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For Better or Worse: A Niche for Notch in Parietal Epithelial Cell Activation

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Abstract

Podocyte (glomerular epithelial cell; GEC) dysfunction and loss are the hallmarks of focal segmental glomerulosclerosis (FSGS). Over the recent years, changes, including activation and proliferation of parietal epithelial cells (PEC) have been increasingly appreciated in FSGS. The functional role of PECs in FSGS is still a hotly debated issue. Here Ueno et al. report that Notch signaling plays a role in orchestrating PEC cell phenotypic changes in FSGS.

Focal segmental glomerulosclerosis (FSGS) is characterized by nephrotic syndrome often leading to a progressive decline in renal function. Glomerular epithelial cells (GEC) or podocytes play a critical role in FSGS development [1, 2]. Sustained activation of developmental pathways, including Notch and Wnt/ β -catenin signaling, have been shown to play a pathogenic role in FSGS [3, 4]. Increased Wnt and Notch expression in terminally differentiated podocytes have been associated with dedifferentiation and podocyte apoptosis [3, 4]. Podocytes are terminally differentiated cells, which are unable to proliferate, therefore once podocyte loss reaches a threshold, irreversible scarring and functional loss develops.

Over the last decade we have learned that most post-mitotic cells, such as β -cells and neurons, are replaceable. However, according to our classic models, differentiated podocytes neither proliferate nor are replaced; could the podocyte then be the only cell in the body that is truly irreplaceable? During the last five years several hypotheses have been put forward as a potential mechanism for podocyte replacement. Bone marrow derived stem cells have been proposed to replace podocytes in renal transplant patient and in models of Alport's disease [5]. Alternatively, the group of Romagnani et al. proposes that PEC cells can differentiate into podocytes and migrate into the capillary tuft via the vascular stalk [6]. Unfortunately these studies relied on expression of marker proteins and in vitro culturing. Future in vivo lineage tagging analyses will be essential to either confirm or refute these hypotheses.

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Disclosure

The authors have nothing to disclose.

PEC cell activation is increasingly recognized and seems to be present in most forms of FSGS [7]. The usually flat appearing PEC become prominent and proliferative, with enlarged nuclei and cuboidal appearance [8]. These activated PEC cells may even repopulate podocytes after high dose angiotensin convertase inhibitor treatment has been reported in a rat FSGS model [9], consistent with the model that PEC cells are podocyte precursors [6]. On the other hand, by using a genetic lineage tagging approach, data from the Moeller group indicates that activated PEC cells invade the affected segment of the capillary tuft, initiate a glomerular and parietal basement membrane adhesion and glomerulosclerosis [10]. These studies indicate that while PEC cell activation appears to be common in FSGS, their specific role remains controversial (Figure1).

What mediates PEC cell activation in FSGS? In this issue, the Nagata group [11] move the story of PEC cells significantly further by being the first to describe Notch signaling in PECs subsequent to directed podocyte injury. As an FSGS model, the authors utilized the LMB2 antibody treated NEP25 transgenic mouse [12]. In their experiments a single dose of LMB2, high enough to induce rapid and progressive focal glomerular collapse, demonstrated a wave of Notch 1 protein expression that was present in podocytes before appearing in the parietal epithelial cells. Expression of the Notch pathway proteins preceded and then persisted, during the generation of hyperplastic parietal epithelial cells. Biopsy samples from patients with collapsing FSGS also demonstrated Notch pathway protein expression in hyperplastic glomerular lesions, indicating that Notch 1 activation is common in different FSGS models.

The temporal and spatial expression of Notch in this FSGS model hints at a functional role in an epithelial to mesenchymal-like transition to create the hyperplastic (activated) parietal epithelia. The loss of tight cell-cell and cell-matrix adhesions and an increase in cellular proliferation and migration are functional hallmarks of epithelial mesenchymal transition (EMT), which appears to be both necessary for physiologic wound healing and responsible for pathologies such as fibrosis and cancer metastasis. One of the most recognized functions of Notch signaling in cancer and development is the ability, and in many cases, necessity, of this pathway to induce EMT [13]. However, whether this transition occurs in the kidney is still unknown. Ueno et al. begin to approach this question with a parietal epithelial cell line. Induction with TGF- β 1 resulted in a significant up-regulation of target genes associated with mesenchymal cell phenotype [11]. Concurrent inhibition of Notch cleavage (and thus signaling) with a gamma secretase inhibitor, DMZ, blocked both EMT gene expression changes and cell migration in response to TGF- β 1, demonstrating a dependence on Notch signaling for induction of EMT-like gene expression in the parietal epithelial cell line.

Based on these in vitro results, and the Notch expression in vivo, the authors surmised that attenuating the Notch pathway in vivo would block the induction of parietal cell hyperplasia and thus the progression of FSGS. However, while application of the Notch inhibitor in vivo blocked the formation of hyperplastic lesions in response to LMB2 antibody treatment, the loss of podocytes was not attenuated and subsequent proteinuria was worsened. The data indicates, that the damage to GECs in this (LMB2-induced) genetic podocyte depletion model may not directly induced by Notch signaling. However, that the formation of hyperplastic PEC lesions was prevented by DMZ treatment pointing to the role of Notch

signaling in the formation of such lesions. The DMZ treatment experiments are an interesting first step to understand the role of Notch in vivo PECs. Based on the combined loss of hyperplastic lesions with worsened renal histopathology it is tempting to surmise that this is proof of a physiologic role for hyperplastic/activated parietal epithelial cells in glomerular disease.

There are several alternative interpretations of these findings. First, it seems that while PEC cell changes and activation are increasingly recognized in FSGS, renal function and albuminuria are more closely linked GEC cell changes. As the NEP25 is a genetically engineered FSGS model, the original GEC cell injury is likely to be independent of Notch signaling. Furthermore, these studies may also be hindered by the use of pan Notch inhibitors. As the recognition of Notch as a major player in glomerulopathies increases, so do the available tools to tease out the role of this important pathway. In mammals, there are 4 different Notch receptors (Notch 1–4) and 6 different canonical ligands (Jagged1, 2 and Delta 1–4). By isolating which specific interactions within the Notch signaling family of ligands and receptors are engaged during the onset of FSGS we may be able to design targeted and safe therapeutics to protect patients before irreversible damage has accumulated. During development, Notch2 plays a critical and non-redundant role in podocyte development, while most studies point to the direction of Notch1 in glomerulosclerosis [11, 14]. In addition, determining the exact location and the timing of the different Notch ligands and isoforms will also be essential to understanding the role of Notch signaling. Previous studies indicated that sustained (tonic) activation of Notch signaling from mature podocytes is necessary and sufficient to induce podocyte damage including apoptosis [4]. The role of single bursts (phasic) of Notch activation remains to be established. And last but not least, we also need to keep in mind the context of Notch activation, including the possible interactions with additional signaling pathways. For example, β -catenin is known to interact with Notch signaling and has also been shown to play an important role in directing PEC versus GEC cellular responses [3].

In summary, a new role for Notch in parietal epithelial cell activation has been established. As the body of literature in this field increases, it will be interesting to see what Notch signaling is able to tell us about the true role of parietal epithelial cells and vice versa.

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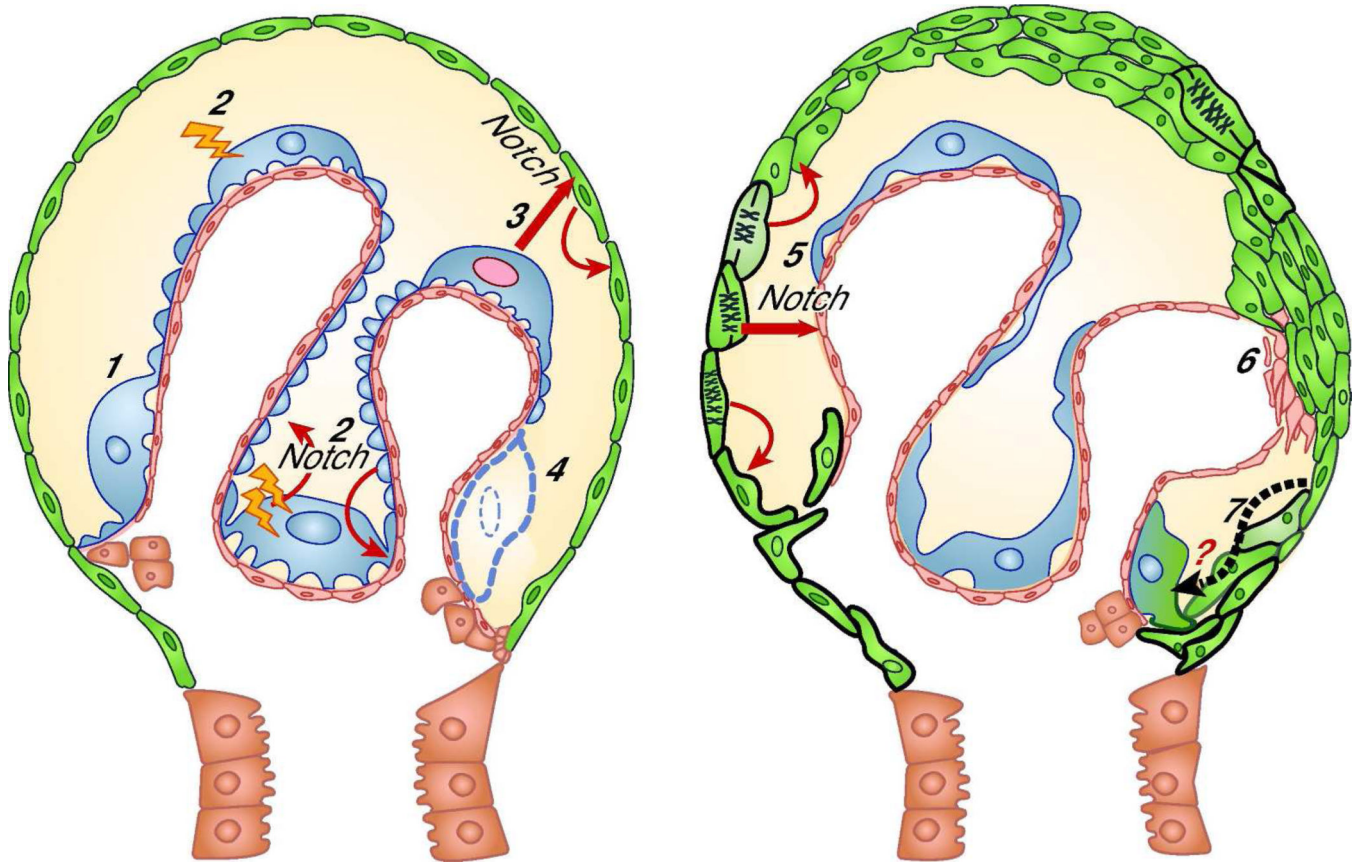


Figure1. Role of Notch signaling in GEC and PEC

Notch signaling is undetectable in healthy podocytes (blue cells) (1). Podocyte damage (such as that caused by the NEP25/LMB2 model) results in significant up-regulation of Notch signaling in GEC (2). Subsequent expression of Notch pathway related proteins are also observed in PEC cells (green cells) (3). Prolonged expression of Notch results in GEC dedifferentiation and eventual podocyte loss (4). Concurrent with podocyte injury and foot effacement, parietal epithelial cell proliferation occurs (5) and synechiae are formed (6). The potential ability of parietal epithelial cells to undergo epithelial to mesenchymal transition and migrate to replace lost podocytes is a current topic of investigation in the field of podocyte biology (7).