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Review article

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# The intelligent podocyte: sensing and responding to a complex microenvironment

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## Abstract

Podocytes are key components of the glomerular filtration barrier — a specialized structure that is responsible for the filtration of blood by the kidneys. They therefore exist in a unique microenvironment exposed to mechanical force and the myriad molecules that cross the filtration barrier. To survive and thrive, podocytes must continually sense and respond to their ever-changing microenvironment. Sensing is achieved by interactions with the surrounding extracellular matrix and neighbouring cells, through a variety of pathways, to sense changes in environmental factors such as nutrient levels including glucose and lipids, oxygen levels, pH and pressure. The response mechanisms similarly involve a range of processes, including signalling pathways and the actions of specific organelles that initiate and regulate appropriate responses, including alterations in cell metabolism, immune regulation and changes in podocyte structure and cognate functions. These functions ultimately affect glomerular and kidney health. Imbalances in these processes can lead to inflammation, podocyte loss and glomerular disease.

## Sections



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## Key points

- Podocytes communicate with mesangial, endothelial and tubular cells through biochemical pathways, contributing to processes such as cell proliferation and tissue repair following kidney injury.
- Podocytes sense their microenvironment and express various receptors and transporters for calcium and nutrients, which influence podocyte structure, function and survival.
- Podocytes are equipped with mechanosensors, enabling them to detect changes in biomechanical forces and respond to stressors such as high intraglomerular pressure, which can disrupt podocyte integrity and contribute to disease.
- Mitochondria have important roles as molecular sensors, integrating signals that affect podocyte metabolism and function; alterations in organelle function can lead to podocyte injury and progression of kidney diseases.

## Introduction

Podocytes are best known for their role as components of the glomerular filtration barrier, which, in a healthy human, filters approximately 180 litres of fluid per day from the glomerular capillaries into the urinary space. Each normal human kidney contains approximately 600 million podocytes[1,2] (that is, approximately 600 podocytes in each of the million glomeruli in each kidney[3]). Podocytes have a remarkable microstructure characterized by a cell body, large primary and secondary cytoplasmic processes, and foot processes that rest upon the glomerular basement membrane (GBM) and interdigitate with foot processes from neighbouring podocytes. Slit diaphragms located between foot processes contain pores with approximate dimensions of 4 nm × 14 nm (ref. 4). Given their critical role in filtration, it is not surprising that podocyte injury, podocyte loss and changes to the podocyte ultrastructure result in a range of chronic kidney diseases (CKDs). Moreover, variants in genes that regulate podocyte development and morphology give rise to a range of inherited podocytopathies[5].

However, podocytes do much more than regulate glomerular filtration. A growing body of evidence demonstrates that podocytes have many other roles through communication with nearby podocytes or other kidney cells. For example, podocytes communicate with mesangial, glomerular endothelial and tubular cells through various biochemical pathways that can involve extracellular vesicles[6] or the secretion of cytokines[7] or other signalling factors[8,9]. For instance, in the context of kidney injury, the secretion of cytokines, growth factors and attractant molecules by podocytes stimulates mesangial and tubular cells to proliferate and migrate[7,10]. In turn, these cells release their own cytokines, growth factors and attractant molecules, which further stimulate the response of podocytes[11].

Podocytes sense their microenvironment through interactions with the extracellular matrix via adhesion molecules expressed on podocyte surfaces and integrin-linking molecules that connect the podocyte cytoskeleton to the extracellular matrix. Podocytes also produce components of the extracellular matrix, such as fibronectin, collagen and laminin, further enabling them to interact with the extracellular matrix and respond to changes in the microenvironment. A variety of receptors expressed on podocytes are also important for processes such as adaptive immunity, endocytosis and podocyte metabolism, contributing to podocyte maturation and adhesion, sodium and calcium homeostasis, and inflammatory processes in the kidney. For example, podocytes sense and respond to changing concentrations of molecular ligands, including pathogens or tissue-damage molecules, by receiving, processing and transducing a suite of chemical signals and sensory stimuli. Mutation and/or dysregulation of these components or processes can contribute to kidney damage and podocytopathies[12–15]. Podocyte sensing of stressors can also lead to podocyte injury, podocyte loss and decreased podocyte density, which are hallmarks of numerous glomerular and non-glomerular kidney diseases[5]. Cellular organelles also act as molecular sensors, signal integrators and transducers to regulate specific functional response in cells[16,17]. For example, mitochondria sense and integrate signals to link metabolic processes with cell function[18]. Importantly, organelles such as mitochondria can communicate with each other via their membrane contact sites through the exchange of lipids, ions, reactive oxygen species (ROS) and other small molecules.

Here, we provide an overview of the varied mechanisms by which podocytes sense and respond to their complex microenvironment and describe how sensing and signalling between podocytes and other kidney cells coordinates and orchestrates processes involved in disease onset and repair.

## Factors that influence podocyte biology

The maintenance of podocyte homeostasis relies on the ability of podocytes to express a range of receptors that sense and interact with molecules expressed by other podocytes and/or the GBM, or with soluble factors released by other cells within the kidney, including endothelial, parietal epithelial and mesangial cells[19] and resident and infiltrating immune cells[20]. Podocytes also express a variety of transport channels that regulate nutrient import and ion balance[19,21,22]. Activation of these receptors and channels triggers signalling pathways that are responsible for maintaining podocyte structure, function and survival. However, imbalances in the number of ligands or molecules that interact with these receptors and/or channels can trigger signalling pathways that impair podocyte function and survival. Thus, the availability of molecules in the podocyte microenvironment must be finely tuned to maintain podocyte health and survival.

### Nutrients

Like most cells, nutrient sensing is crucial for podocyte function and survival. Human podocytes express the glucose transporters GLUT1 and GLUT4, which facilitate glucose uptake in an insulin-independent and an insulin-dependent manner, respectively[23]. Podocytes are sensitive to insulin and increase glycolysis upon long-term insulin stimulation, leading to modifications in mitochondria dynamics[24]. They also capture LDL via CXCL16 and LDL-receptors, and free fatty acids through CD36, and respond to lipid accumulation by promoting free fatty acid and cholesterol efflux through the ATP-binding cassette transporter A1 (ABCA1). Thus, podocytes possess the necessary machinery required to store, metabolize and remove lipids[23,25]. Despite the importance of amino acid metabolism for kidney function and homeostasis[26], little is known about the expression and function of amino acid transporters in podocytes. In zebrafish, deletion of the neutral amino acid transporter, *Lat3*, which is normally expressed on the apical surface of podocytes, impairs podocyte development[27]. In rats, LAT3 is upregulated in podocytes during starvation, in association with AKT1 phosphorylation[27]. Another study reported that levels of LAT2 were upregulated in a rat

model of crescentic glomerulopathy[28]. These nutrient transporters fulfill the energetic demands of cells and supply essential substrates to organelles such as the mitochondria, the endoplasmic reticulum (ER) and the lysosomes, thereby linking nutrient sensing to the maintenance of organelle homeostasis[25] (Fig. 1).

Although podocytes rely on glucose and lipids as energy sources, excessively high levels of glucose levels (as in diabetic kidney disease, DKD) and of lipids can induce podocyte apoptosis. Exposure of the CIHP-1 human podocyte cell line to hyperglycaemic conditions induced cell apoptosis. In that study, hyperglycaemic conditions also increased release of the cytokines IL-1β, IL-6 and TNF, and the chemokine MCP-1[29], suggesting that podocytes respond to high glucose levels by secreting cytokines that can instruct neighbouring glomerular cells and/or recruit immune cells, giving rise to inflammatory processes. Lipotoxicity has also been linked to the development and progression of proteinuric kidney conditions such as DKD and focal segmental glomerulosclerosis (FSGS)[25]. Although the molecules and mechanisms that underlie lipid-mediated podocyte injury remain largely unknown, several key molecules have been identified. DOCK5 is an approximately 180-kilodalton protein that activates small GTPases and is downregulated in kidney samples from people with proteinuric kidney diseases[12]. In a mouse model of proteinuric kidney injury, podocyte-specific deletion of *Dock5* increased free fatty acid uptake by CD36 via upregulation of LXRα, exacerbating podocyte injury and glomerular pathology[30]. By contrast, levels of CCDC92 — a member of the coiled-coil-domain-containing protein family, which has roles in coronary diseases and type 2 diabetes — are increased in kidney tissue of people with DKD and correlate positively with lipid accumulation. CCDC92 is a negative regulator of ABCA1 expression, a transmembrane protein that is widely expressed across different tissues and is involved in the efflux of phospholipids and intracellular cholesterol from the membrane[31]. By driving the degradation of ABCA1 in the podocyte proteasome, CCDC92 promotes lipid accumulation in podocytes[32] (Fig. 1). Diabetic mice with podocyte-specific deletion of *Ccdc92* demonstrated lower levels of ectopically deposited lipids (that is, lipid accumulation in non-adipose tissue) and reduced podocyte injury compared to that of diabetic wild-type mice[33]. Another example is TRIM3, an E3 ubiquitin ligase that ubiquitinates PPARα to inhibit its activity, which consequentially inhibits fatty acid oxidation in the podocyte. Levels of TRIM3 are increased in humans with CKD and in mouse models of proteinuric CKD, particularly in podocytes of injured glomeruli[34]. Ectopic overexpression of TRIM3 via injection of a pcDNA vector (pHA-Trim63) exacerbated lipid deposition and mitochondrial dysfunction, and impaired fatty acid oxidation in mice with adriamycin-induced nephropathy. Conversely, shRNA-mediated blockade of TRIM3 expression restored these parameters[34].

### Calcium

Virtually all calcium ($Ca^{2+}$) filtered by glomeruli is reabsorbed in the nephron tubules via a tightly controlled mechanism that maintains whole-body $Ca^{2+}$ homeostasis[35]. $Ca^{2+}$ has a critical role in maintaining the structure, motility, cytoskeletal remodelling, function and survival of podocytes. $Ca^{2+}$ entry into the podocyte is regulated by $Ca^{2+}$ receptors such as the N-type calcium channel (Cav2.2)[36] and transient receptor potential canonical (TRPC) channels[37] on the podocyte surface. Activation of these channels leads to increased $Ca^{2+}$ levels in mitochondria, the ER, endosomes and other organelles, where it acts as an important second messenger in organelle–organelle and organelle–cell communication (Fig. 1). Diabetic mice with deletion of the Cav2.2 channel have lower levels of albuminuria than do diabetic wild-type mice. Similarly, pharmacologic blockade of N- and L-type calcium channels in a mouse model of diabetic nephropathy improved glomerular morphology more than just blockade of L-type calcium channels. Moreover, inhibition of Cav2.2-specific channels decreased depolarization-dependent calcium responses in cultured podocytes, and abolished the reduction in nephrin expression induced by TGF-β[36].

### Oxygen levels

Low oxygen levels (hypoxia) are sensed in podocytes through activation of hypoxia-inducible factor 1 (HIF-1), which as described later, is associated with the upregulation of HIF-target genes and progressive glomerular damage, suggesting a prominent role for hypoxia in glomerular pathology[38]. Ischaemia and hypoxia are risk factors for CKD[39]; both can cause tubulointerstitial fibrosis and can also induce glomerular damage[40]. Insights into the underlying mechanisms come from studies of conditionally immortalized mouse podocytes, which demonstrate reduced viability and misarrangement of actin microfilaments following exposure to hypoxic conditions[41].

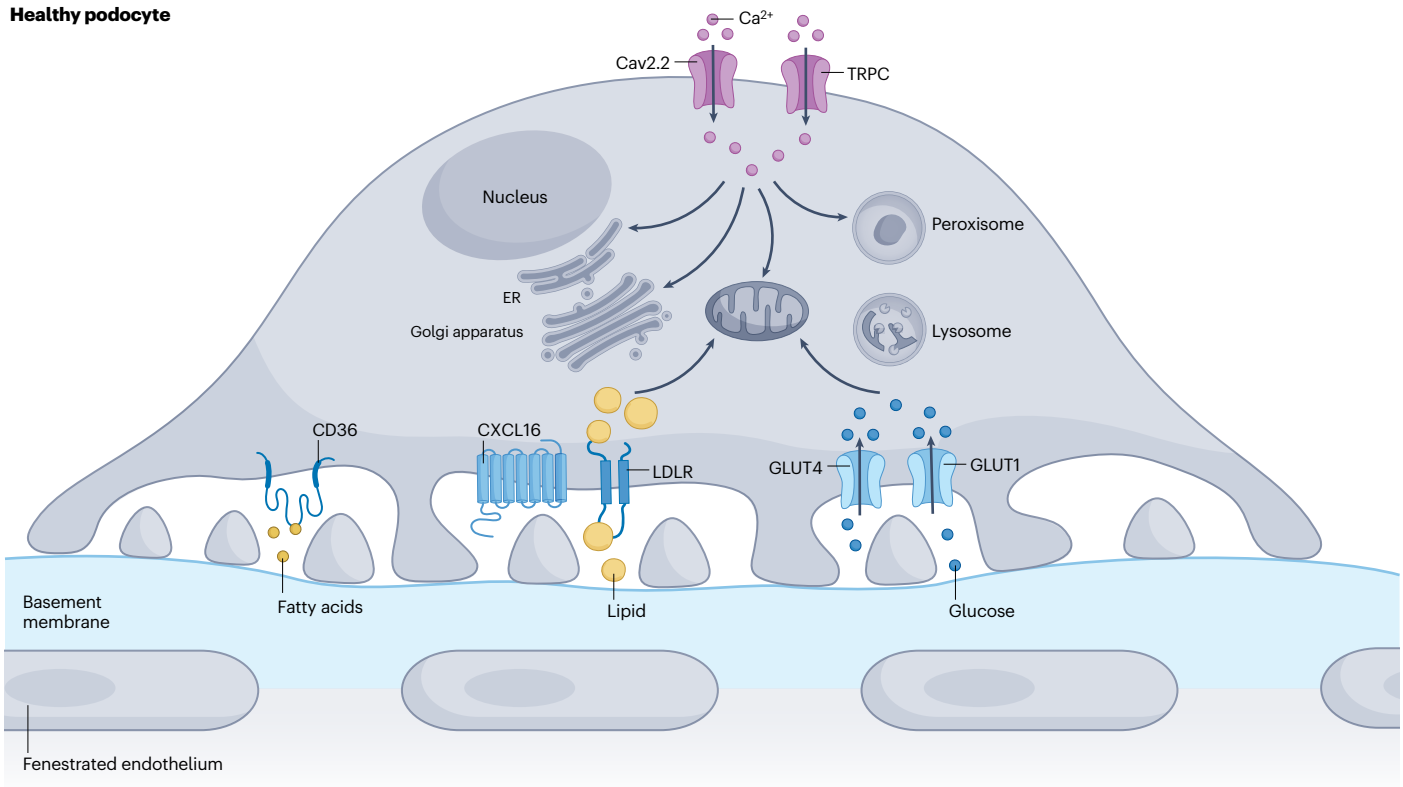
Conversely, hyperoxia (that is, exposure to elevated levels of oxygen)[42] can also damage podocyte structures, particularly the actin cytoskeleton. Insights from animal studies suggest that the induction of oxidative stress in the context of hyperoxia can result in podocyte dysfunction, detachment and apoptosis, ultimately compromising glomerular filtration[43]. However, at least one study has shown that exposure of neonatal mice to hyperoxic gas does not adversely affect kidney development during the period of postnatal nephrogenesis. Specifically, the researchers did not observe evidence of abnormal renal morphology, or alterations in glomerular size or maturation in affected neonates[44]. Together, these findings suggest that oxygen levels differentially influence podocytes according to developmental stage.

## Sensing of injury and stress

Podocytes exhibit a remarkable ability to respond to environmental changes originating from local and distant sources, including the gut, liver, heart, brain and adipose tissue. In fact, podocytes may display a level of adaptability akin to that of immune cells, relying on precise and sensitive mechanisms to sense and respond to a range of physiological changes and potential insults. Depending on the nature of the insult, podocyte responses can promote tissue repair or lead to tissue fibrosis. Improved understanding of the mechanisms by which podocytes perceive and respond to extracellular signals is crucial for the development of interventions that promote tissue repair and slow or reverse the progression of CKD.

### Innate immune receptors

Innate immune receptors aid the ability of immune cells to detect and respond to pathogens and tissue damage. Like immune cells, podocytes express a range of innate immune receptors, including Toll-like receptors (TLRs), Nod-like receptors (NLRs) and RIG-I-like receptors (RLRs), which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (Fig. 2). Expression of these innate immune receptors enables podocytes to respond to minor immune challenges and supports tissue repair. However, dysregulation of innate immune receptor activation can lead to the development of glomerulonephritis and proteinuria. Activation of podocyte TLRs has been linked to the pathogenesis of some conditions such as lupus nephritis, IgA nephropathy and DKD[45,46].


Healthy podocyte
Ca2+
Cav2.2
TRPC
Nucleus
Peroxisome
ER
Golgi apparatus
Lysosome
CD36
CXCL16
LDLR
GLUT4
GLUT1
Basement membrane
Fatty acids
Lipid
Glucose
Fenestrated endothelium

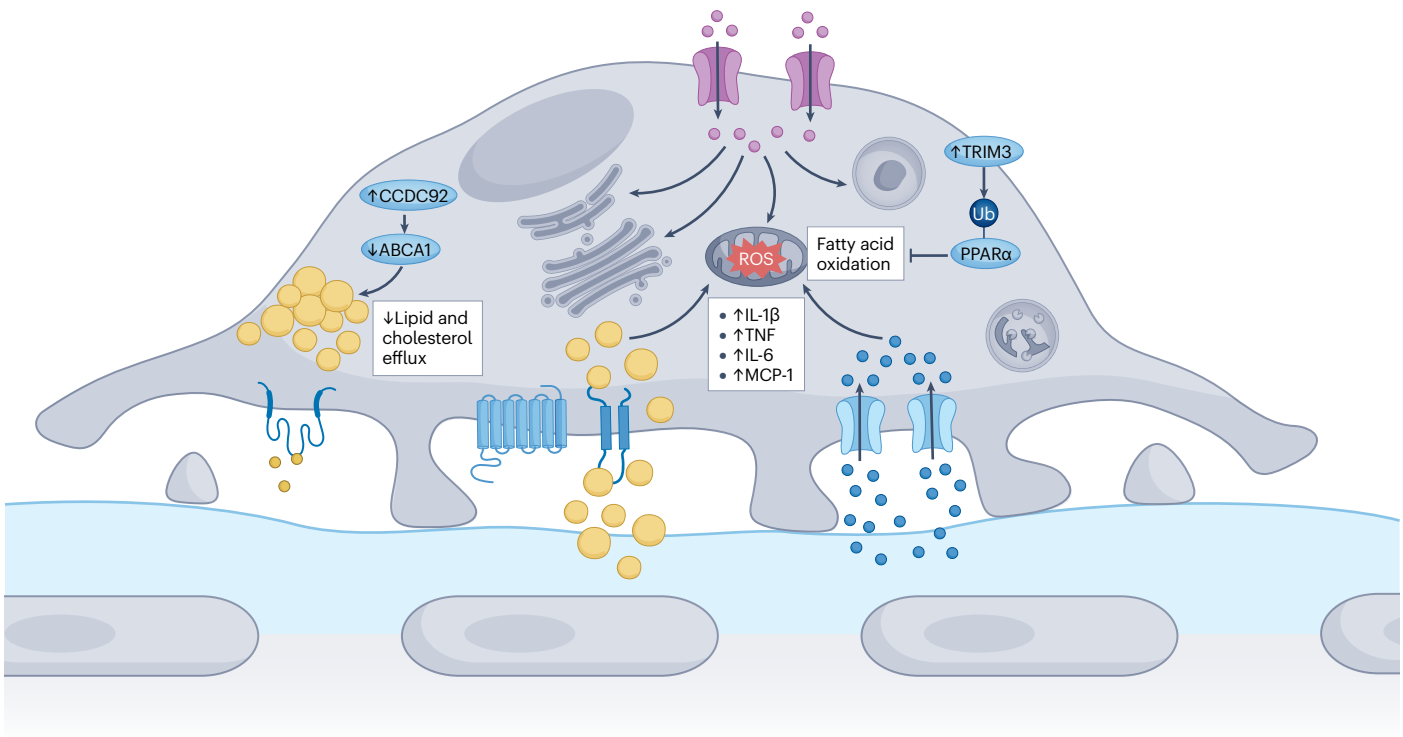

Diseased podocyte
↑CCDC92
↓ABCA1
↓Lipid and cholesterol efflux
ROS
Fatty acid oxidation
↑TRIM3
Ub
PPARα
• ↑IL-1β
• ↑TNF
• ↑IL-6
• ↑MCP-1

**Fig. 1 | Podocyte features during homeostasis and disease. a**, Nutrients, such as glucose, lipids and free fatty acids are taken up into podocytes by the transporters GLUT1 and GLUT4 (glucose), LDLR and CXCL16 (LDL), and CD36 (free fatty acids). Catabolism of these nutrients provides the substrates necessary to maintain podocyte health. $Ca^{2+}$ homeostasis, maintained by transporters like transient receptor potential canonical (TRPC) and the N-type calcium channel (CAV2.2) also contribute to organelle homeostasis. **b**, High levels of glucose can stimulate the production of reactive oxygen species (ROS) by mitochondria as well as the production of cytokines, such as IL-1β, TNF, IL-6 and MCP-1. Similarly, increased expression of CCDC92 in the context of high lipid levels leads to downregulation of the cholesterol and lipid efflux transporter, ABCA, exacerbating lipid accumulation and lipotoxicity. These effects are further exacerbated by increases in levels of the E3 ubiquitin ligase, TRIM3, which ubiquitinates and subsequently inhibits PPARα, impairing fatty acid oxidation.

For example, activation of TLR4 in podocytes in streptozotocin-treated mice triggers the release of inflammatory mediators and disrupts the podocyte cytoskeleton, key events in the development of proteinuria and kidney damage[47]. Furthermore, stimulation of human podocytes by TLR3 agonists increased levels of pro-inflammatory cytokines and chemokines, upregulated the co-stimulatory molecule CD80 and cathepsin L, and downregulated the podocyte actin-associated protein, synaptopodin, resulting in cytoskeletal alterations[48,49]. Cathepsin L is a lysosomal cysteine protease that is involved in protein degradation, antigen processing and tissue remodelling. Elevated cathepsin L levels are associated with tissue damage as a consequence of excessive protein breakdown. In essence, although cathepsin L is vital for normal cellular function, its dysregulation can lead to pathological tissue remodelling, associated with podocyte injury and glomerular damage. Although the signalling events through which TLR activation leads to podocyte injury are unclear, they seem to be independent of the TLR adaptor protein, MyD88 (ref. 50). Inflammasome receptors are also expressed in podocytes, and podocyte-specific expression of the NLRP3 inflammasome has been associated with the progression of DKD[51], and podocyte injury in the context of obesity[51,52], lupus nephritis[53] and IgA nephropathy[54]. RLRs, such as RIG-I, LGP2 and MDA5, are RNA sensors in the cytosol that when activated induce a signalling pathway to increase type I interferon and thereby induce an antiviral immune response[55]. RIG-I and MDA-5 are expressed in and induce antiviral immunity in human and mouse podocytes[56]. To what extent RLR activation affects podocyte-related diseases remains to be addressed.

The GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway acts as a sensor of cytoplasmic foreign and host DNA and has emerged as a mediator of inflammation, infection, cellular stress and tissue damage[57]. In this pathway, double-stranded DNA in the cytosol, released from microbes or dying cells, binds cGAS to induce the synthesis of cGMP-AMP (cGAMP), which induces the activation of STING in the ER and triggers the production of type 1 interferon and cytokines through the NF-kB and TBK1–IRF3 signalling pathways[58,59]. In a mouse model of diabetes and obesity, lipotoxicity and BAX-mediated release of mitochondrial DNA into the cytosol activated the cGAS–STING pathway and impaired podocyte function[60]. In a separate study, the cGAS–STING pathway was activated in mouse models of DKD and Alport syndrome, whereas administration of a STING agonist induced albuminuria and podocyte loss in otherwise healthy mice[61].

Interplay exists between innate immune receptors and metabolic processes, either through the physical contact of organelles or through the modulation of common signalling pathways. For example, in addition to promoting fatty acid uptake, the fatty acid transporter CD36 enhances podocyte injury by inducing NLRP3 inflammasome activation in lupus glomerulonephritis[62].

## Organelle sensing

A growing body of literature recognizes that cellular organelles have important roles as molecular sensors, as integrators of signals and as transducers that prompt specific functional responses within cells[16]. In particular, mitochondria have been extensively studied for their ability to sense and integrate various signals, thereby connecting metabolic pathways with cellular functions[63] (Fig. 2). The kidney is a highly metabolic organ that is rich in mitochondria; importantly, a notable association exists between disease progression and mitochondrial dysfunction in people with advanced CKD[64]. The roles of other organelles in this context, such as the ER, the Golgi apparatus, peroxisomes, lysosomes, endosomes and lipid droplets require further investigation[65], but in general these organelles communicate with each other through the exchange of lipids, ions, ROS and other small molecules at regions where their membranes are closely juxtaposed by membrane contact sites.

The sensing function of organelles is not exclusively regulated by active molecules such as ligands, but can be triggered by various stimuli including mechanical, temperature, sensory, gustatory and oxygen-availability cues. Indeed, studies have demonstrated alterations in the expression of temperature-, voltage- and mechano-sensing receptors and channels in kidney cells in response to different stimuli and across different conditions. One notable group of receptors in this regard are the transient receptor potential (TRP) channels — a 28-member family of ion channels[66–68] that are highly expressed in various cell and tissue types[69]. These are polymodal channels, meaning that they can be activated by a range of external and internal stimuli including temperature, voltage, pH, mechanical forces, and both natural and synthetic ligands[70]. Additionally, TRP channels exhibit permeability to various cations, with a particular affinity for $Ca^{2+}$ (ref. 71). As mentioned above, $Ca^{2+}$ serves as a vital intracellular messenger that initiates and transduces signalling cascades. Complex $Ca^{2+}$ flux networks exist within the ER, mitochondria and lysosomes in kidney cells[35,72]. TRP channels are also widely distributed across different segments of the nephron[66,73]. Interestingly, administration of dietary capsaicin to a mouse model of DKD activated TRPV1, leading to the inhibition of ER–mitochondria interactions in podocytes and reducing mitochondrial dysfunction[74]. Another TRP channel, TRPC6, is expressed in podocytes as a component of the glomerular slit diaphragm[66], and can be activated by mechanical strain, changes in intracellular $Ca^{2+}$ concentrations, and signalling molecules like angiotensin II (ANGII) and ROS[22,75]. Dysregulation of TRPC6 activation in response to dysregulated $Ca^{2+}$ influx can trigger podocyte injury and kidney disease[22]. Mutations in TRPC6 can also induce podocyte damage, leading to progression of CKD and familial FSGS[66]. The role of TRPC5 (a non-selective cationic channel that can also transport $Ca^{2+}$) in kidney physiology and pathophysiology is controversial. In contrast to a 2017 study, which reported a role for TRPC5 ion channel activity in RAC1-induced podocyte cytoskeletal modelling[75], a 2023 study reported that the role of TRPC5 in podocytes is redundant with that of TRPC6, since the overexpression or absence of TRPC5 did not ameliorate proteinuria induced by constitutive activation of RAC-1[76]. Other receptors expressed by podocytes, such as the angiotensin II type 1 and the angiotensin II type 2

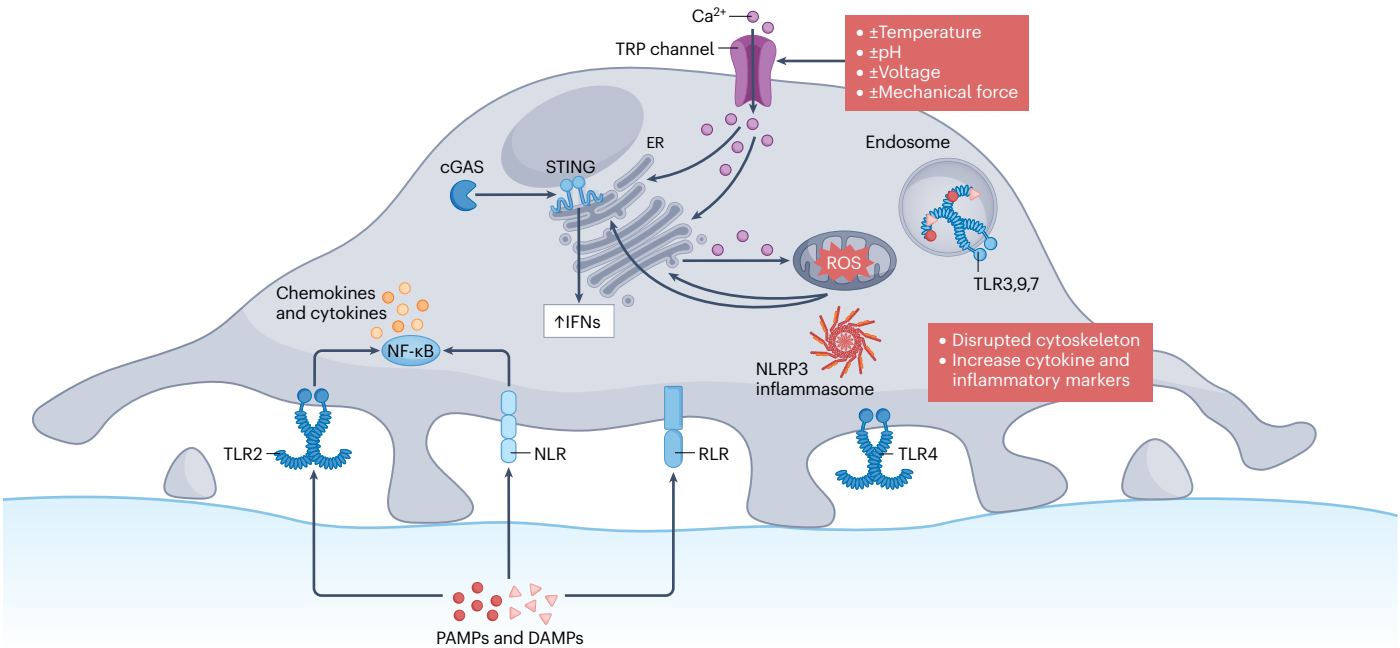



**Fig. 2 | Podocyte sensing of the microenvironment.** Podocytes act as sentinel cells in glomeruli, perceiving small changes in the environment through an array of different mechanisms and molecules. Beyond nutrient transporters (shown in Fig. 1), podocytes express a range of innate immune receptors, including the Toll-like receptors TLR4, TLR2, TLR3, TLR9 and TLR7, Nod-like receptors (NLRs), RIG-I-like receptors (RLRs) and the NLRP3 inflammasome, which enable the podocyte to recognize and respond to pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). The cGAS–STING pathway also responds to the presence of foreign and host DNA within the cytosol to mediate damage response pathways. Furthermore, in response to changes in temperature, pH, voltage and mechanical force, the transient receptor potential (TRP) channels are activated, which increases $Ca^{2+}$ influx and signalling networks between podocyte organelles, and increases the production of reactive oxygen species (ROS) by mitochondria to maintain organelle function. ER, endoplasmic reticulum; IFN, type 1 interferon.

receptors (AT1R and AT2R), also contribute to organelle signalling. Activation of AT1R by ANGII can lead to vasoconstriction, inflammation and oxidative stress. Moreover, ANGII-induced AT1R activation stimulates apoptosis through the ER stress pathway. By contrast, activation of AT2R counteracts the detrimental effects of AT1R activation by inducing the production of nitric oxide and increasing intracellular levels of $Ca^{2+}$, which influence organelle physiology[77–80].

## Mechanosensation

Mechanosensation is traditionally associated with specialized mechanosensory cells like neurons and involves the conversion of physical forces into electrochemical signals[81]. It is now recognized that pathophysiological microenvironments can remodel cellular responses and affect factors such as adhesion molecules, ion channels and cytoskeletal proteins through the activation of mechanotransduction pathways[82].

Podocytes possess remarkable mechanotransduction abilities, enabling them to sense and respond to injury or stress[83,84]. Increases in biomechanical forces associated with hyperfiltration, including tensile stress and fluid flow shear stress, exert direct influences on podocyte structure and function. High intraglomerular capsular pressure or glomerular hypertension negatively influences podocyte biology, leading to podocyte injury, morphological and functional alterations, and disease progression[85]. Notably, the stretching and mechanical stress that results from high intraglomerular capsular pressure can disrupt the delicate podocyte structure, culminating in podocyte detachment from the GBM. Moreover, high intraglomerular capsular pressure can elicit changes in podocyte gene expression, leading to the upregulation of genes associated with inflammation, fibrosis and oxidative stress[86]. These alterations in gene expression contribute to podocyte dysfunction and exacerbate kidney damage. In addition, the increased pressure can disrupt the structure of podocyte slit diaphragms, increasing the permeability of the glomerular filtration barrier and allowing proteins and macromolecules to pass into the urinary space. Therefore, high intraglomerular capsular pressure has far-reaching implications for podocyte function and kidney health[87,88].

Stretch-activated ion channels are stimulated in response to mechanical stretching of the plasma membrane and may be involved in transducing mechanical forces into biochemical signals, modulating cell function and cytoskeletal dynamics[89,90]. PIEZO is a mechanosensory ion channel with two family members described to date: PIEZO1 and PIEZO2. PIEZO 1 senses disturbances in blood flow and regulates angiogenesis by influencing endothelial cell alignment, migration and gene expression in response to mechanical cues, whereas PIEZO2 is associated with touch and proprioception. PIEZO2 also has a role in regulating urinary bladder control and coordinating micturition[91]. PIEZO 2 also localizes to glomerular mesangial cells and renin-producing juxtaglomerular cells, where its expression level changes in response to diverse pathological stimuli[92,93]. In a mouse model of dehydration, researchers observed that Piezo2 levels decreased in mesangial cells but increased in juxtaglomerular cells, which produce renin. Additionally, when Piezo2 was knocked down in cultured juxtaglomerular cells, expression of the renin gene *Ren1* dropped, both under normal

conditions and when the cells were mechanically stretched. These findings point to an important role for Piezo2 in controlling glomerular function and maintaining fluid balance in the body[93,94]. A 2019 study used reporter mice to demonstrate expression of Piezo1 in the urinary tract, and possibly in podocytes[94]. Findings from subsequent studies suggested that these receptors are important for detecting injury or pressure changes in podocytes and in transducing metabolic signals.

In a mouse model of aldosterone-infused and salt-loaded hypertension, the elevated expression of Piezo1 in podocytes was reversed by administration of an antihypertensive drug. Similar increases in Piezo1 expression were observed in cultured podocytes under mechanical stress and were associated with podocyte injury[85]. A second study confirmed the expression of Piezo1 in mouse podocytes and described the expression of Piezo 1 in *Drosophila* nephrocytes (which resemble podocytes) and human podocytes, where it co-localized with synaptopodin. Deletion or overexpression of Piezo1 was detrimental to nephrocyte morphology and function, suggesting that expression of these mechanosensing channel receptors may be tightly regulated under homeostatic conditions[95].

Other mechanoreceptors on podocytes include kinases, purinoreceptors and primary cilia. Sterile 20-like kinase (SLK) responds to mechanical stress, mediates signalling pathways relevant to cytoskeletal dynamics and cell survival, and has been implicated in podocyte injury[96]. Focal adhesion kinase (FAK) is another signalling protein that also has a role in mechanotransduction by linking integrin-mediated adhesion to downstream signalling pathways[97]. In podocytes, FAK may be involved in sensing and responding to mechanical cues, regulating cell adhesion, migration and cytoskeletal rearrangements. Inhibition of FAK in podocytes reduced albuminuria and foot process effacement in experimental models of kidney injury[98]. P2X purinoreceptors, such as P2X7R and P2X4R, are ATP-gated ion channels that detect mechanical stress and transmit signals, including in podocytes[89]. Notably, mechanical activation of P2X7R or P2X4 triggers $Ca^{2+}$ influx[99,100]. In line with these findings, multiphoton microscopy studies have demonstrated that podocytes can sense mechanical overload and metabolic alterations via TRPC6 and P2Y2 receptors, leading to increased intracellular $Ca^{2+}$ levels[100]. Expression of the actin-binding proteins, filamin A and B, is also upregulated under conditions of mechanical stress in podocytes, associated with decreased expression of the podocyte-specific protein synaptopodin and changes to the actin cytoskeleton[101].

Primary cilia can also function as mechanoreceptors in certain cell types and have a crucial role in sensing various environmental cues. These microtubule-based organelles are expressed on the apical surface of developing podocytes and act as mechanosensors to detect fluid flow and mechanical forces[102]. Although their role in developing podocytes is not well understood, they may be involved in signalling pathways that regulate migration and metabolic alterations[103,104]. Podocyte cilia disappear in adulthood.

Downstream signalling pathways involved in podocyte injury or stress responses mediate the effects of mechanical stimuli on podocyte responses. For example, the actin filament-binding protein Afadin is essential for the RhoA–ROCK-dependent formation of actin stress fibres in podocytes, and therefore has a crucial role in mediating mechanotransduction[105]. The actin nucleating complex Arp2/3 is vital for the formation of foot processes and adaptation of the podocyte to the mechanical requirements of the glomerular filtration barrier, in line with its role in the podocyte response to stress signals[105]. The Hippo pathway is a highly conserved signalling pathway that regulates organ size and cell proliferation. In the podocyte, activation of the Hippo pathway seems to occur through changes in proteins localized to focal adhesion and cell–cell junctions[106]. For example, proteins at the slit diaphragm can recruit and inactivate the large tumour suppressor kinases 1 and 2 (LATS1/2)[107], which are responsible for phosphorylating and inhibiting transcriptional coactivators YAP and TAZ. This mechanism is linked to podocyte injury, proteinuria and glomerulosclerosis in immortalized human podocytes and in experimental models of podocyte injury[106,108]. In line with these findings, podocyte-specific deletion of TAZ induced proteinuria in mice as young as 4 weeks old[109]. In *Drosophila*, activation of the mechanosensitive filamin orthologue Cheerio protected nephrocytes depleted of diaphragm components, whereas activation of Hippo blocked this protective effect[101,110]. Together, these data suggest that maintenance of podocyte morphology regulates the Hippo pathway, which contributes to the control of podocyte size.

### pH

Even minor fluctuations in pH can trigger changes in cellular processes. For example, a drop in extracellular pH from 7.4 to 6.5 in the kidney shortly after the induction of ischaemia induces the activation of acid-sensing channels that promote apoptosis in proximal tubular cells[111]. Evidence also suggests that pH can affect immune-cell activation; however, these insights are mainly derived from the study of solid tumours, which present in an acidic microenvironment. Moreover, existing reports are contradictory, with some reports suggesting that high concentrations of protons in the context of low pH can act as DAMPs and activate pro-inflammatory immune cells, whereas others have described immunosuppressive effects of low pH[112].

Stimuli that lower intracellular pH have long been associated with podocyte injury. A 2014 study showed that injured podocytes decreased intracellular pH, leading to activation of cathepsin L. Interestingly, diseased podocytes increase glutamine uptake by increasing amino acid transporter expression. The absence of glutamine further decreases intracellular pH, whereas glutamine supplementation alkalizes pH, protecting LPS-stimulated podocytes[113]. ANGII also increases the intracellular pH of podocytes, leading to superoxide anion production and apoptosis[114]. How podocytes perceive extracellular pH remains to be determined.

## Factors that influence podocyte metabolism

Like all cells, podocytes must integrate the many external signals they receive in order to respond appropriately. The mTOR complex comprises two subcomplexes (mTOR complex 1 (mTORC1) and mTORC2) and acts to sense and integrate a variety of environmental cues, including nutritional, energy and stress-related cues, to regulate the growth and homeostasis of a variety of systems[115]. In podocytes, the mTOR complex controls growth, survival and metabolism, with dysregulation of mTOR activity observed in DKD and a range of glomerular diseases in humans and in animal models[116], suggesting that mTOR has a role in mediating the effects of hyperglycaemia and other stressors on the podocyte. A 2019 study in cultured podocytes showed that the adverse effects of high glucose on podocyte viability were partially suppressed by the mTORC1 inhibitor rapamycin and further suppressed by a dual mTORC1 and mTORC2 inhibitor[117]. Abnormal mTORC1 activation has also been linked to podocyte loss, GBM thickening, mesangial expansion and proteinuria in people with DKD and mouse models of DKD[118] (Fig. 3). Podocyte hypertrophy has been identified as a compensatory mechanism that can regulate glomerular integrity in diseases such as FSGS and DKD. In mice, pharmacological blockade of mTOR signalling

dampens the hypertrophy of remaining podocytes during acute podocyte loss, culminating in albuminuria and glomerulosclerosis[119]. The compensatory pathways used by the hypertrophic podocytes remain to be determined.

Podocytes of mice with podocyte-specific deletion of mTOR demonstrate an accumulation of autophagosomal vesicles and defects in autophagic flux, associated with proteinuria[120]. A separate study showed that simultaneous deletion of mTORC1 and mTORC2 from mouse podocytes during normal development induced glomerular lesions, highlighting the importance of both mTOR complexes for podocyte homeostasis[118]. In line with these findings, mTOR inhibition in kidney transplant recipients and in cultured human podocytes decreases nephrin expression, negatively affecting glomerular barrier permeability[121].

Like mTOR, AMPK is a nutrient-sensing kinase that also has an important role in podocyte homeostasis, particularly in the context of DKD and glomerular filtration barrier integrity[116]. In people with DKD, dysregulation of AMPK signalling is associated with GBM thickening, glomerular mesangial cell hypertrophy and podocyte loss[122] (Fig. 3). AMPK induces the depolymerization of actin filaments and the dilation of arteries without changing $Ca^{2+}$ levels, suggesting that AMPK might affect artery resistance through cytoskeletal dynamics[123] and indicating a potential role in the regulation of podocyte function beyond traditional metabolic pathways[124]. AMPK might also regulate autophagic protection against injury[125]. Moreover, a 2023 study demonstrated that interplay between Protein kinase G type Iα (PKGI) and AMPK in cultured rat podocytes may influence GBM permeability to albumin[124].

Mouse podocytes exhibit low mitochondrial density compared to that of renal tubular cells, and thereby rely primarily on anaerobic glycolysis and less on mitochondria-dependent metabolic pathways such as the TCA cycle and fatty acid oxidation[126]. Anaerobic glycolysis, which is typically seen in highly proliferating cells such as cancer cells, converts glucose into pyruvate, and then into lactate rather than into acetyl-CoA. This shift accelerates the production of ATP and enhances the availability of metabolites for biosynthetic processes. The activation of HIF-1α and other signalling pathways drives this metabolic adaptation, for example, by increasing levels of glycolytic enzymes[127].

Numerous findings suggest that HIF-1α affects the development of kidney fibrosis[128,129]; however, contradictory reports exist as to whether HIF acts as a pro-fibrotic or anti-fibrotic effector. For example, enhanced HIF-1α activity has been associated with the epithelial-to-mesenchymal transition (EMT) in mouse primary proximal tubular epithelial cells in vitro and with tubulointerstitial injury in people with CKD[130]. In experimental settings, inhibition of HIF-1α mitigated glomerular and tubulointerstitial damage induced by ANGII infusion[131,132], and reduced kidney expression of collagen and α-actin following chronic ischaemia or hypoxia[129]. Conversely, activation of HIF for 8 days alleviated kidney inflammation in mice with unilateral ureteral obstruction (UUO)-induced CKD[133]. Mouse podocytes cultured in 33 mM of glucose also activate HIF1a. This activation leads to decreased E-cadherin and increased α-SMA and FSP1, suggesting a link between glucose metabolism and the EMT in podocytes[134].

In fact, HIF-1α stands out as a key regulator of cellular processes, with roles in energy metabolism, the response to oxidative stress and cell survival, particularly under hypoxic conditions. In response to chronic hypoxia, elevated levels of HIF-1α are associated with detrimental effects, including the podocyte EMT, slit-diaphragm dysfunction, foot-process effacement and cytoskeletal derangements[135]. These

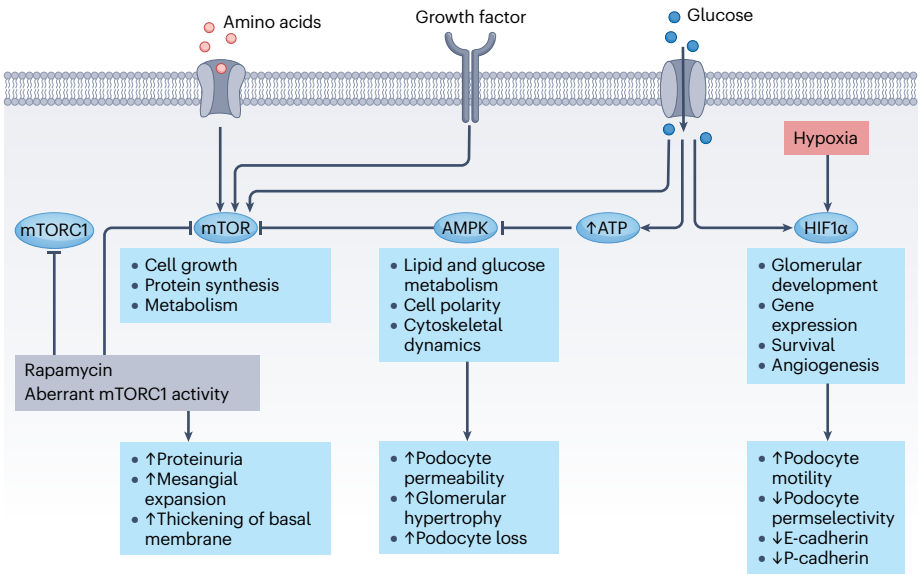



**Fig. 3 | Energy-sensing molecules as integrators of signals in the podocyte.** Activation of mTOR (mechanistic target of rapamycin) occurs in response to nutrient sensing and stimulates signalling pathways that increase cell growth, protein synthesis and cell metabolism. The absence of mTOR or presence of the mTORC1 inhibitor, rapamycin, is associated with proteinuria, mesangial expansion and thickening of the glomerular basement membrane, indicating that fine-tuning of mTOR activation is important for podocyte health. AMPK is activated by decreasing the ratio of ATP to AMP and leads to increased lipid and glucose metabolism, changes in cell polarity and cytoskeletal dynamics, and podocyte permeability, glomerular hypertrophy and podocyte loss. HIF-1a can be activated by glycolysis and hypoxia. Its activation is associated with glomerular development, enhanced expression of hypoxia-inducible genes, angiogenesis and survival. HIF-1 activation also increases podocyte motility but decreases the expression of molecules such as cadherins, which are important for maintaining podocyte integrity.

changes impair the efficiency of glomerular filtration and lead to glomerulosclerosis and proteinuria[135]. Podocyte-specific deletion of *Vhl*, which encodes von Hippel–Lindau protein — a protein that interrupts HIF degradation — induced rapidly progressive glomerulonephritis in mice[136].

HIF-1α also stabilizes and stimulates the transcription of genes involved in angiogenesis, including *VEGF*, which is highly expressed by podocytes[137]. In rats, HIF-1α accumulation following hypoxia resulted in elevated zinc finger E-box binding homeobox 2 (ZEB2), decreased expression of E- and P-cadherin, and decreased podocyte permselectivity[138]. Similarly, inhibition of HIF-1α led to decreased fibrosis in a UUO model[139]. Conversely, RNA silencing experiments showed that inhibition of HIF-1α in podocytes enhanced the transcription of hypoxia-inducible genes, suggesting that HIF-1α has a protective role in podocytes[140]. All of these alterations in HIF-1α seem to affect podocyte-specific gene-expression patterns. These experimental findings highlight the diverse and sometimes contrasting roles of HIF-1α in kidney pathophysiology, underscoring the complexity of its involvement in kidney responses to hypoxic conditions and injury. However, since the precise role of HIF-1α seems to be controversial or may be context-dependent, more studies are necessary, including those that use single-cell RNA-sequencing and HIF-1a deletion specifically in podocytes to illuminate the role of HIF-1α in CKD (Fig. 3).

## Organelle sensing

Podocyte injury can result from disorders or other injurious stimuli that affect transcriptional regulators, the slit diaphragm, the assembly or function of the actin-based cytoskeleton, as well as membrane and cytoplasmic proteins. In addition, podocyte injury can result from disorders or injurious stimuli that affect organelles, which, as described earlier, can sense changes in the microenvironment[12]. Here we describe how organelles and inter-organellar signalling respond to adverse conditions within the podocyte microenvironment.

### Mitochondria

Under physiological conditions, podocytes use glucose as their predominant fuel, which is processed by anaerobic glycolysis to produce ATP and lactate[126]. However, podocyte metabolism can shift in the context of dysregulated lipid flux and/or lipid accumulation by increasing the β-oxidation of fatty acids in mitochondria to fuel the tricarboxylic acid (TCA) cycle and produce ATP[126,141–144]. Of note, aberrant mitochondrial homeostasis has been implicated in podocyte injury and a range of podocytopathies[12]. A 2014 study demonstrated an association between podocyte mitochondrial damage and dysfunction of adjacent endothelial cells in mice with doxorubicin-induced FSGS, suggesting impaired β-oxidation[145]. Another study reported that the basal oxygen consumption rate (OCR, from which mitochondrial respiration can be inferred, referred to here as mitochondrial function) of cultured mouse podocytes increased after exposure to high glucose or TGF-β. These findings suggest that the glucose flux generates pyruvate, which in mitochondria is converted into acetyl-CoA to enter the TCA cycle, and indicate that the induction of metabolic changes in podocytes occurs in response to external stimuli associated with DKD[146]. In the context of diabetes, impaired glycolysis results in inadequate energy supply to podocyte foot processes, ultimately contributing to podocyte injury and apoptosis[147]. Decreased glycolytic flux in podocytes exposed to ANGII leads to ATP deficiency, cytoskeletal remodelling and apoptosis[148]. These findings suggest that increased glycolysis may represent a potential therapeutic strategy to treat podocyte injury[149].

Beyond their roles in energy metabolism, mitochondria regulate $Ca^{2+}$ signalling, redox homeostasis and apoptosis[150]. In healthy podocytes, ROS are produced in a controlled manner and serve as signalling molecules regulating podocyte morphology, actin cytoskeleton dynamics and foot-process architecture. ROS signalling is also involved in the regulation of mitochondrial function, autophagy and podocyte survival. However, excessive ROS production or the impairment of antioxidant defenses can lead to oxidative stress, which can contribute to podocyte injury, dysfunction and apoptosis. Oxidative-stress-induced podocyte injury is a hallmark of several kidney diseases, including DKD and glomerulosclerosis[150,151].

Mitochondrial dysfunction in podocyte injury is also intricately linked to changes in damaged mitochondria with unstable mitochondrial DNA, ATP synthesis, ROS production, $Ca^{2+}$ signalling, mitophagy and mitochondrial dynamics[152]. In addition, terminally differentiated podocytes enhance both anaerobic glycolysis and mitochondrial metabolism in a context-dependent manner to meet their energy demands[11,153]. This metabolic shift is accompanied by increased resistance to oxidants, as evidenced by heightened antioxidant enzyme activities, H-ferritin expression and activity of the metabolic regulator pyruvate kinase M2 (PKM2)[153,154]. In vitro, deletion of PKM2 in differentiating podocytes reduced podocyte energy metabolism and led to defects in cell differentiation[153]. Mice with podocyte-specific deletion of *Pkm2* exhibited increased albuminuria and podocyte injury. In addition, ornithine catabolism is upregulated in podocytes under conditions of glycolytic stress, which activates mTOR signalling and cytoskeletal remodelling in DKD[147].

Excessive lipid accumulation can also lead to cellular dysfunction in podocytes, characterized by mitochondrial oxidative stress, actin cytoskeleton remodelling and inflammatory responses, potentially resulting in podocyte hypertrophy, detachment and death[155]. Sphingolipid metabolism is crucial for the structural and functional integrity of podocytes; dysregulation of sphingolipid signalling is implicated in the pathogenesis of nephrotic syndrome and podocyte injuries[148].

The accumulation of mitochondrial phospholipids such as cardiolipin, in the podocytes of mouse models of DKD and people with DKD also correlates negatively with kidney function[156]. This accumulation is associated with mitochondrial damage (including cristae rupture and mitochondrial swelling) and fragmentation, increased ROS production and enhanced apoptosis, through upregulation of ALCAT1[156]. It is also associated with ABCA1 deficiency, which as mentioned earlier, is involved in lipid efflux. Podocyte-specific deletion of *Abca1* worsens DKD in mice, leading to mitochondrial dysfunction, increased oxidative stress and podocyte injury[157]. Indeed, and as mentioned earlier, lipid accumulation in the kidney parenchyma — especially in podocytes and tubular cells — is a hallmark of CKD, even in the absence of systemic hyperlipidaemia. The uptake of abnormal levels of lipids is mediated by the actions of lipid transporters such as CD36 and FATP2, and binding proteins such as FABPs. Moreover, impairment of mitochondrial fatty acid oxidation in podocytes and proximal tubular cells occurs, owing to downregulation of key regulators such as PPARα, AMPK and PGC-1α. In addition, the reduced expression of transporters such as ABCA1 leads to intracellular cholesterol accumulation and cellular stress[158].

Mitophagy, defined as the selective degradation of damaged or dysfunctional mitochondria through autophagy, also has a crucial role in maintaining mitochondrial quality and cellular homeostasis in podocytes. In healthy podocytes, mitophagy ensures the prompt removal of impaired mitochondria, preventing the accumulation of dysfunctional organelles that could trigger oxidative stress and cellular

dysfunction (Fig. 4). Given the high energy demands of podocytes and their constant exposure to metabolic and haemodynamic stressors, the regulation of mitophagy in podocytes is particularly important. Mitophagy is orchestrated by a network of signalling pathways and key molecular players, including PTEN-induced kinase 1 (PINK1), PARKIN and other autophagy-related proteins[159]. These pathways are activated in response to mitochondrial stress or damage, which prompts the recruitment of autophagosomes that engulf and degrade impaired mitochondria. Conversely, impaired podocyte mitophagy has been observed in conditions such as DKD, glomerulosclerosis and acute kidney injury[159]. Diminished mitophagy may lead to accumulation of damaged mitochondria, resulting in heightened oxidative stress, inflammation, cell injury and compromised integrity of the filtration barrier[159].

## Peroxisomes

Peroxisomes are essential intracellular organelles that are found in all human cells except erythrocytes. Like mitochondria, peroxisomes have crucial roles in cellular metabolism, particularly in the metabolism of fatty acids and in ROS production[160]. Although both mitochondria and peroxisomes are involved in fatty acid β-oxidation, mitochondria use acetyl-CoA to generate ATP, whereas peroxisomes metabolize very-long-chain fatty acids to produce medium-chain fatty acids like docosahexaenoic acid (DHA), as well as hydrogen peroxide ($H_2O_2$) and acetyl-CoA[160,161]. In addition to metabolizing very-long-chain fatty acids, peroxisomes participate in the α-oxidation of branched-chain fatty acids[162], as well as amino acid and ethanol catabolism, bile acid and steroid hormone biosynthesis, gluconeogenesis and the formation of plasmalogen — a type of glycerophospholipid that is a crucial component of plasma membranes and myelin sheaths. Moreover, in addition to generating $H_2O_2$ as a byproduct of β-oxidation, peroxisomes are responsible for degrading cytotoxic $H_2O_2$ through the actions of peroxidases such as catalase, and for producing and metabolizing ROS such as nitric oxide and superoxide radicals[160,161].

The number of peroxisomes increases through the fission of existing peroxisomes (the autonomous pathway) or through their de novo biogenesis, which occurs through the merging of pre-peroxisomal vesicles that bud off the ER and the import of matrix proteins synthesized by ribosomes[160,163,164]. The kidney and liver have the highest concentration of peroxisomes, and are therefore the organs most affected by disorders that affect peroxisomal biogenesis. Kidney manifestations are a common symptom of diseases that result from variations in peroxisomal genes. For example, 70% of people with Zellweger syndrome, which is caused by dysfunctional peroxisome assembly, develop cysts in the kidney cortex[165].

Peroxisomes also have key roles in inflammation, apoptosis, ageing and age-related conditions such as diabetes mellitus and cancer[166]. Mice with deletion of *Pex11a*, which encodes a protein involved in peroxisome elongation and fatty acid β-oxidation, have reduced numbers of functional peroxisomes in their proximal tubule cells, associated with lipid accumulation and CKD[167]. In podocytes, peroxisomes have important roles in maintaining cellular function and integrity through the processing of fatty acids and regulation of lipid droplets. These functions are vital for the structure and function of podocytes since, as described earlier, disturbances in lipid metabolism can result in podocyte dysfunction and damage. A 2021 study reported that peroxisomal dysfunction in podocytes is linked to impaired lipid metabolism and increased susceptibility to glomerular injury[168].

The nuclear receptor PPARγ, which controls the expression of peroxisomal genes and lipid metabolism, has protective functions in podocytes[169]. For example, in a model of puromycin aminonucleoside (PAN)-induced nephropathy, treatment with the PPARγ agonist pioglitazone reduced proteinuria to a level comparable to that produced by high-dose glucocorticoid therapy and effectively mitigated podocyte injury[170]. Conversely, excessive expression of the PPARγ coactivator, PGC1α, which is mainly known for its role in mitochondrial biogenesis, disrupted mitochondrial function leading to podocyte proliferation and dedifferentiation[171]. Since PGC1α acts as co-activator of PPARγ, these findings suggest a potential indirect impact of PPARγ on peroxisome function in podocytes. Activation of PPARγ may also improve the ability of podocytes to manage fatty acid levels, reduce their expression of profibrotic TGFβ and inhibit apoptosis[172].

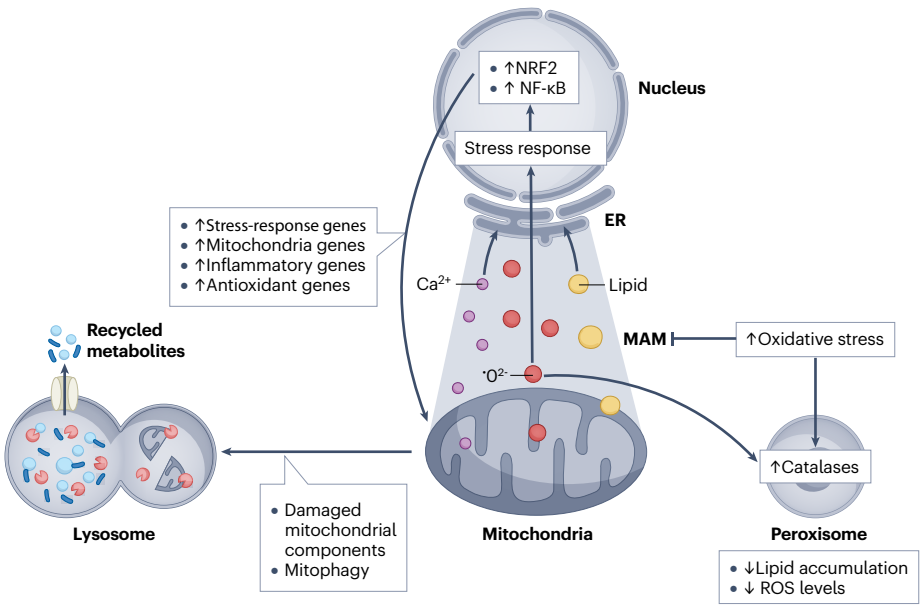



**Fig. 4 | Mitochondria are at the centre of organelle communication in podocytes.** Under conditions of stress, the excess production of reactive oxygen species (ROS) by mitochondria induces stress-response pathways in the nuclei, such as those that involve activation of NRF-2 and NF-kB, which coordinate the expression of antioxidant defence, mitochondria biogenesis and inflammation genes. Mitochondria also exchange molecules, ions and nutrients with the endoplasmic reticulum (ER) via the mitochondria ER-associated membrane (MAM), which are important for the cellular response to injury. Disruption of the MAM induces oxidative stress. Lysosomes remove cellular waste, including damaged mitochondria, and thereby contribute to mitochondria and cell homeostasis. Peroxisomes control lipid levels in podocytes by metabolizing long- and medium-chain fatty acids and by reducing levels of ROS such as hydrogen peroxide and superoxide anions through their metabolism.

Peroxisomes also have roles in detoxifying ROS and managing oxidative stress in podocytes. The generation and elimination of ROS by peroxisomes is crucial for sustaining redox equilibrium within podocytes and preventing oxidative harm. Peroxisome dysfunction in tubular cells[173] and podocytes can lead to elevated oxidative stress, furthering cellular injury and contributing to development of kidney diseases.

### The endoplasmic reticulum

Interactions between mitochondria and the ER are more frequent than interactions between other organelles[174]. A seminal study from 2019 provided support for this notion and demonstrated that DNA released by dysfunctional mitochondria influences ER function and induced tubular inflammation in a model of cisplatin-induced acute kidney injury[175]. ER stress, resulting from perturbations in protein folding or $Ca^{2+}$ imbalance, can be triggered by various pathological conditions, leading to glomerular injury[64]. The unfolded protein response (UPR) is activated in response to ER stress and aims to restore ER homeostasis. However, persistent UPR activation can lead to podocyte injury and apoptosis[176]. XBP1 is a transcription factor that is important for the UPR and alleviating ER stress and is indispensable for the integrity of the filtration barrier. Podocyte-specific deletion of Xbp1 and Sec63 — a heat-shock protein chaperone required for protein folding in the ER — induced albuminuria and foot-process effacement in mice[177]. In another study, inhibition of ER stress mitigated tubular atrophy, kidney fibrosis and the transition from acute kidney injury to CKD in mice[178].

ER stress and the UPR have been implicated in proteinuric diseases and in podocyte injury[179,180]. High glucose stimulates ER stress in podocytes through activation of ERK and mTOR signalling pathways, leading to apoptosis[181]. Autophagy seems to be a mechanism involved in the podocyte response to ER stress[182]. Finally, interference with the UPR by deletion of the UPR transducer in podocytes can lead to injury and albuminuria[183].

### Lysosomes

Lysosomes contribute to the degradation and recycling of cellular waste and damaged proteins through autophagy. Lysosomal dysfunction and/or compromised autophagy can therefore lead to build-up of aggregated proteins and damaged organelles, causing cellular stress and impaired podocyte function[184,185]. A 2014 study demonstrated that lysosomes are involved in the endocytosis of albumin by human urine-derived podocyte-like epithelial cells. In a transgenic mouse model of Denys–Drash-associated nephrotic syndrome, the researchers further showed that lysosomal dysfunction, as evidenced by increased podocyte expression of lysosome-associated membrane protein-1 (LAMP-1), can lead to podocyte injury and glomerulosclerosis[186]. A separate study showed that lysosomal-dependent autophagy was improved in podocytes from people with biopsy-proven diabetic nephropathy following administration of resveratrol plus vitamin E, associated with reduced apoptosis and improvements cytoskeletal architecture[187].

### The Golgi apparatus

In healthy podocytes, the Golgi apparatus is involved in the post-translational modification of proteins before they are transported to their final destination. These modifications include glycosylation, phosphorylation, sulfation and proteolytic cleavage, and are essential for the proper function and localization of podocyte proteins involved in cell adhesion, cytoskeletal dynamics and filtration barrier integrity. Glycosylation is a particularly common post-translational modification in podocytes and involves the addition of sugars to proteins to form glycoproteins. This modification is crucial for protein folding, stability and recognition by cell-surface receptors. For example, podocalyxin — a transmembrane protein that is highly expressed in podocytes — undergoes extensive glycosylation in the Golgi apparatus. Glycosylation of podocalyxin is important for its proper localization at the apical surface of podocyte foot processes and for its role in maintaining the negatively charged glycocalyx, which is critical for barrier function[188]. Sulfation involves the addition of sulfate groups to proteins and is important for their proper function. For example, sulfation of heparan sulfate proteoglycans in the GBM contributes to its negatively charged matrix, which is crucial for maintaining barrier selectivity[189]. Abnormalities in podocyte Golgi function can result in glomerular damage[190]. For instance, active vesicular transport in the Golgi apparatus is essential for foot-process formation and maintenance in cultured podocytes[191]. Importantly, impairment of Golgi function can hinder the transport and secretion of podocyte-specific proteins that are essential for maintaining the structure and function of the filtration barrier[192,193].

## Organelle crosstalk in podocyte injury

Bidirectional communication between mitochondria and the nucleus is crucial for podocyte functioning in health and disease. For example, mitochondrial-derived ROS serve as signalling molecules that influence gene expression in the nucleus to activate stress-response pathways. Conversely, the nucleus regulates mitochondrial function by controlling the transcription of mitochondrial genes involved in energy metabolism and the oxidative stress response. In podocytes, mitochondrial dysfunction and oxidative stress induce the activation of stress-response pathways, such as those that involve nuclear factor erythroid 2-related factor 2 (NRF2) and nuclear factor kappa B (NF-κB), which coordinate the expression of antioxidant defence and inflammation genes in response to cellular damage[194].

Interplay between mitochondria and the ER at mitochondria-associated ER membranes (MAMs) also facilitates lipid exchange, signalling-molecule exchange and $Ca^{2+}$ exchange, which are crucial for the cellular response to injury. In podocytes, communication between mitochondria and the ER through MAMs modulates $Ca^{2+}$ homeostasis, lipid metabolism and cell viability. Perturbation of MAMs and compromised ER–mitochondria crosstalk can impair podocyte mitochondrial function, heighten oxidative stress and contribute to cell injury[195].

Mitochondria and lysosomes also engage in inter-organellar communication pathways that govern mitochondrial quality control and mitophagy — processes that are important for the targeted degradation of dysfunctional mitochondria. Lysosomes preserve mitochondrial health through mitophagy, by removing damaged components, including damaged mitochondria, and recycling metabolites, thereby fostering cellular homeostasis. Dysregulated mitophagy may result in dysfunctional mitochondrial accumulation, heightening oxidative stress and contributing to podocyte injury[12,196].

Interactions between microtubules and actin filaments modulate mitochondrial positioning and dynamics within cells and are important for cell function. In the context of injury, disorganization of cytoskeletal components can affect mitochondrial distribution, fusion–fission dynamics, and contribute to mitochondrial dysfunction[197,198] (Fig. 4). These disruptions have the potential to cause podocyte dysfunction and injury[12,159].

## Conclusions

Sensing of the external microenvironment by podocytes and the resultant organellar crosstalk influence podocyte gene expression, with subsequent paracrine effects on nearby glomerular cells. A complete

understanding of the effects of nutrient-sensing and mechano-sensor molecules on organelle–organelle communication will clarify the mechanisms by which these interactions influence podocyte differentiation and function. This information is expected to provide the foundations for the development of more precise therapies to prevent and treat podocyte, glomerular and kidney diseases.

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## Author contributions
V.A.-O. and N.O.S.C. researched data for the article. J.F.B, V.A.-O. and N.O.S.C. contributed substantially to discussion of the content. All authors reviewed and/or edited the manuscript before submission.

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