costs, made genetic testing more accessible and less time-consuming [18, 19, 32]. Mutation analysis should be offered to all individuals who manifest with SRNS before the age of 25 years, especially to those with congenital (less then three months), infantile (3–12 months), familial and syndromic SRNS, as well as in resistance to calcineurin inhibitors, and before kidney transplantation [19, 20, 32, 33].

PODOCYTE-TARGETED THERAPIES

Podocyte- targeted therapy can be carried out by inhibition of rennin angiotensin aldosterone system (RAAS), administration of immunosuppressive drugs and through the methods that achieve regeneration of the podocytes [7, 32, 34, 35, 36].

RAAS inhibition has been demonstrated to lower proteinuria by 40–50% in patients with SRNS [32]. In the PodoNet cohort, RAAS inhibition alone was associated with partial proteinuria remission in 21% and even maintained complete remission in 27% of patients [32]. RAAS blockade by either angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers achieves a renoprotective effect primarily by inhibiting vasoconstriction of the efferent arterioles and thus reduces intraglomerular pressure and hyperfiltration. However, the beneficial effect of these drugs can be realized also by direct action on the glomerular cells including the podocytes [37, 38]. Studies have shown that ACE type 2 (ACE2) which is found in the podocyte body and in the slit diaphragms has the potential to antagonize the action of Ang II [37]. In addition, Ang-(1–7) has been demonstrated to attenuate podocyte injury by down regulation of MAPK (p38, ERK1/2 and JNK) phosphorylation [38].

Advances in podocyte biology and pathogenesis of proteinuric disease unveiled unexpected mechanisms of action of widely used immunosuppressive drugs, which are independent of their traditional immunomodulatory function [39]. Glucocorticoids and levamisole have non-immune mediated, reno-protective effects on podocytes; they stabilize actin (increase of nephrin and activity of Rho-A), attenuate podocyte apoptosis (restoration of Bcl-2 and reduction of p53) and thereby prolong the survival of the podocytes [38]. Non-immunologic effect of calcineurin inhibitors, (CsA and FK506) is realized by preventing synaptopodin degradation by cathepsin L and thus they increase the stability of podocyte cytoskeleton [39]. Rituximab also improves stability of actin cytoskeleton. The mechanism of this action is achieved by rituximab binding to acid sphingomyelinase-like phosphodiesterase 3b protein (SMPDL-3b), a putative acid-sphingomyelinase (ASMase) [39]. The restoration of SMPDL-3b expression in podocytes by rituximab prevents the disruption of stress fiber (synaptopondin) and podocyte apoptosis. Abatacept acts to stabilize actin cytoskeleton by blocks B7-1 signaling and restoring β1 integrin activation [39]. However, Rapamycin, which inhibits mTOR activity, may have dual effects on podocytes, positive effect by suppressing autophagy as documented in diabetic nephropathy) and negative one, by development of podocyte damage and increase proteinuria. In general, the beneficial effects of immunosuppressive drugs in the treatment of hereditary podocytopathy are small in relation to adverse effects of

this therapy. The findings in the PodoNet cohort argue against a relevant nephroprotective effect of calcineurin inhibition – or other immunosuppressive therapies – in children with genetic forms of SRNS and support the notion that such patients should be spared immunosuppressant side effects [32, 36]. A promising example of an innovative gene specific treatment option is successful use of CoQ10 in children with SRNS due to genetic defects leading to CoQ10 deficiency [32].

Finally, having in mind that podocytes are postmitotic cells, the identification of effective ways to promote podocyte regeneration has become a major focus for therapeutic research. The two progenitor pools have recently been identified in multiple studies: parietal epithelial cells, and cells of renin lineage [40]. A reasonable podocyte replacement goal should be to simply increase podocyte number to that above the critical scarring threshold (20% podocyte loss), which limits/prevents segmental sclerosis progressing to global.

CONCLUSION

Effective podocyte depletion is the common driving force of the progressive podocytopathies. The classification of podocyte diseases needs to be improved by new markers of podocyte phenotype that will override traditional morphologic analysis and will serve as new bases for therapeutic intervention. The primary clinical focus in prevention should be to reduce the factors that can damage the podocytes and cause hyperperfusion/hypertrophy of the glomerulus. Nowadays, a control of systemic and intraglomerular hypertension (pharmacological blockade of angiotensin II) has a central role in the prevention strategy while a regeneration of podocytes by stem cells is therapeutic strategy of the future.

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Подоцитопатије

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САЖЕТАК

Подоцитопатије укључују широк спектар примарних или секундарних гломерулопатија које су последица оштећења подоцита. Могу се јавити услед конгениталних или стечених поремећаја транскрипционих регулатора, измењених компонената дијафрагме прореза, абнормалног састава или функције актинског цитоскелета, дисфункције мембранских или цитоплазматских протеина и оштећења митохондрија. На штетне утицаје подоцити реагују губитком ножних наставака, апоптозом и некрозом, застојем у развоју повезаним са пролиферативном активношћу и мезенхимно-епителном транзицијом. На основу хистопатолошких налаза, подоцитопатије се деле на нефропатију са минималним променама, фокалну сегментарну гломерулосклерозу, дифузну мезангијалну склерозу и колапсну гломерулопатију, а у односу на етиологију могу бити идиопатске, генетске и реактивне.

Дијагноза подоцитопатија се може поставити на основу морфолошких и имунохистохемијских промена, плазматских и уринарних биомаркера и налаза генетских мутација. Примарни клинички фокус у превенцији подоцитопатије треба да буде смањење фактора који могу да оштете подоците и изазову хиперперфузију/хипертрофију гломерула. Савремена контрола системске и интрагломерулске хипертензије фармаколошком блокадом ангиотензина II је централна у стратегији превенције, а регенерација подоцита матичним ћелијама је терапија будућности.

Кључне речи: нефротски синдром отпоран на стероиде; гломерулосклероза; губитак ножних наставака подоцита; мезенхимално-епителна транзиција