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Review

Glomerular development – Shaping the multi-cellular filtration unit

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ABSTRACT

The glomerulus represents a highly structured filtration unit, composed of glomerular endothelial cells, mesangial cells, podocytes and parietal epithelial cells. During glomerulogenesis an intricate network of signaling pathways involving transcription factors, secreted factors and cell–cell communication is required to guarantee accurate evolvement of a functional, complex 3-dimensional glomerular architecture. Here, we want to provide an overview on the critical steps and relevant signaling cascades of glomerular development.

Contents

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1. Nephrogenesis & nephron induction – road map for glomerular development

The glomerulus as the most proximal part of the nephron is the essential functional unit for renal filtration. The filter itself is composed of a multi-layered and -cellular barrier, including the fenestrated endothelium of glomerular capillaries, the glomerular basement membrane and the slit-diaphragm, connecting adjacent podocyte foot processes [1–3]. Malfunction in any of these components results in the loss of size- and charge-selective filtration, clinically characterized by proteinuria [4]. The complex cellular architecture of the glomerulus is based on a tightly orchestrated developmental program involving the interplay of numerous transcription factors, paracrine secretory pathways and epigenetic control mechanisms.

Ontogenetically three stages of kidney differentiation can be distinguished beginning with the pronephros, followed by the mesonephros and finally resulting in the metanephric kidney (for excellent review see [5]). During mammalian kidney development the pronephros and mesonephros represent only transient structures, while the metanephric kidney persists. The developmental program of the metanephric kidney is characterized by reciprocal interplay between the ureteric bud and the metanephric mesenchyme [6], resulting in the formation of the renal vesicle (Fig. 1). This first initiation step of glomerular development occurs around E11.5 in murine organogenesis and around the 5th week of gestation in humans [7]. Both, the ureteric bud (UB) and the metanephric mesenchyme (MM) originate from the intermediate mesoderm: while the UB forms from the caudal portion of the nephric duct, the metanephric mesenchyme condensates in close proximity to the UB. Previous studies using different experimental approaches have deciphered the underlying signaling pathways in the reciprocal interplay between MM and the UB. While UB tips lead to condensation and organization of the loosely arranged MM, branching of the UB is elicited in turn (for excellent review [5,8]). The MM contributes to the development of all proximal components of the nephron, while collecting ducts, renal calyces and the remaining urinary tract collection system will emanate from the UB [8].

With the condensation of the MM the renal vesicle is formed representing the earliest epithelial structure of the future nephron. Therefore, the inductive signals of the UB do not only lead to a morphological change in the MM, but also activate a mesenchymal to epithelial transition. Furthermore, a decisive fate specification occurs around this developmental stage, characterized by a division into either Foxd1 or mainly Six2 positive progenitors. While Foxd1 positive populations will give rise to several different cell types such as mesangial cells or angioblasts, all epithelial cell types of the nephron originate from the Six2 positive progenitor population [9].

The condensation of the MM and formation toward the renal vesicle structure marks the initiation of nephron development characterized by a mesenchymal to epithelial transition. The sequence of developmental steps has mainly been classified by underlying morphological characteristics. After initial condensation of the renal vesicle, the comma-shaped bodies are formed (Fig. 1). With the formation of a cleft in the more distal part of the comma-shaped bodies, the next morphological level, the S-shaped body, is determined. Cells directly adjacent to the cleft are specified toward the podocyte population, whereas cells in the more caudal region of the S-shaped body will give rise to the proximal tubule compartment. At this stage of glomerular development paracrine signaling is of particular importance: VEGF secreted by premature podocytes attracts endothelial cell progenitors to migrate into the S-shaped body cleft [10,11]. The intruding endothelial cells probably derive from angioblasts, which originated from the non-nephron progenitor cells of the metanephric mesenchyme [12]. The exact origin of mesangial cells (metanephric mesenchyme versus multipotent hematopoetic progenitor lineage), which also intrude at this stage into the cleft, is still unresolved [13,14]. Ongoing maturation then finally leads to the fully developed glomerulus, consisting of 4 highly specified cell populations represented by the fenestrated endothelium, mesangial cells, podocytes and the parietal epithelial cells of the Bowman's capsule.

2. Gaining foothold – decisive steps in podocyte development

2.1. Formation of the slit diaphragm

The first podocyte precursor cells might be specified around the comma-shaped body stage. During further development of the glomerulus podocytes undergo a dramatic change in cellular morphology and concomitantly loose typical characteristics of classical epithelial cells. At the very early stage of glomerular maturation, podocytes represent a classical columnar epithelium (comma-shaped body), but with the intrusion of endothelial cells and unfolding of capillary loops these cells start to dramatically expand their apical surface seemingly resulting in a translocation of their apical cell-junctional belt toward the basal side. This apical membrane expansion not only leads to a change in cellular architecture, but is at the same time accompanied by a sequential change of cell-junctional protein expression (Fig. 2).

While cadherins and tight junction proteins like ZO-1 predominate in the apical junctional belt [15,16] super IgG family proteins like Nephrin and NEPH1 are started to be expressed at basal cell–cell contact sites after apical podocyte membrane expansions [17–19]. Thus, tight junctions are restructured and replaced by a unique, modified adherens-junction like contact, termed the slit diaphragm [18]. This morphogenetic switch is paralleled with the increased expression of specialized apical surface proteins such as the sialoglycoprotein Podocalyxin which contributes to the highly negative charge on the podocyte cell surface [20]. Interestingly, a reappearance of tight junctions and apical transition of junctional components can be observed in glomerular diseases [20,21].

The morphogenetic transformation of podocytes from a columnar epithelium toward a highly arborized cellular morphology with interdigitating foot processes suggests an utmost importance for underlying polarity programs. In general, epithelial apicobasal cell polarity is organized by the asymmetric localization of three main polarity complexes: (a) The apical Crumbs complex (Crumbs, PALS1 and PATJ), (b) the apical PAR complex and (c) the basolateral Scribble complex (Scribble, DLG and LGL [22,23]). A series of recent studies could demonstrate the fundamental role of the Par/aPKC polarity complex for podocyte development, as various mouse models deficient for *aPkc* in the podocyte result in loss of podocyte foot processes and congenital nephrotic syndrome [24–27]. Furthermore, a genetic screen in zebrafish also identified *Crumbs* (crb2b) to be required for podocyte foot process development [28]. In contrast, conditional knockout of the basolateral polarity protein Scribble was not associated with any obvious podocyte defects [29].

2.2. Morphogenetic programs controlling the development of podocyte foot processes

One main feature of podocytes, aside from the unique slit diaphragm junction, is their peculiar morphology with primary and secondary processes, which was naturally eponymous for this cell type (from Greek "πούς *pous*", genitive "ποδός *podos*"). Together with the slit diaphragm, podocyte foot processes (FPs) are intimately involved in the integrity of the glomerular filtration barrier and any form of podocyte malfunction results in a uniform pathological response which is termed podocyte foot process effacement