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Review article

Nephrin and Podocalyxin - New Podocyte Proteins for Early Detection of Secondary Nephropathies

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Abstract

In the last two decades a great progress was observed in understanding of podocytes, their specific structure and function identifying many specific podocyte proteins, such as nephrin and podocalyxin. Podocytes form the final barrier to plasma proteins leakage. Nephrin as a main component of the filtration diaphragm forms a physical barrier while podocalyxin as sialoglycoprotein forms an electrostatic barrier. Podocyte damage, i.e. podocytopathies and their loss through urine-podocyturia, are crucial in pathogenesis and progression of nephropathies with proteinuria as main clinical manifestation. In podocytopathies, nephrin and podocalyxin appear in the urine before proteinuria and microalbuminuria which were previously considered as earliest markers of nephropathies. Nephrinuria and podocalyxuria indicate damage of the podocytes on glomerular level and/or presence of apoptotic and necrotic podocytes in urine. These urinary markers are also important in early diagnosis of secondary nephropathies such as diabetic, lupus and hypertensive nephropathy as the most common causes of end-stage renal failure (ESRF). These markers are also important in the prediction of preeclampsia, which is the most common complication in pregnancy. In this review we elaborate in dept the main structural and functional features of podocytes and their specific proteins, nephrin and podocalyxin, summarizing the recent literature data on their importance in the early diagnosis of the most common secondary nephropathies.

Keywords: nephrin, podocalyxin, podocytes, podocytopathies, secondary nephropathies

Introduction

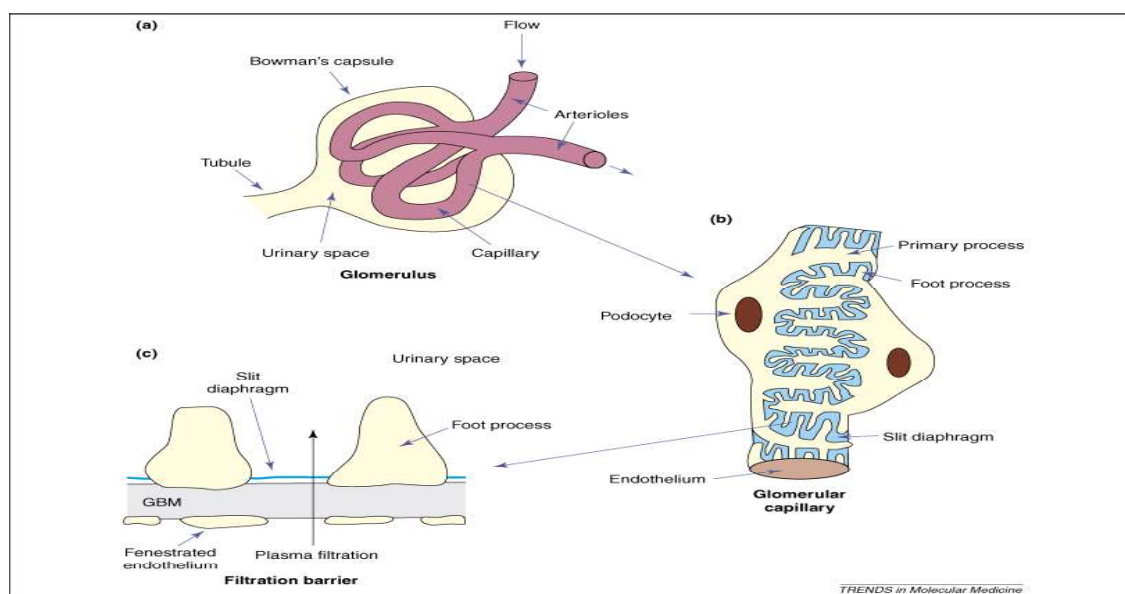Nephrin and podocalyxin are specific podocyte proteins. Podocytes are terminally differentiated cells creating

Fig. 1. a) Structure of the glomerulus b) structure of the glomerular filtration barrier c) structure of the slit diaphragm [3]

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the visceral epithelial layer of the glomerulus. The glomerulus is a network of capillary loops surrounded by the Bowman's capsule and performs the first step of blood filtering. As a selective filter, based on its size and charge, the glomerulus allows passage of materials that circulate through blood, creating primary ultrafiltrate. This selectivity is based on the structural integrity of the three main components of the glomerular filtration barrier: the fenestrated vascular endothelium, the glomerular basement membrane (GBM), and the visceral epithelium overlying the GBM. Podocytes as a part of glomerular filtration barrier have foot processes that encircle the GBM. The interdigitating foot process of podocytes is joined by a slit diaphragm. Slit diaphragm is described as a zipper-like interaction of membrane proteins such as nephrin molecules between neighboring podocyte foot processes. The slit diaphragm has an essential role in size selectivity of the glomerular filtration barrier [1,2]. Figure 1 illustrates the structure of the glomerulus, glomerular filtration barrier and filtration diaphragm also called slit diaphragm.

Nephrin - (NPH), structure and function

Nephrin was first discovered in 1998 as a mutant product of NPHS1 gene, which was first cloned by Kestila and colleagues in children with Finnish type of congenital nephrotic syndrome-(Congenital nephrotic syndrome of the Finnish type-CNF). CNF is an autosomal recessive disease characterized by massive proteinuria in utero and symptoms of nephrotic syndrome (hypoalbuminemia, hyperlipidemia and swelling) that occur in the first days after birth. Renal biopsy in these children shows obliteration of podocyte foot processes and lack of slit

diaphragm [4]. In mice inactivation of NPHS1 gene causes massive proteinuria and death in the first 24 hours after birth [5]. This suggests the importance of nephrin in the process of glomerular filtration as a structural component of the slit diaphragm. Nephrin is exclusively expressed by podocytes but also may be expressed in brain, lymphoid tissue, heart, testis, placenta and β cells of the Langerhan's islets of the pancreas [6]. NPHS1 gene is located on chromosome 19 (19q13.1), organized in 29 exons [7]. Nephrin has 1241 amino acids with molecular weight of 180 kDa (135 kDa without posttranslational modification). It is a transmembrane glycoprotein belonging to the immunoglobulin super-family of cell-adhesion receptors. It contains eight extracellular Ig like domains, followed by a fibronectin type III-like module, a short transmembrane domain and a cytoplasmic C-terminus. Cytoplasmic segment contains nine tyrosine residues which are phosphorilated in interaction with other nephrin molecules, a process which is very important in the intracellular signaling. Nephrin has three cysteines in the extracellular segment that are important in the podocyte foot process interaction, described as zipper interaction in the center of the slit diaphragm. As a major component of the slit diaphragm, nephrin forms the physical barrier to plasma proteins [8]. Nephrin is important in organization and maintainance of integrity of podocyte cytoskeleton and as a signal molecule, through several signaling pathways, regulates the shape and structure of the podocytes and slit diaphragm [9,10]. Nephrin is located laterally on the foot processes and it is a major component of the slit diaphragm (Figure 2).
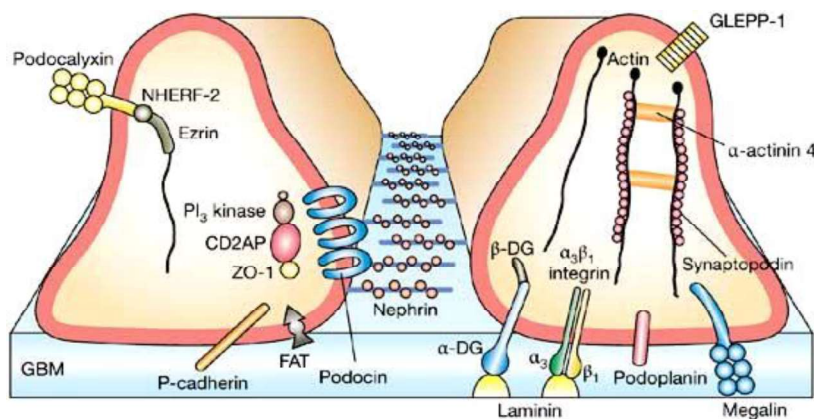

Fig. 2. Arrangement of the podocyte foot process and slit diaphragm proteins. Localization of nephrin and podocalyxin in podocytes [11]

Podocalyxin - (PODXL), structure and function

Podocalyxin is an anionic transmembrane protein localized at the apical surface of the podocytes (Figure 2); it may also be expressed on the surface of hematopoietic

progenitor cells, vascular endothelial cells, neurons and numerous tumor cells [12]. Podocalyxin is a main sialoglycoprotein of the podocyte glycocalyx, which primarily has been identified in mice, and later in the humans. As sialoglycoprotein, podocalyxin forms the

electrostatic barrier to plasma proteins. Podocalyxin is a member of the CD34 (Cluster of Differentiation 34) family with a molecular weight of 140 kDa. The extracellular part of podocalyxin is rich in serine, threonine and proline, containing O-glycosylated, sialysed and N-glycosylated domain. The intracellular part has several phosphorylation sites along one protein interaction domain, through which domain, podocalyxin interacts with Na / H exchanger regulatory factor 1 and 2 (NHERF1 and NHERF2) [13-16]. Podocalyxin interacts with ezrin molecules that are part of the podocyte cytoskeleton [17]. Podocalyxin is important in the development of glomeruli and mice that do not express podocalyxin were found to have disrupted architecture of the podocytes and showed absence of foot processes and slit diaphragm [18]. Since sialomucin has cell-cell antiadhesive effect, which is important to keep the filtration pores open and prevent conglomeration of the parietal and visceral epithelial layer of Bowman's capsule. All these processes are important to keep the normal glomerular filtration [14]. Podocalyxin is a major hallmark of podocyte phenotype and preferred protein marker for the detection and identification of podocyte with immunofluorescence technique in bioptic material and urine.

Podocytopathies

In recent years the attention of scientists, especially nephrologists and pathologists, has been focused on the role of podocytes in the pathogenesis of glomerulopathies or nephrotic syndrome. Furthermore, a great progress has been achieved in the study of the biology of podocytes, their function and mechanisms of their impairment. The response to injury of podocytes as highly differentiated cells is not typical and once they are damaged, there is a progression towards glomerulosclerosis [19,20]. The etiology of podocytopathies may be different: immunological, mechanical, infectious, metabolic, toxic, genetic etc. Reaction of podocytes to etiological factors can be different:
1. foot process effacement without changes in the number of podocytes,
2. apoptosis and loss of podocytes,
3. changes in development of podocytes and their proliferation,
4. de-differentiation.

Hence, based on the histological changes there are four types of podocytopathies:
1. minimal change nephropathy with normal number of podocytes,
2. focal segmental glomerulosclerosis with podocytopenia,
3. diffuse mesangial sclerosis with low proliferative index,
4. collapsing glomerulopathy with high proliferative index [21].

Diagnosis of podocytopathies includes morpho-pathological examination by light and electron microscopy of bioptic kidney material, immunohistochemistry-identification of specific proteins of podocytes in the bioptic material, detection and quantification of circulating biomarkers, detection and quantification of urinary biomarkers (Enzyme-linked immunosorbent assay (ELISA), Western blot, immunoflorescence, flow cytometry, mass spectrometry and Reverse transcription polymerase chain reaction (RT-PCR) for detection of mRNA of specific podocyte proteins), genetic analyses in hereditary podocytopathies [2,22].

Diagnostic relevance of nephrin and podocalyxin in secondary nephropathies

Specific podocyte proteins, nephrin and podocalyxin are relatively new urinary markers for detection of nephropathies. The diagnostic advantages of these markers are: high specificity, non-invasive detection, monitoring of nephropathies, and they can be measured by relatively simple and sensitive methods such as ELISA. This is in agreement with the statement of Walter Piering, MD: "Urine is the liquid biopsy of the kidney". Relevance as an early diagnostic marker is reserved for secondary nephropathies such as diabetic, lupus, hypertensive and preeclampsia. Early nephropathy detection may allow timely treatment and prevention for the need of renal replacement therapy as well as significant reduction of complications and mortality in these patients.

Nephrinuria and podocalyxuria in diabetic nephropathy

The podocytopathies play a critical role in the early functional and structural changes of diabetic kidney disease [23]. In diabetic nephropathy (DN) there is a decreased podocyte number and/or density as a result of apoptosis or detachment, GBM thickening and a reduction in nephrin protein in the slit diaphragm with podocyte foot process effacement [24]. Pathohistologically, DN begins with hypertrophy and hyperactivity of podocytes which lead to damage of the slit diaphragm. In advanced stage there is an ensuing atrophy of podocytes, narrowing of the foot processes, fragmentation and detachment of podocytes from GBM. All these changes lead to proteinuria [24,25]. Thus, a significant increase of foot processes width is noted in histomorphological studies in diabetic patients with advanced nephropathy and proteinuria [26]. Diabetic Pima Indians with clinical nephropathy have fewer glomerular epithelial cells compared to those with less-advanced renal disease and also there is a correlation between the number of podocytes and the degree of proteinuria. In this study, it has been shown that the number of glomerular podocytes is the best predictor of glomerular damage in diabetics [27]. In another cohort study including patients with type 2 diabetes a significant reduction was found in the number of glomerular podocytes

even in the normoalbuminuric patients [28]. In one Japanese study podocytes were detected in the urine in 53% of microalbuminuric patients and 80% of macroalbuminuric patients with type 2 diabetes. In the same study, trandolapril reduced urinary albumin excretion, as well as urinary podocytes in patients with DN. This study showed that podocyturia can be a useful marker for disease activity and trandalopril can be useful drug in DN [29]. All these studies suggest that morphological changes in podocytes are present before appearence of proteinuria. In the study of Patari, nephrinuria was present in 30% of normoalbuminuric, 17% of microalbuminuric, 28% of macroalbuminuric, 28% of new-microalbuminuric patients and 0% in control subjects. This study reconfirmed that nephrinuria may have a prognostic value in DN [30]. It was also observed that the number of urinary podocalyxin-positive elements (PCX+EL) may be significantly increased in the early course of DN compared to health controls and correlated well with the clinical diagnosis of DN, especially in the stage of normoalbuminuria [31]. Hara *et al.* found that urinary podocalyxin was significantly higher in 53.8% of normoalbuminuric, 64.7% of microalbuminuric and 66.7% of macroalbuminuric patients with DN. Thus, podocalyxin measured in urine by the ELISA method can be used as a marker for early detection of diabetic nephropathy [32].

Nephrinuria and podocalyxuria in preeclampsia

Preeclampsia is a pregnancy-specific disorder associated with significant maternal-fetal morbidity and mortality. Hypertension (>140/90 mm Hg) and proteinuria (>300 mg in a 24-hour urine) are the main clinical manifestations of preeclampsia, which usually occurs after 20 weeks of gestation. Preeclampsia is a secondary nephropathy that includes damage to podocytes and their loss on glomerular level that leads to proteinuria. One study demonstrated that podocyturia was present in pregnant women who developed preeclampsia, at a time when hypertension and proteinuria were absent, suggesting that podocyturia may serve as a predictive marker in preeclampsia. In addition, there was a positive correlation between the number of podocytes and the degree of proteinuria, suggesting that podocyte loss may be related to the onset and severity of proteinuria [33]. In a study of Garovic *et al.* podocyturia exhibited 100% sensitivity and 100% specificity in the diagnosis of preeclampsia [34]. On the other hand, in the study of Wang urine nephrin and podocalyxin levels were found significantly higher in women with preeclampsia compared to those in normal pregnants [35]. Son *et al.* also found a positive correlation between urinary nephrin and proteinuria, creatinuria and diastolic blood pressure in preeclamptic women, which indicate the importance of nephrin in the pathogenesis of proteinuria in preeclampsia and the ability to be a reliable indicator of renal damage [36]. On the other hand, Jim *et al.* found that

nephrinuria had 57% sensitivity and 58% specificity as a diagnostic tool in preeclampsia [37]. In pregnant women with preeclampsia and eclampsia in Paraguay elevated concentrations of podocalyxin in urine were found regardless of the presence of proteinuria. In fact, podocalyxin concentration in urine correlated with the degree of damage to podocytes [38]. In the same study the quantification of urinary podocalyxin was made by the ELISA method as a relatively inexpensive, simple and also a useful method for detecting damage of podocytes.

Nephrinuria and podocalyxuria in hypertensive nephropathy

Hypertensive nephropathy or hypertensive nephrosclerosis is a medical condition referring to damage to the kidney due to the high blood pressure. This is the second most common cause of ESRF [39]. Podocyte damage is important in the pathogenesis of hypertensive nephropathy, but human data on the mechanisms of damage to podocytes in hypertension are yet limited. However, it is supposed that mechanical damage of podocyte cytoskeleton is crucial in pathogenesis of the hypertensive podocytopathy [40]. Patohistological examination of bioptic material in hypertensive adult Africans showed that 13% of them presented with typical focal segmental glomerulosclerotic lesions [41]. The study of Wang demonstrated the presence of podocytopenia on glomerular level and reduced intrarenal gene expression of podocyte-associated molecules in patients with hypertensive nephropathy. These findings were in correlation with renal function and the degree of renal fibrosis, suggesting that podocyte loss may play an important role in the pathogenesis of hypertensive nephropathy [42].

Nephrinuria and podocalyxuria in lupus nephropathy

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease characterized by the production of antinuclear antibodies. As a multi-organ disease SLE involves the kidney. Lupus nephritis (LN) patients present with proteinuria that has generally been associated with immune complex deposition in the glomerular capillary wall and endo-capillary proliferation and inflammation [43]. A decreased number of glomerular podocytes, an association between proteinuria and decreased podocyte numbers in lupus glomerulus and an increased excretion of urinary podocytes in patients with lupus nephritis have been recently found [44]. Interestingly, it has also been found that in patients with SLE there are increased urinary levels of podocyte proteins, nephrin and podocalyxin. Thus, urinary podocalyxin/creatinine ratio may be used as a non-invasive marker for pathological impact of SLE on the kidney [45].

Conclusion

Nephrin and podocalyxin are relatively new markers for detection of podocytopathies. They appear in urine before microalbuminuria and proteinuria and therefore may be useful in the early diagnosis of secondary nephropathies. They have a great importance as auxiliary tools in the diagnosis, differential diagnosis and prognosis in primary nephropathies, reducing the requirement of indications for renal biopsy. The meaning of early diagnostic markers is reserved for secondary nephropathies because in the primary nephropathies proteinuria is often the first clinical manifestation. Nephrin and podocalyxin are important as markers for early detection of secondary nephropathies such as diabetic, lupus, and hypertensive, which are the most common causes of end-stage renal disease. These markers are also important in the prediction of preeclampsia as a leading cause of complications during pregnancy. Early detection of these secondary nephropathies will allow timely treatment and reduce complications and mortality. The advantage of these urinary markers is high specificity and sensitivity for secondary nephropathies and ability to be measured by relatively inexpensive, simple and non-invasive methods. Nephrin and podocalyxin have a promising potential as diagnostic and prognostic markers for clinicians and researchers, but more extensive clinical research is required to assess their true diagnostic and prognostic value. These markers are also new potential therapeutic targets in renal diseases.

Conflict of interest statement. None declared.

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Original article

Lung Cancer in Renal Transplant Recipients

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Abstract

Introduction. Although the incidence of malignancy has increased after solid organ transplantation, data on lung cancer in this group of patients is scarce. The aim of this study was to determine clinical characteristics and outcome of patients who developed lung cancer after renal transplantation.

Methods. Among a cohort of 1658 patients who received a transplant at our institution and were followed-up between 1973 and 2014, five patients developed lung cancer. We analyzed risk factors, transplantation characteristics, treatment options and survival.

Results. Lung cancer was diagnosed in 5 patients (0.3%). Time to diagnosis after the transplant procedure ranged from 26 to 156 months (mean 115 months). All of them had a smoking history. Tumors were classified as IIB (20%), IIIA (40%), and IV (40%). Histological types included adenocarcinoma (80%) and there was one case of sarcomatoid carcinoma (20%). One patient had concomitant thyroid papillary carcinoma. Radiotherapy was applied in 2 patients, 2 underwent chemotherapy (erlotinib and combination of carboplatinum and etopozide in one patient each), and 2 died within one month after the diagnosis from disseminated malignant disease. Patients with stage IIIA survived 14 and 24 months after the diagnosis. The patient with sarcomatoid cancer underwent thoracotomy with a complete resection, lost his graft function and died 7 months after the diagnosis.

Conclusion. Lung cancer is relatively rare malignancy in renal transplant recipients, but associated with high mortality. Smoking is a significant risk factor, thus smoking cessation should be promoted among renal transplant recipients, as well as regular screening for lung cancer.

Keywords: lung cancer, kidney transplantation, smoking

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Introduction

Renal transplantation is a life-prolonging treatment for end-stage kidney disease patients, but it increases risk for developing cancer, mostly because of medications administered to suppress the immune system and prevent rejection of the organ [1-4]. In developed countries most common posttransplant malignancies are skin cancer, Kaposi's sarcoma, renal and thyroid cancer and lymphoproliferative disorders [5,6]. Although the incidence of malignancy has increased after solid organ transplantation, data on lung cancer in this group of patients is scarce.

The aim of this study was to determine clinical characteristics and outcome of patients who developed lung cancer after renal transplantation.

Materials and methods

In this retrospective study, hospital files of 1658 renal transplant recipients who received renal allograft at the University hospital centre Zagreb between 1973 and 2014 were reviewed. We obtained data about smoking history, dialysis vintage, type of immunosuppression, time after transplantation until development of malignancy, tumor classification, histological type, treatment approach and outcome.

Descriptive statistical analysis was used. Data were compared with results from other countries.

Results

Patients' characteristics, treatment and outcome

Among a cohort of 1658 patients who received a transplant at our institution and were followed-up between 1973 and 2014, 5 patients developed lung cancer. Time to diagnosis after the transplant procedure ranged from 26 to 156 months (mean 115 months). All patients who developed lung malignancy had a long-term (more than 20 years) smoking history.

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