Minimal change disease as a modifiable podocyte paracrine disorder

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Nephrotic syndrome is a common illness dating back to the 15th century and known to affect both children and adults [1]. There are three distinct histological variants of primary idiopathic nephrotic syndrome, minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN), which is rare in children. In clinical practice, ~95% MCD patients respond to corticosteroids, while most FSGS patients are resistant to steroids therapy [2].

Pathophysiologically, the constellation of features that characterize nephrotic syndrome stems from primary alterations of the permselectivity barrier of the glomerular capillary wall, allowing increasing loss of plasma proteins into the urine [1,3]. Morphologically, the renal filtration barrier consists of three layers, the glomerular fenestrated endothelial cells (GECs), the glomerular basement membrane (GBM) and podocytes with their foot processes [3]. The GECs are covered by a surface layer made of negatively charged glyocalyx, thus contributing to the charge selectivity of the filter [3,4]. The GBM is an extracellular matrix that helps to form the structure of the glomerular capillary wall and also provide a heavily negative charge [3,4]. Podocytes have been intensely studied to better define how these cells react during health and disease [3,4]. Despite significant progress in understanding the kidney ultrafiltration barrier, the molecular mechanisms of nephrotic syndrome and how it relates to its specific entities are still unclear. This is a particularly difficult problem as the initial structural changes inside the glomerulus are indistinguishable and often benefit from additional clinical responses such as a successful trial of steroids which rather points to MCD as supposed to FSGS or MN.

In a recent issue of Nature Medicine, Clement et al. [5] identified a role of angiopoitin-like-4 (ANGPTL4) in glucocorticoid-sensitive nephrotic syndrome. ANGPTL4 belongs to a group of proteins, that are structurally similar to the angiogenic factors angiopoietins but angiopoietins-like proteins do not bind to either the angiopoietin receptor Tie2 or the related protein Tie1 and thus are orphan ligands [6]. ANGPTL4 has been implicated in hypertriglyceridemia [7] and tumor metastasis [8]. In human, ANGPTL4 is ubiquitously expressed but particularly enriched in the liver and adipose tissue [9]. Prompted by the fact that hyperlipidemia is one of the major features of nephrotic syndrome, Clement et al. [5] explored the expression of ANGPTL4 in MCD and found it upregulated in the serum as well as in podocytes in experimental models of MCD as well as human MCD. With the help of genetic models, they found that mice without endogenous ANGPTL4 are protected from lipopoly saccharide (LPS)-induced proteinuria. In contrast, rats that overexpress ANGPTL4 in podocytes develop large-scale albuminuria, loss of GBM charge as well as podocyte foot processes effacement [5], suggesting a causative role of ANGPTL4 in MCD.

This novel study performed by Clement et al. is particularly interesting to both nephrologists and renal researchers in several aspects. Firstly, ANGPTL4 expression seems glucocorticoid sensitive. The use of steroids in treatment of nephrotic syndrome has been in practice for many years, but unfortunately little is know about its working mechanisms [10]. Notably, Clement et al. [5] reported the expression of ANGPTL4 to be reduced after glucocorticoid treatment, suggesting that ANGPTL4 can be considered a steroid sensitive target in podocytes in vivo. More studies are warranted to explore if podocyte ANGPTL4 is a direct target for steroids. Secondly, Clement et al. identified the effect of ANGPTL4 on both GBM and podocytes. They found loss of GBM charge as well as significant podocyte foot process effacement in the transgenic rats with specific podocyte ANGPTL4 overexpression [5]. This finding addresses one of the key questions many nephrologists often ask, which layer of the renal ultrafiltration barrier is important for the development of proteinuria, GEC, GBM or podocyte and their foot processes? The study by Clement et al. [5] further suggests that it is a series of events involving all three layers, but it may start from podocyte where factors like ANGPTL4 or vascular endothelial growth factor (VEGF) [11] are induced to work in a paracrine and autocrine fashion. Thirdly, Clement et al. found different roles for glomerular produced ANGPTL4 and systemic ANGPTL4. They observed that enhanced circulating level of ANGPTL4 in the transgenic rats which specifically express ANGPTL4 in the adipose tissue does not cause marked proteinuria, whereas, transgenic rats which express podocyte-derived ANGPTL4 develop heavy proteinuria [5]. They attributed this difference to the variation in ANGPTL4 sialylation. Unlike the circulating ANGPTL4 which comes from the adipose tissue, induced expression of podocyte-
produced ANGPTL4 is hyposialylated [5]. Sialylation is the addition of N- or O-substituted derivatives of neuraminic acid that is crucial for a variety of cellular functions, such as cell adhesion or signal recognition and regulation of the biological stability of glycoproteins [12]. While ANGPTL4 produced at normal levels undergoes physiological sialylation, there is insufficient sialylation in conditions with increased production of podocyte ANGPTL4.

The concept of circulating permeability factor in MCD and/or FSGS has intrigued many of us for decades, with no such factor identified yet for MCD [13]. Clement et al. suggest that ANGPTL4 in MCD might represent a podocyte-derived factor that may act in an autocrine or paracrine manner (Figure 1) and thus quite in contrast to FSGS, where circulating factors, such as soluble urokinase receptor (suPAR) or cardiomyrophin-like cytokine 1 (CLC-1) play an important role [14]. Together with many other reports [15,16], it is reasonable to state that MCD and FSGS are two different disease entities rather than a continuous spectrum of one disease with both presenting under the umbrella of nephrotic syndrome. Lastly, Clement et al. found that ANGPTL4 caused glomerular injuries could be relieved by pharmaceutical sialylation. Feeding podocyte ANGPTL4 transgenic rats, the sialic acid precursor N-acetyl-D-mannosamine (ManNAc) results in a decrease of albuminuria by 40% [5]. Treatment of MCD with sialic acid precursors may therefore represent a novel nutritional therapeutic strategy to alleviate the symptoms of nephrotic syndrome in MCD.

Fig. 1. Schematic of systemic and glomerular pathways leading to human MCD. Literature supports the notion that T- and/or B-cell mediated events lead to a yet to be identified circulating factor that harms glomerular cells causing MCD. According to Clement et al., podocyte-derived ANGPTL4-expression is induced in MCD but insufficiently sialylated, causing disturbance of the GBM as well as endothelial cells in a paracrine fashion.

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References


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