



# Biomarkers in the Differential Diagnosis of Podocytopathies

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## Editorial

The spectrum of podocyte diseases consists of primary and secondary disorders, including congenital nephrotic syndrome of the Finnish type, Focal Segmental Glomerulosclerosis (FSGS), Minimal Change Nephropathy (MCN), as primary, and hypertensive, diabetic and aging nephropathy, as secondary disorders. MCN and FSGS are the principal causes of nephrotic syndrome in children and adults, but they also share many histological findings. Podocyte injury and fusion of foot processes, with or without podocyte hypertrophy and hyperplasia, and only scarce inflammatory findings are common findings in both diseases. Differential diagnosis is usually difficult, as the sclerotic lesions in FSGS are by definition focal and segmental in nature and can easily be missed in a small kidney core [1]. These two diseases have totally different response to treatment and different long-term outcome [2,3]. Why should these two primary glomerular disorders starting by the same cellular injury end up in so different ways? Is there a possible marker to distinguish them when biopsy findings are not sufficient and predict outcome and response to treatment? Cytokines, chemokines, growth factors are produced by resident or infiltrated cells and are the main players in the pathogenesis and progression of histological changes [4,5]. Identification of biomarkers definitely associated with particular histological findings should be extremely useful in distinguishing between FSGS and MCN, but also in differentiation of FSGS subtypes (FSGS not-otherwise specified, hilar FSGS, tip-lesion, collapsing, cellular) [4,6].

Many investigators have tried to identify molecules circulating in serum, excreted in urine or expressed on renal tissue that could possibly be connected by the specific diagnosis of glomerulopathy. suPAR is proved to act as a permeability factor in FSGS, and for many years it was anticipated to be solution to FSGS enigma. It's urinary and serum levels could predict response to treatment, relapse and also recurrence of disease after transplantation. suPAR also seemed to discriminate FSGS from other primary diseases, even from MCD [7]. However, repeated research gave conflicted results [8], and the Nephrotic Syndrome Study Network (NEPTUNE) showed that suPAR levels were correlated with renal function impairment in several primary glomerular diseases, and were not associated with FSGS after adjustment of eGFR [9].

Urinary analysis applying Proteomics has also been performed in patients with nephrotic syndrome and showed that fragments of albumin, A1 antitrypsin (A1AT) and Tamm-Horsfall protein were the prominent macromolecules in FSGS and MCN patients [10,11]. Increased urinary excretion of Apo-1b was found in FSGS patients with relapse or FSGS recurrence after transplantation. Also, uromodulin peptides were increased, and a1-antitrypsin and b2-microglobulin were reduced in the urine of FSGS patients [10].

Other substances such as CD80 and MMP9 have recently been proposed as to potentially differentiate FSGS from MCD [4,12]. Metalloproteinases (MMPs), a family of zinc-dependent proteinases, are expressed on mesangial cells and podocytes. According to their impact in degradation and turnover of extracellular matrix (ECM) proteins MMPs are subdivided into 30 different classes. MMP-9 is correlated with the degradation of type IV collagen and development of fibrosis. MMP-9 is not normally expressed on the glomeruli, but has been described in Henoch-Schoenlein purpura, IgA nephropathy, and poststreptococcal glomerulonephritis, and its urinary excretion was increased at early stages of FSGS [12-14]. Degradation of MMP-9 is inhibited by Neutrophil gelatinase-associated lipocalin (NGAL) which stabilizes and expands its activity. The ratio of MMP-9/NGAL in urine was increased in children with FSGS and has been proposed as a marker discriminating FSGS from MCN [12].

Other molecules, such as cardiotrophin-like cytokine-1 (CLC-1), soluble urokinase receptor [15], TNF- $\alpha$  [16], MCP-1 [17] and TGF- $\beta$ 1 [18] were significantly increased in the urine of FSGS

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patients compared to MCD. Vascular permeability factor (VPF) and hemopexin are produced by circulating T cells after stimulation by several cytokines (IL-2, IL-5, IL-12 and IL-18), they are implicated in the development of proteinuria and are increased in the urine of children with MCN [19,20].

In our laboratory, we have previously found significant reduction in urinary levels of EGF in FSGS patients, compared to MCD, and also a negative correlation with the degree of glomerulosclerosis and tubular atrophy. Furthermore, urinary levels of EGF at time of diagnosis could predict long term renal function outcome of FSGS and response to treatment [21]. Someone could argue that EGF is produced by tubular epithelial cells, and thus, its reduction may only represent advanced tubular atrophy. However, EGF receptor which is expressed at tubular epithelial cells, after activation by urinary proteins, seems to have a central role in this procedure. EGFR is used by EGF and TGF, which antagonize for the receptor, and also, have opposite results [22]. As TGF urinary levels are significantly increased, and the same time EGF are reduced in FSGS patients, there is possible connection to EGFR activation, but this needs further investigation.

We have recently studied the urinary excretion of Th1 and Th2 cytokines in patients with FSGS and MCN. Members of the Th1 cytokines, INF- $\gamma$ , TNF- $\alpha$ , IL-2, IL-12 and IL-23, are the main mediators of cellular immunity and participate in proinflammatory and autoimmune responses [23]. Th1 cytokines are produced as a response to infection and, as pre-inflammatory cytokines, activate macrophages, neutrophils, NKCs and memory cells. Conversely, Th2 cytokines including IL-4, IL-5, IL-13, and IL-10, are anti-inflammatory mediators, mainly associated with humoral immunity and are responsible for anti-inflammatory and allergic reactions, including IgE excretion, eosinophil and B-cell activation and antibody production [24]. Although none of the cytokines measured could differentiate between FSGS and MCD, Th1 cytokines seemed to be important mediators in the pathogenesis and progression of FSGS, while Th2 cytokines were important in MCN.

Although FSGS used to be considered as a Th2 mediated disease, recent findings are controversial. In vitro studies have shown that IL-2, a Th1 cytokine, induces protein leakage when incubate podocyte cell cultures. The same cytokine can cause podocyte injury by activating the IL-2R expression on murine podocytes. Furthermore treatment with rituximab reduced IL-2(+)/CD3(+) and IFN- $\gamma$ (+)/CD3(+) levels FSGS patients [25,26].

Conversely, Th2 cytokines seem to be important mediators in MCN. Association of MCN with allergy, atopic disorders and Hodgkin's disease is well known [27,28]. Allergic reactions are associated with a Th2 shift of immune response, suggesting a pathogenetic role of these cytokines in MCN. IL-13 has recently been implicated in the up-regulation of B7-1 and down-regulation of nephrin and podocyn expression of podocytes in WKY rats, leading to proteinuria and MCD. IL-4 and IL-13 are increased during active phase of the disease. Some investigators have also described increased serum levels of IL-4, IL-13 and IgE in MCD regardless active or remission phase [29].

Differential diagnosis between FSGS and MCN is usually difficult, as the two diseases share common clinical and histological findings. The exact knowledge of etiology, pathogenetic mechanisms and immune reactions that are activated and take place during the progression of each disease will help to discriminate between them

and predict renal function outcome and response to treatment.

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