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Signal transduction in podocytes—spotlight on receptor tyrosine kinases

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Abstract

The mammalian kidney filtration barrier is a complex multicellular, multicomponent structure that maintains homeostasis by regulating electrolytes, acid–base balance, and blood pressure (via maintenance of salt and water balance). To perform these multiple functions, podocytes—an important component of the filtration apparatus—must process a series of intercellular signals. Integrating these signals with diverse cellular responses enables a coordinated response to various conditions. Although mature podocytes are terminally differentiated and cannot proliferate, they are able to respond to growth factors. It is possible that the initial response of podocytes to growth factors is beneficial and protective, and might include the induction of hypertrophic cell growth. However, extended and/or uncontrolled growth factor signalling might be maladaptive and could result in the induction of apoptosis and podocyte loss. Growth factors signal via the activation of receptor tyrosine kinases (RTKs) on their target cells and around a quarter of the 58 RTK family members that are encoded in the human genome have been identified in podocytes. Pharmacological inhibitors of many RTKs exist and are currently used in experimental and clinical cancer therapy. The identification of pathological RTK-mediated signal transduction pathways in podocytes could provide a starting point for the development of novel therapies for glomerular disorders.

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Introduction

Podocytes are highly specialized cells with a unique structure and function. These cells, which are located adjacent to the glomerular capillaries and form part of the glomerular filtration barrier, have microtubule-based cellular extensions known as primary processes, and actin-based membrane extensions known as foot processes.[1] The foot processes form distinct subcellular compartments within the podocyte and enable spatially and temporally distinct metabolic and signalling activities. As a result of their unique location at the interface of blood and urine, podocyte membranes comprise three distinct signalling platforms: the sole plate (baso-lateral membrane attached to the glomerular basement membrane [GBM]), slit diaphragm (cell-to-cell junction formed between adjacent podocytes), and apical membrane, which is bathed in urine (Figure 1).[2] The existence of a 'subpodocyte' space within the glomerulus that might restrict fluid and solute movement across the glomerular capillary wall and generate concentration gradients of signalling molecules within the foot processes has also been suggested.[3] Although both primary processes and foot processes receive signals, current research is mainly focused on signals that are generated at the foot processes. Podocytes express a number of signal transduction receptors, including receptor tyrosine kinases (RTKs), G-protein coupled receptors (GPCRs) and nuclear receptors.[4,5] Integrins also have essential roles in podocytes, and mediate cell matrix adhesion as well as outside-in signalling, which has been reviewed previously.[6] In this Review, we summarize the basic principles of signal transduction and discuss the physiological and pathological roles of RTK signalling in podocytes.

Signal transduction

First messengers

In the biological context, signal transduction refers to the mechanisms that permit external chemical signalling molecules—the first messengers—to direct cell activities. On a molecular level this process is difficult because the cell membrane, although very thin, is impermeable to ions and polar molecules, including amino acid derivatives, peptides and proteins. With a few exceptions (steroid hormones, thyroid hormones and prostaglandins), first messengers induce cellular changes without penetrating the target cell. They bind to receptors on the cell surface, thereby serving as extracellular soluble ligands of these receptors (Figure 2). The binding of only a few ligand molecules to cell-surface receptors might induce remarkable changes within the cell as it becomes activated. The evolution of receptors together with the first messengers (hormones, neurotransmitters, cytokines and growth factors) enabled membrane-impermeable external signals to influence cell behaviour and function and conferred high specificity and precise control in terms of the extent and duration of signalling.[7] The concept of specific receptors for ligands predates the discovery of the first hormones and hormone receptors, and can be attributed to studies published in 1878 that identified the mutual antagonism of the poisons atropine and pilocarpine,[8,9] which bind muscarinic cholinergic receptors.

Second messengers

As first messengers cannot enter the cell, their receptors activate intracellular substitutes or second messengers, such as 3′ 5′ cyclic adenosine monophosphate, calcium ions, diacylglycerol, and phosphorylated inositol lipids, in response to ligand binding. These second messengers interact either directly or indirectly (via adaptor proteins) with a specific set of enzymes, and regulate enzymatic activity and access to substrates. As most of these enzymes are protein kinases or phosphatases, the majority of cellular responses to the stimulation of cell-surface receptors are eventually mediated by protein phosphorylation or dephosphorylation.[10] The enzymes act directly on target structures or activate additional enzymes to generate a stepwise process of consecutive enzymatic activation, known as a signal transduction cascade. This cascade enables signals to be amplified (or alleviated) as they travel, and to branch out into many different signalling pathways. One first messenger can, therefore, stimulate many responses. Depending on the ultimate target of a particular signalling pathway (gene promoters and structural DNA components in the nucleus, the cytoskeleton, or metabolic factors in the cytoplasm, mitochondria and other organelles), a variety of cellular responses are possible.[7]

Receptors

Signal transduction receptors can be broadly divided into three classes (Figure 2). First, receptors that penetrate the plasma membrane and either have intrinsic enzymatic activity (such as RTKs) or are coupled to intracellular enzymatic activity (such as cytokine receptors). Second, receptors characterized by seven transmembrane spanning domains (also known as serpentine receptors or GPCRs) and coupled to intracellular proteins that bind and hydrolyze GTP. Third, nuclear receptors that bind to a ligand, translocate into the nucleus and directly affect gene transcription.

Receptor tyrosine kinases

Erickson and colleagues' discovery that v-Src (the protein encoded by the transforming gene of Rous sarcoma virus) is a protein kinase was a landmark event in the late 1970s.[11] In 1980, Hunter and Sefton reported that v-Src phosphorylates tyrosine residues in substrate proteins and v-Src became the first tyrosine kinase to be identified.[12] In the same year, epidermal growth factor receptor (EGFR) was shown to be a protein tyrosine kinase that is activated when bound to epidermal growth factor (EGF),[13] and became the first RTK to be identified. The insulin receptor was identified as a RTK a couple of years later.[14]

The discovery that many growth factor receptors are protein tyrosine kinases stimulated the search for physiological substrates. Surprisingly, the most prominent substrates seemed to be the receptors themselves.[15] This finding made more sense in the late 1980s, when Pawson and colleagues showed that proteins containing Src homology 2 (SH2) domains interact directly with activated RTKs[16] by binding phosphorylated tyrosine residues within a specific amino acid motif.[17] Receptor autophosphorylation is critical to induce binding sites for cytoplasmic proteins with SH2 domains, which then stimulate downstream signalling pathways.[17] Many SH2-proteins also contain Src homology 3 (SH3) domains, which bind proline-rich motifs in target proteins and thereby serve as a molecular link between tyrosine

phosphorylation mediated by receptor and nonreceptor tyrosine kinases and downstream signalling molecules.[18] About 100 SH2 and 250 SH3 domains are encoded in the human genome, underlining their importance in the assembly of specific protein complexes into signalling modules.[19,20] Since the discovery of SH2 and SH3 domains, the number of protein–protein and protein–phospholipid interaction signatures found in proteins that are part of signal transduction pathways, and link a particular upstream effector containing a particular binding domain to a specific downstream target protein that has a compatible acceptor motif, has exponentially increased.[21]

Structure

The two main groups of tyrosine kinases—cytoplasmic nonreceptor tyrosine kinases and RTKs—share the same tyrosine kinase module.[22] RTKs are present in all metazoans, but are not found in lower eukaryotic organisms, such as yeast and bacteria.[22] The number and complexity of RTKs increased during evolution, possibly in association with the acquisition of new cellular functions or regulatory processes.[7] In humans, the RTK family is comprised of 58 members, which are encoded by separate genes.[22] All RTKs share a common overall composition comprising an extracellular ligand-binding region, a single-pass transmembrane domain, and an intracellular kinase domain, which is sometimes split into two parts.[15,22] The RTKs have been subdivided into 20 subfamilies based on the presence of various extracellular domains, including immunoglobulin-like and cysteine-rich domains.[23]

Activation

RTKs exist as monomers, and ligand binding induces receptor dimerization—the first step in receptor activation.[15] Several growth factors (including vascular endothelial growth factor [VEGF] and platelet-derived growth factor [PDGF]) exist as homodimers, whereas others (including EGF and fibroblast growth factors [FGFs] act as monomers and form a 2:2 ligand to receptor stoichiometry.[23] In many cases, ligand binding requires specific coreceptors (transmembrane proteins or components of the extracellular matrix) and receptor activation leads to the formation of a high-molecular-weight signalling complex at the cell surface. Receptor dimerization results in the transphosphorylation of several tyrosine residues in the intracellular part of the RTK, which is catalysed by the kinase domain.[14] By contrast, the most complex members of the RTK family, the insulin and insulin-like growth factor (IGF) receptors, exist as disulphide-linked heterotetramers in the inactive state.[24] Phosphorylated tyrosine residues in RTKs serve as docking sites for adaptor proteins (such as growth factor receptor-bound protein 2 and SHC-transforming protein 1) and enzymes (such as phospholipase C-γ, Ras-associated GTPase activating protein 1 and phosphoinositide 3-kinase) that contain SH2 domains. These RTK-binding proteins carry the signal forward, leading to activation of specific downstream signalling cascades.[15]

Key roles

The majority of growth factors induce their cellular effects by binding RTKs.[15] Many growth factors are quite versatile, whereas others are specific to particular cell types. This specificity is explained by the patterns of expression of their RTKs. Growth factors control several cellular processes, including cell proliferation, differentiation, survival and migration. RTKs, therefore, have key roles in maintaining tissue homeostasis during the

development and adult life of multicellular organisms.[23] Unsurprisingly, deregulated RTK signalling has been linked to various human diseases, including cancer.[25] Mechanisms that might contribute to aberrant RTK activation in carcinogenesis include gene amplification, chromosomal translocation, point mutation, autocrine activation and impaired receptor downregulation.[26] RTKs that are altered in human cancer include members of the EGFR, PDGF receptor (PDGFR), VEGF receptor (VEGFR) and FGF receptor (FGFR) families.[27] Growth factors and their receptors participate in promoting several steps of carcinogenesis, including clonal cancer cell expansion, epithelial–mesenchymal transition (EMT), invasion and angiogenesis.[25]

Receptor tyrosine kinases in podocytes

Mature podocytes are post-mitotic cells that cannot undergo cell division.[28] The effects of growth factors on podocytes must, therefore, be different from their ‘classic’ effects in other cell types and must not involve the induction of cell proliferation. Hypertrophic growth of podocytes accompanied by mitosis serves as a compensatory mechanism in situations of podocyte injury and loss.[29] However, the activation of mitogenic programmes in podocytes is thought to lead to aberrant mitosis and cell death, a mechanism termed mitotic catastrophe.[30] As growth factors are mitogenic, they might be involved in the induction and fine regulation of mitotic events in podocytes, and the potential beneficial versus pathological effects of these events.

To date, at least 15 RTKs have been implicated in podocyte biology (Table 1). Expression of most of these RTKs in podocytes was confirmed by determining the effects of treatment with the respective ligands on cultured podocytes or mouse glomeruli. Only a few RTKs have been shown to be present in podocytes using immunohistological analyses. Prominent examples of RTKs that have a role in podocytes include members of the VEGFR, FGFR, EGFR, and PDGFR families, hepatocyte growth factor (HGF) and the insulin receptor.

Insulin

The effects of insulin and IGF on podocytes and glomerular filtration are discussed briefly here and in detail elsewhere.[31–34] Podocytes were identified as a direct target for insulin in 2005.[35] Glomerular dysfunction in insulin-resistant patients was initially thought to be related to the actions of insulin on the vasculature.[36,37] However, the effects of insulin on podocytes,[35] combined with increasing evidence that podocyte dysfunction has an important role in the pathogenesis of diabetic nephropathy,[38] indicates that insulin signalling is crucial for the regulation of podocyte function. Insulin stimulates nephrin-dependent prosurvival cascades that involve activation of AKT,[39,40] and mice with podocyte-specific deletion of the insulin receptor develop features of diabetic nephropathy, including albuminuria, podocyte apoptosis and glomerulosclerosis.[40] These findings support the hypothesis that impaired insulin signalling in podocytes has a causative role in renal pathology in patients with diabetes.

The precise functions of insulin signalling in podocytes are unclear, but most likely involve regulation of the actin cytoskeleton.[40] Reversible effects of insulin on podocyte morphology might explain why insulin infusions cause transient proteinuria in healthy individuals.[41]

Interestingly, insulin also increases the cell-surface localization of glucose transporter type 1 and glucose transporter type 4, resulting in increased glucose uptake.[35] This finding indicates that podocytes can respond to insulin in a similar way to the 'classic' insulin target tissues, such as skeletal muscle, liver and fat. Whether glucose uptake into podocytes is physiologically relevant (for example, during the postprandial period), and whether it has a role in insulin-mediated changes in podocyte morphology, remains unclear.

Vascular endothelial growth factor

VEGFR–VEGF signalling has been intensively studied and most likely serves as an important communication route to coordinate endothelial and podocyte function within the glomerulus.[42,43] The precise source of the ligand and localization of the receptor are still under debate, and results of experimental studies are contradictory. Expression of VEGFR1 and/or VEGFR2 in podocytes[44–46] and direct effects of VEGF on cultured podocytes, including positive effects on cell survival,[47] have been reported. In addition, mice with podocyte-specific overexpression of VEGF undergo pathological alterations, including foot process effacement,[48,49] further indicating that podocytes respond to VEGF and might use VEGF signalling as an autocrine regulatory system.

By contrast, podocyte-specific deletion of *VEGFR2* in mice did not alter glomerular function or ameliorate the glomerular phenotype induced by VEGF over-expression.[50] As global deletion of *VEGFR2* results in vascular defects, including defects in the glomerular microvasculature,[50] this finding suggests that VEGF signalling has paracrine functions within the glomerulus, with the podocyte as the source of the ligand, and the endothelium as the target. Clearly, more research is needed to understand the role of VEGF signalling in podocytes and determine whether endothelial cells also signal to podocytes via VEGF. Most likely, VEGF affects multiple cell types and exerts multiple effects on patho-physiological processes in the glomerulus. The current controversies regarding VEGF signalling in podocytes illustrate the complexity of this field and the limitations of experimental *in vitro* and *in vivo* models to determine precise communication routes between cells and the localization of individual signalling events. The analyses of other ligand and receptor systems, including the ones discussed below, face similar challenges.

Fibroblast growth factors

Physiological role

The FGF family consists of 22 members[51,52] with various functions depending on their target tissues, including regulation of cell proliferation, survival, migration and differentiation.[53] Their biological effects on target cells are mediated by interaction with one of four widely expressed FGFRs (FGFR1, FGFR2, FGFR3 and FGFR4).[54] FGFR signalling is critical for the growth and patterning of all renal lineages during the early and late stages of kidney development.[55] A soluble dominant-negative receptor that binds several FGF isoforms can abolish renal development,[56] indicating that FGF–FGFR signalling is essential for the process. Mature podocytes express FGFR1 and FGFR2,[57,58] as well as several FGF family members (including FGF1, FGF2, FGF7 and FGF10).[57,59–61] Within the glomerulus, FGF2 has mitogenic effects on podocytes,[60] mesangial cells[62,63] and endothelial cells.[64] As

mesangial cells also express FGF2,[62] autocrine and paracrine FGFR signalling is likely to be an important regulatory component of podocyte function and form part of an intraglomerular communication system. As for other secreted factors and signalling mediators, to experimentally determine the exact communication routes and to separate the FGF source from its target, whose identity and degree of involvement might vary dependent on the physiological or pathological context, will be challenging.

Current understanding of the physiological role of FGF–FGFR signalling in the regulation of podocyte and overall glomerular function is limited. FGFs are thought to be required for proper podocyte differentiation and to be involved in podocyte recovery after glomerular injury.[57,65] FGF2 is upregulated during podocyte differentiation and remains highly expressed in mature podocytes.[65] Murine podocytes that lack FGF2 do not undergo EMT; their post-mitotic differentiation is blocked, they cannot upregulate the expression of key regulators of podocyte differentiation and function (such as synaptopodin and Wilms' tumor suppressor gene [WT-1]), and they fail to reorganize their actin cytoskeleton into a stress-fibre pattern and extend cellular process.[57]

Although several FGFs bind FGFR1 and FGFR2, which are expressed in podocytes, surprisingly few studies have investigated the roles of FGFs other than FGF2 in these cells. FGF4 can induce internalization and enrichment of nephrin in intracellular vesicles, and accelerates ubiquitination of nephrin and podocin in murine podocytes that lack CD2-associated protein (CD2AP).[66] FGF4-induced activation of mitogen- activated protein kinase (MAPK) and AKT signalling is decreased in podocytes that lack CD2AP, suggesting that this adaptor protein is important for the activity of RTKs such as FGFR.[67]

Pathological role

Given the mitogenic nature of FGFs, it is not surprising that this family of growth factors has also been linked to the induction of injury in the mature kidney. FGF2 is involved in tubulointerstitial damage by increasing the proliferation of tubular epithelia cells[68] and renal fibroblasts.[69] Furthermore, several animal studies have shown that FGF2 can induce glomerular injury. In rats, long-term treatment with FGF2 results in conspicuous structural changes in the glomeruli, consisting of hypertrophy, widespread vascular degeneration,[70] and the development of a focal segmental glomerulosclerosis (FSGS)-like phenotype.[71] In response to FGF2 treatment, rat podocytes seem to re-enter the cell cycle and undergo mitosis, but are unable to complete cytokinesis. The process, therefore, results in the generation of multi-nucleated cells and might lead to podocyte degeneration.[71] The majority of podocytes in FGF2-treated rats exhibit degenerative changes including cell body attenuation, extensive pseudocyst formation, foot process effacement and detachment from the GBM. Interestingly, the glomerular pathology in these rats includes hypertrophic growth of podocytes.[70,71] Our unpublished work indicates that in podocytes, FGF2 can activate nuclear factor of activated T cells (NFAT), which is a potent inducer of cellular hypertrophy in other post-mitotic cells, such as cardiac myocytes.[72] It is intriguing to speculate that FGF2-induced activation of the calcineurin–NFAT signalling axis might be an important mechanism of FSGS-like injury, a view that is supported by the finding that podocyte-specific activation of NFAT causes podocyte damage and proteinuria.[73,74]

Injection studies in rats with passive Heymann nephritis (PHN), a model of membranous glomerulonephritis, have shown that FGF2 can also augment pre-existing podocyte damage and accelerate glomerulosclerosis.[58,75] In these rats, FGF2 increased podocyte mitosis and ploidy by changing expression of cell-cycle regulators, such as p21, and eventually induced podocyte apoptosis.[75] FGF2 injections also increase podocyte injury in models of other diseases, including diabetic nephropathy.[76] In rats treated with puromycin aminonucleoside (PAN), a model of foot process effacement and minimal change disease (MCD)-like alterations, expression of FGF2 and the four FGFR isoforms were increased in podocytes.[77,78] Interestingly, FGF2 injection in this model markedly increased podocyte damage and proteinuria, whereas injection of an FGF2-neutralizing antibody suppressed podocyte injury and reduced foot process effacement.[77,78] These studies suggest that FGF2 accelerates podocyte injury by inducing mitosis.

Few human studies have investigated the potential association between FGF2 expression and glomerular disease. The lack of clinical studies might be related to the paracrine nature of FGF2 signalling; local changes in the expression and/or release of FGF2 (rather than increases in plasma levels that can easily be detected by ELISA) are expected to underlie tissue injury.[79] Interestingly, in a clinical study in which patients with angina pectoris received a single intracoronary injection of recombinant FGF2, the participants developed proteinuria that correlated with the FGF2 dose.[80] In addition, increased FGF2 activity has been reported in plasma from diabetic patients with overt proteinuria,[81] and increased glomerular accumulation of FGF2 has been shown in patients with HIV-associated haemolytic uraemic syndrome.[82]

These findings indicate that FGF2 can induce podocyte injury, and it is likely that FGF2 signalling in podocytes regulates actin dynamics and consequently cell morphology and function. Both FGF2 deficiency and elevated FGF2 signalling might be detrimental, as podocytes that lack FGF2 fail to develop stress fibres,[57] and rats treated with PAN show increased FGF2 expression and podocyte injury.[77,78] The release of FGF2 from glomerular sources (including podocytes) during injury might represent an important mechanism by which podocyte damage is enhanced or becomes self-sustained. This pathological effect might involve an increase in FGFR1 expression in podocytes.[58] Unlike the majority of secreted proteins (such as hormones and growth factors), FGF2 lacks a classic peptide signal sequence for endoplasmic reticulum targeting and secretion via the Golgi system.[84] Therefore, it was initially assumed that cytosolic FGF2 can only be released by plasma membrane disruption and serves as an endogenous amplifier of cytotoxic damage following immune-mediated injury to cells, such as mesangial injury in rats with anti-Thy1.1 glomerulonephritis.[84] However, a specific FGF2-release mechanism that is independent of the endoplasmic reticulum has now been identified, indicating that FGF2 can also be released from living cells as part of normal cell-to-cell communication.[85]

The extracellular matrix (ECM) has a key role in storing and sequestering FGFs and in concentrating FGFs around their receptors, thereby regulating FGF signalling. Heparin sulphate and heparin sulphate proteoglycans (HSPGs) are essential coreceptors for FGF-induced FGFR activation.[86] It has been postulated that FGF2 produced by podocytes is stored in the GBM, and might stimulate podocyte proliferation in response to podocyte

injury and loss.[60] Furthermore, WT-1 regulates expression of 6-O-endosulphatases, which are critically involved in the maintenance of the glomerular filtration barrier by modulating the bioavailability of signalling molecules including FGF2.[87] Mice that are deficient in the extracellular sulphatases Sulf1 and Sulf2, which remodel the heparan sulphate 6-O-sulfation pattern in the ECM, show increased FGF2-induced activation of the MAPK pathway and develop age-dependent proteinuria as a result of ultrastructural abnormalities in podocytes and endothelial cells.[87] This phenotype is similar to that observed in children with *WT1* mutations, which are associated with the severe, early-onset nephrotic syndrome, Denys-Drash Syndrome (DDS).[88] The possibility exists that FGF2 signalling in podocytes might also mediate the glomerular phenotype in children with DDS.

A genome-wide association study, which included 195 patients with biopsy-proven nephrotic syndrome, showed that single nucleotide polymorphisms in the *GPC5* gene, which encodes glypican-5, were associated with the disease.[89] Glypicans belong to the family of cell surface HSPGs and bind a multitude of growth factors, including FGF2.[90] Glypican-5 enhances FGF2 signalling in podocytes and promotes their dedifferen-tiation.[89] In proteinuric mice, *Gpc5* knockdown using systemic injections of short-interfering RNA ameliorated proteinuria and reduced pathological changes, even after the development of nephrotic syndrome, indicating a role of glypican-5 in FGF2-induced podocyte injury *in vivo*.[89] Interestingly, combined injection of PAN and FGF2 is a fast and homogenous way of inducing podocyte injury and nephrotic syndrome-range proteinuria in mice.[89] These mice develop massive proteinuria within 5 days after combined injection, but this does not occur if only one of these substances is injected. Proteinuria lasts for at least 10 days and mice develop an FSGS-like histological phenotype with extensive foot process effacement and tubulointerstitial damage. This mouse model demonstrates pathological effects of FGF2 on the glomerular filter, at least in the context of co-existing pathological stimuli, and could be used as a model of nephrotic syndrome to study FSGS-like mechanisms.

Platelet-derived growth factors

The four PDGF family members, (PDGF-A, PDGF-B, PDGF-C and PDGF-D) act as disulphide-linked dimeric growth factors. The PDGFRs exist as α-chains and β-chains that can form homodimers and heterodimers.[91] In mesangial cells, PDGFs are autocrine regulators of cell proliferation and migration as well as ECM production, and are involved in mesangial expansion in renal disease.[92] The expression of PDGF-B and PDGFR-β is increased in glomerular lesions in patients with diabetic nephropathy or IgA nephropathy, and in rodent models of renal ablation and glomerulonephritis.[93–96] PDGF-D can induce mesangial cell proliferation *in vitro* and is a mediator of mesangial-proliferative nephritis *in vivo*.[97–99]

As they express PDGF-D[100] but not PDGFR-β,[101,102] which is required for PDGF-D responsiveness,[103] podocytes seem to function as a source but not a target of PDGF-D. In transgenic mice, podocyte-specific overexpression of PDGF-D induces proliferative glomerulonephritis, widespread glomerulosclerosis, tubulointerstitial injury and proteinuria.[104] Interestingly, podocyte injury in these mice includes foot process effacement, podocyte dedifferentiation (indicated by reduced expression of nephrin and podocin) and

podocyte loss.[104] Two possibilities exist, podocytes might respond directly to PDGF-D in an autocrine fashion, or PDGF-D expressed by podocytes might act on mes-angial cells, which then respond by sending out a different pathological signal that induces podocyte injury. To date, very little is known about a potential podocyte– mesangial crosstalk, and these transgenic mice might provide the first evidence that podocyte-specific over-expression of a growth factor is capable of inducing paracrine cell proliferation in the glomerular tuft upstream of the filtration flow. Podocytes might locally alter their PDGF release in response to injury, and this alteration might induce intraglomerular damage, such as the mesangial expansion observed in FSGS.

Hepatocyte growth factor

HGF was originally identified as a potent mitogen for hepatocytes.[105,106] However, HGF acts on various cell types and exhibits pleiotropic activities during embryogenesis and tissue repair.[107] The mitogenic and morphogenic properties of HGF suggest that this growth factor participates in tissue regeneration not only by stimulating cell proliferation, but also by promoting cell motility and spatial organization.[107] The biological activities of HGF are mediated by a single HGF receptor (HGFR, also known as MET),[108] which is predominantly expressed in epithelial cells in various organs, whereas HGF is primarily derived from the mesenchyme.[109] This separation of ligand and receptor suggests paracrine roles of HGF.

In the kidney, HGF expression is limited to non-epithelial cells, whereas HGFR is ubiquitously expressed.[110] HGF has antifibrotic effects and stimulates tubular cell mitogenesis and morphogenesis, preventing the onset and progression of a variety of progressive kidney diseases, including diabetic nephropathy.[111,112] Glomerular effects of HGF are supported by evidence from *in vivo* studies in which administration of recombinant HGF protein or cDNA ameliorated proteinuria in mouse models of diabetic and PAN nephropathy.[113–115] Furthermore, injection of HGF suppressed foot process effacement and attenuated albuminuria in mice with lipopolysaccharide-induced podocyte injury.[116] Interestingly, mice with podocyte-specific deletion of HGFR develop normally without pathological lesions or proteinuria,[117] indicating that HGF signalling is not required for podocyte maturation, survival and function under normal conditions. However, after doxorubicin treatment, HGF-knockout mice developed more-severe podocyte injury and albuminuria than did their wild-type littermates, indicating that HGF has protective functions in podocytes.[117] Furthermore, ectopic HGF expression protected wild-type mice from the detrimental effects of doxorubicin, but did not protect mice with podocyte-specific HGFR depletion. The protective role of HGF in podocytes seems to include antiapoptotic effects,[113,117,118] preservation of the actin cytoskeleton,[115] and maintenance of nephrin and synaptopodin expression.[116,117] As HGF regulates EMT in other renal cell types, such as tubular epithelial cells,[119,120] and podocytes undergo EMT after injury,[121,122] HGF might also have a role in preserving podocyte structure and function after injury, thereby preventing the development of proteinuria.

Epidermal growth factor

EGFRs are widely expressed and their activation is involved in the regulation of many cellular processes, including cell proliferation, differentiation and survival.[123] Overexpression or overactivation of EGFRs is associated with various cancers, and genetic alterations in erbB2 (also known as HER2), a member of the EGFR subfamily of RTKs, have been implicated in about 30% of all epithelial cancers.[124] EGFRs are promising targets for an expanding class of anticancer therapies, including the FDA approved drugs trastuzumab, erlotinib and gefitinib, and many other agents that are currently in development or clinical trials.[125,126]

EGF and related growth factor peptides, such as heparin-binding EGF-like growth factor (HB-EGF) and transforming growth factor-α (TGFα), are transmembrane proteins, which are cleaved and transformed into soluble active ligands by metalloproteinases.[123] EGF has a number of key roles in the kidney, contributing to cell proliferation and survival, renal metabolism and renal development.[127,128] Some EGFR ligands have been implicated in experimental models of progressive kidney injury.[129–131] EGFRs are expressed in podocytes[132–134] and EGF seems to trigger the proliferation and differentiation of podocyte precursor cells in isolated glomeruli.[135]

HB-EGF–EGFR signalling might be involved in angiotensin II-mediated effects on podocytes. Angiotensin II induces the release of HB-EGF from podocytes, which in turn activates MAPK signalling pathways in an autocrine fashion via EGFR activation.[136] Angiotensin II might also transactivate EGFR signalling.[136] Furthermore, treatment of angiotensin II-infused rats with pharmacological EGFR inhibitors reduced glomerular cell proliferation without lowering the animals' elevated blood pressure.[137] EGFR has been suggested to have a pivotal role in the induction of renal hypertrophy, by regulating cell growth and proliferation and mediating the actions of angiotensin II.[138] This hypothesis is supported by findings in experimental models of diabetes with angiotensin II-dependent hypertension in which EGFR inhibition attenuated glomerular enlargement in association with podocyte preservation and a reduction in albuminuria.[139]

Interestingly, in a rat model of anti-GBM disease, HB-EGF expression was increased in podocytes and application of anti-HB-EGF blocking antibody reversed acute glomerular injury.[140] A subsequent study confirmed *de novo* expression of HB-EGF in podocytes and parietal epithelial cells in mice with rapidly progressive glomerulonephritis (RPGN) and in biopsy samples from patients with RPGN.[141] HB-EGF is expressed in tubular cells, but is not present in normal glomerular epithelial cells.[142] However, HB-EGF is expressed during proliferation and dedifferentiation of podocytes in glomerulonephritis.[140] In a mouse model of anti-GBM disease, activation of EGFR in podocytes by HB-EGF resulted in the development and progression of RPGN, and in cultured podocytes, EGFR activation caused cell dedifferentiation and conversion to a proliferative and migratory phenotype.[141] Pharmacological blockade of EGFR improved the course of RPGN in mice, prevented infiltration of inflammatory cells, and suppressed proteinuria. Most importantly, podocyte-specific, temporally controlled ablation of either EGFR or HB-EGF reduced the severity of glomerular injury and prevented renal failure and death.[141] As selective deletion of HB-EGF

in haematopoietic cells did not alter the course of the disease, HB-EGF expression in podocytes, but not in T cells or macrophages, seems to induce and drive the glomerular pathogenesis. Also, as other EGFR ligands (TGFα and epiregulin) failed to induce podocyte injury *in vitro*, HB-EGF seems to be the primary causative factor. This elegant study indicates that interference of EGF–EGFR signalling in podocytes might serve as a new therapeutic avenue to target cresentic and immune-mediated glomerular disease. In addition, treatment with the anti-EGFR small-molecule inhibitor erlotinib was able to rescue the glomerular phenotype of mice 4 days after induction of injury, suggesting that treatment of patients with manifested RPGN might be possible. It will be interesting to investigate if EGFR inhibitors are effective in the treatment of human RPGN, and if EGFR signalling is involved in the development of other types of glomerular disorders.

Conclusions

Podocytes are perhaps the most important contributor to a properly functioning glomerular filtration barrier, and the signals that converge on these post-mitotic cells are numerous and complex. A series of receptors— including RTKs—on the cell surface receive and process signals that enable podocytes to adapt to their environment and respond to chemical and biophysical cues. This knowledge has changed the anatomical view of the filter barrier from a rigid sieve to a physiological multicellular circuit that is highly dynamic and modifiable,[4] and has resulted in the identification of RTKs as promising drug targets for glomerular diseases. In the past two decades, a myriad of cell signalling pathways and networks of extreme complexity, with multiple interconnections and feedback loops have been discovered. This complexity is impressively illustrated by the EGFR signalling node, which includes 211 distinct reactions and 322 components.[143] However, what determines the hierarchy of signals received by podocytes, and how these cells determine which signals do not require a response, is not well understood. To better understand these phenomena and unravel the multiple signalling pathways that lead to podocyte injury and recovery, a combination of genetic, *in vitro* and biochemical studies is required. Such an approach should help to decipher the roles of podocytes and RTK signalling in health and disease as well as increase our understanding of how these cells integrate a plethora of converging signals into a hierarchical response that regulates proper kidney filtration.

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Key points

- Podocytes respond to hormones and growth factors that are present in the circulation or locally produced in the glomerulus
- A variety of receptors on the cell surface are thought to enable podocytes to respond to these external stimuli
- The podocyte response to growth factors does not involve cell proliferation, but does include mitosis and hypertrophic cell growth, eventually leading to pathological alterations
- Growth factors signal via receptor tyrosine kinases (RTKs), which are promising targets for cancer therapy
- To understand and interfere with the pathological effects of growth factors on podocytes and the glomerular filter, their precise receptors must be identified and characterized
- RTK inhibitors that are already used in cancer therapy might be promising new treatment options for proteinuric kidney diseases

Review criteria

A search for original articles published between 1990 and 2013 and focusing on podocyte biology and signal transduction was performed in MEDLINE and PubMed. The search terms used were “podocyte”, “receptor tyrosine kinases”, “growth factors” and “signal transduction”, alone and in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

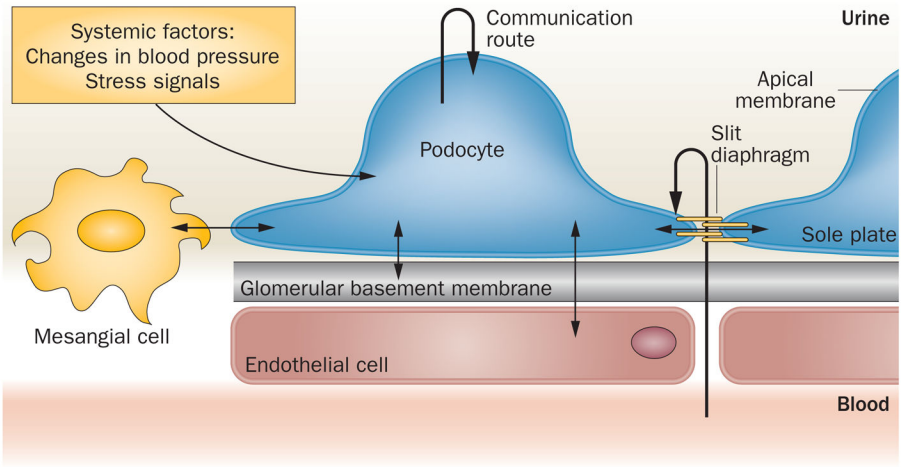

Figure 1.

Podocytes form complex communication networks with their environment and are in constant contact with a variety of signal sources and receivers, including other glomerular cell types and the extracellular matrix. They also signal to neighbouring podocytes, enabling coordination of podocyte function in the glomerulus. Podocytes are exposed to a myriad of potential signalling molecules present in the circulation as well as biophysical cues, such as changes in blood pressure.

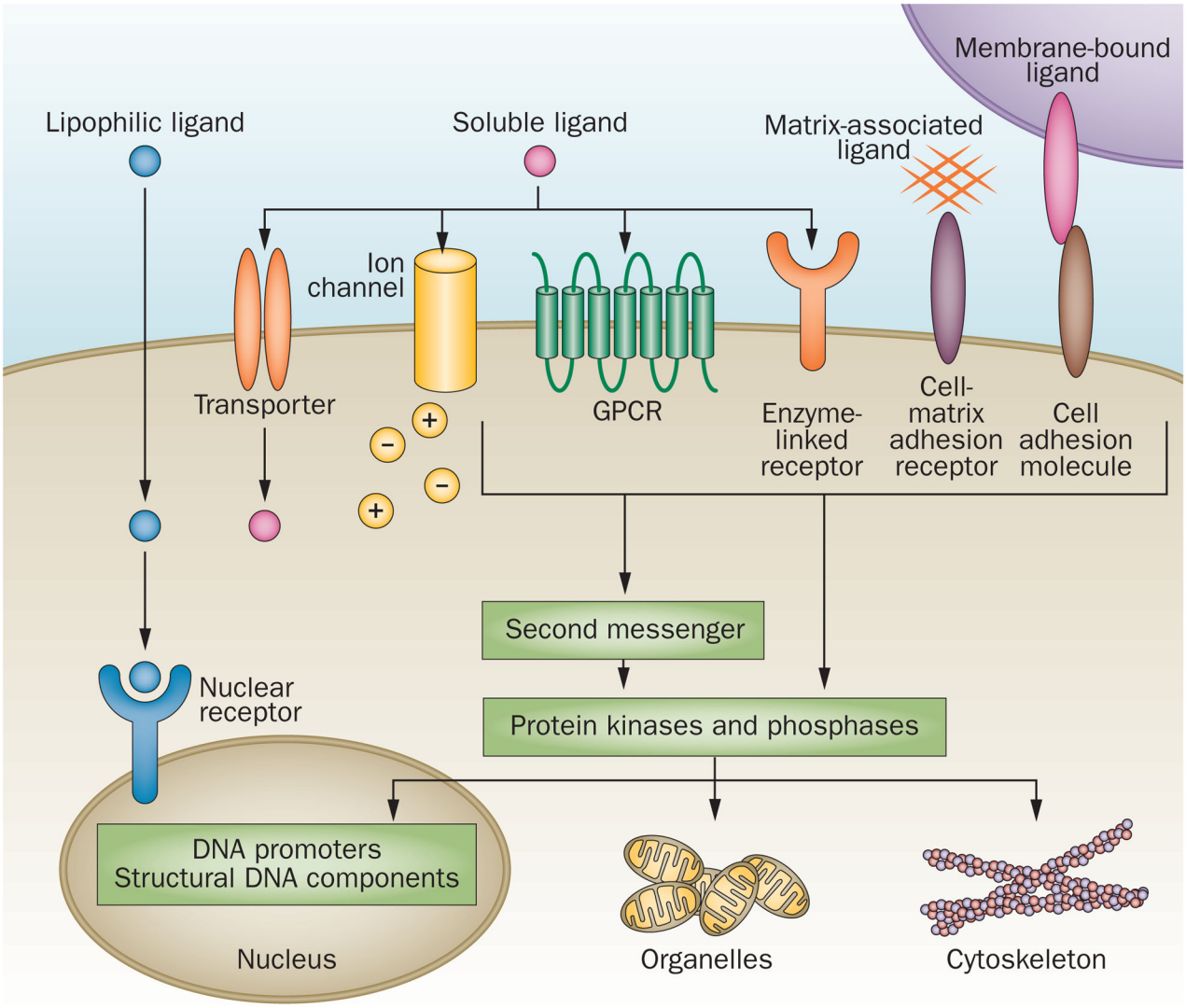

Figure 2.

Cell signalling receptors differ in their mechanisms of activation and signal transmission, subcellular localization, and ligand binding. They can be broadly classified into three groups: GPCRs, receptors with enzyme-linked activities (such as receptor tyrosine kinases) and cytokine receptors. Some receptors mediate cell-to-cell or cell-to-matrix contact by binding transmembrane proteins or extracellular proteins, respectively, and link cell adhesion to outside-in and inside-out signalling. Ligand binding ultimately leads to the activation of second messengers, protein kinases and phosphatases that modify and determine the phosphorylation state of a variety of target proteins and thereby regulate all aspects of cell function and structure. Some ligands that induce signalling via receptor binding are transported across the cell membrane via the receptor, or induce transport of other extracellular molecules or ions that have intracellular effects, which might not involve a second messenger system. Lipophilic ligands that can cross the cell membrane by simple

diffusion target intracellular receptors that act directly as transcriptional regulators.
Abbreviation: GPCR, G-protein coupled receptor.

Table 1

Roles of receptor tyrosine kinases in podocytes

Receptor tyrosine kinase	Ligand	Physiological role	Pathological role	References
Tie-1 Tie-2*	ANG 1 ANG 2	Mediates crosstalk between podocytes and endothelial cells	Induces apoptosis of glomerular endothelial cells and proteinuria	145,146
Unknown‡	ANGPTL3 ANGPTL4	Regulates cell motility, promotes cell adhesion and protects against injury-induced cell detachment	Induces proteinuria and MCD-like injury	147–149
Unknown§	CTGF	Maintains actin cytoskeleton and cell morphology under stress	Promotes podocyte injury and loss in diabetes	150–153
DDR1	Type IV collagen	Maintains structural integrity of the GBM and preserves foot process and slit diaphragm structure	Serves as positive feedback loop with inflammatory response in glomerulonephritis	154,155
EGFR	EGF HB-EGF TGFα	Mediates proliferation and differentiation during development and hypertrophic growth of mature cells	Promotes angiotensin II-mediated injury, dedifferentiation and conversion into a proliferative and/or migratory phenotype in rapidly progressive glomerulonephritis	135–137, 141
EphB	Ephrin B1 Ephrin B2‖	Mediates maintenance of the slit diaphragm and prosurvival signalling during transient capillary collapse	Unknown	155,156
FGFR	FGF2 FGF4	Mediates proliferation and differentiation (epithelial–mesenchymal transition) during development and regeneration after injury	Increases nephrin ubiquitination and internalization and induces actin rearrangement, cell hypertrophy, mitosis (resulting in aneuploidy), foot process effacement and focal segmental glomerulosclerosis-like injury	57,58,66, 70,71
HGFR (MET)	HGF	Mediates antiapoptotic and protective effects and preserves the structure of the actin cytoskeleton, slit diaphragm and foot processes	Unknown	110,115–117
IGF-IR	IGF-I IGF-II	Promotes podocyte survival and outgrowth, maintains glomerular filtration barrier	Unknown	157–160
IGF-IIR (M6P)	α-GalA	Mediates endocytotic uptake of α-GalA.	Mediates accumulation of glycosphinglolipid deposits in podocytes in Fabry disease	161
Insulin receptor	Insulin	Promotes glucose uptake into podocytes, maintains the glomerular filtration barrier and regulates expression of VEGF-A and TRPC6	Induces proteinuria in diabetic nephropathy	40,163,164
NTR¶	Neurotrophins (NGF, BDNF)	Mediates antiapoptotic effects and might protect against calcium-induced mitochondrial swelling	SNPs of neurotrophins and NTRs are associated with susceptibility, pathological advancement, podocyte foot process effacement, and	165,166

Receptor tyrosine kinase	Ligand	Physiological role	Pathological role	References
			development of proteinuria in children with IgAN	
PDGFR	PDGF	Unknown	Induces podocyte dedifferentiation and loss, and foot process effacement	101,102,105
Ret	GDNF	Mediates prosurvival effects and serves as adaptive response for remodelling and repair, also involved in podocyte development	Unknown	167,168
VEGFR1[#] VEGFR2[**]	VEGF	Mediates crosstalk between podocytes and endothelial cells and maintains the integrity of the glomerular endothelium	Increases in ligand levels results in various types of podocyte injury (including MCD-like and collapsing glomerulopathy)	48–50,169

[*] Tie-1 and Tie-2 are expressed in glomerular endothelial cells, whereas ANG 1 and ANG 2 are expressed by podocytes.

[‡] ANGPTLs do not bind to Tie-1 or Tie-2. Their receptors are not well described but might include integrins.

[§] Several RTKs, including PDGFR, VEGFR and NTR, function as CTGF receptors in other cell types. Nonreceptor tyrosine kinases can also mediate CTGF effects in other cell types.

[||] Ephrin ligands are membrane bound and can function as signalling receptors (reverse signalling).

[¶] Seems to be expressed only in mitochondria of undifferentiated, proliferating podocytes.

[#] Also exists in a truncated soluble form that might serve as decoy receptor for VEGF and PlGF and can contribute to endothelial dysfunction and proteinuria in pre-eclampsia.[169]

[**] In the glomerulus, podocytes seem to be the main source of VEGF, whereas endothelial cells receive the signal via VEGFR2. VEGF might also bind neuropilin-1 and neuropilin-2.

Abbreviations: α-GalA, α-galactosidase A; ANG, angiopoietin; ANGPTL, ANG-related protein; BDNF, brain derived neurotrophic factor; CTGF, connective tissue growth factor; DDR1, discoidin domain receptor tyrosine kinase 1; EGF, epidermal growth factor; EGFR, EGF receptor; EphB, ephrin type B receptor; FGF, fibroblast growth factor; FGFR, FGF receptor; GBM, glomerular basement membrane; GDNF, glial cell-line derived neurotrophic factor; HB-EGF; heparin-binding EGF-like growth factor; HGF, hepatocyte growth factor; HGFR, HGF receptor; IgAN, IgA nephropathy; IGF-I, insulin-like growth factor 1; IGF-II, insulin-like growth factor II; IGF-IR, IGF-I receptor; IGF-IIR, IGF-II receptor; M6P, mannose 6-phosphate receptor; MCD, minimal change disease; NGF, β-nerve growth factor; NTR, neurotrophin receptor (also known as trkA and p75NTR); PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PlGF, placental growth factor; SNP, single nucleotide polymorphism; TGFα, transforming growth factor-α; TRPC6, transient receptor potential cation channel 6; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.