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REVIEW

The Ca^{2+}-actin-cytoskeleton axis in podocytes is an important, non-immunologic target of immunosuppressive therapy in proteinuric kidney diseases

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Abstract
The integrity of the filtration barrier of the kidney relies on the proper composition of podocyte interdigitating foot processes. Their architecture is supported by a complex actin-cytoskeleton. Following podocyte stress or injury, podocytes encounter structural changes, including rearrangement of the actin network and subsequent effacement of the foot processes. Immunosuppressive drugs, which are currently used as treatment in proteinuric kidney diseases, have been shown to exert not only immune-mediated effects. This review will focus on the direct effects of glucocorticoids, cyclosporine A, tacrolimus, mycophenolate mofetil, and rituximab on podocytes by regulation of Ca^{2+} ion channels and consecutive downstream signaling which prevent cytoskeletal rearrangements and ultimately proteinuria. In addition, the efficacy of these drugs in genetic nephrotic syndrome will be discussed.

Keywords Glucocorticoids · Cyclosporine A · Tacrolimus · Mycophenolate mofetil · Rituximab · Non-immunologic effect on podocytes

Introduction

The filtration barrier of the kidney consists of three layers, the fenestrated endothelium lined with glycocalyx, the glomerular basement membrane (GBM), and the podocytes with the slit diaphragm (SD) bridging their interdigitating foot processes (FPs). The architecture of podocytes is mainly supported by a complex network of the actin-cytoskeleton. Upon podocyte stress or injury, the actin-cytoskeleton of podocytes undergoes rearrangements of the actin network resulting in subsequent FP effacement (FPE) [1]. It has been proposed that FPE initially might be a compensatory attempt of podocytes to prevent detachment. However, if the insult is prolonged, detachment often cannot be avoided. Recent studies have shown that the nephroprotective effect of renin-angiotensin-aldosterone system inhibitors are associated with the inhibition of a Ca^{2+} ion channel and its downstream signaling, which prevented cytoskeletal rearrangements in podocytes and proteinuria [2–6]. Other immunosuppressive drugs, which are regularly used to treat proteinuric kidney diseases, have also been shown to exhibit additional direct effects on the Ca^{2+} ion channels and the actin-cytoskeleton beyond their role in systemic immunosuppression and thus directly protect podocytes. Therefore, this review will focus on these drugs and their effect on the Ca^{2+}-actin-cytoskeleton axis.

Ca^{2+} signaling and the actin-cytoskeleton in podocytes

Ca^{2+} signaling in podocytes

Ca^{2+} signaling is initiated by an increase of the intracellular calcium concentration ($[Ca^{2+}]_i$). The influx of Ca^{2+} can originate from the extracellular space or intracellular Ca^{2+} stores such as the endoplasmic reticulum (ER) and the mitochondria [7]. The binding of Ca^{2+} induces structural and conformational changes in various calcium-binding proteins, thereby modulating their activity and function in downstream signaling cascades to regulate cell motility and

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survival. The level of $[Ca^{2+}]_i$ is meticulously regulated by the coordinated activity of ion channels, molecular pumps and cytosolic Ca^{2+} buffers, all of which cooperate to maintain low $[Ca^{2+}]_i$ at baseline and enable responsive calcium-dependent signaling pathways.

Ca^{2+} signaling has emerged as a central element in podocyte damage. Kerjaschki suggested that an increase in $[Ca^{2+}]_i$ is an early event in podocyte injury [8]. Indeed, altered Ca^{2+}-signaling has been reported in several circumstances of podocyte injury. Either as a direct cause of focal segmental glomerulosclerosis (FSGS) caused by the gain-of-function mutation in transient receptor potential cation channel member 6 (*TRPC6*) [9] or as a uniform response to stress in this cell type, e.g., in protamine sulfate nephropathy [10] or in complement C_{5b-9} complex-mediated podocyte injury [11]. Moreover, significantly elevated Ca^{2+} levels can be measured in response to podocyte injury using in vivo $[Ca^{2+}]_i$ imaging [12]. This increase in $[Ca^{2+}]_i$ leads to cytoskeletal disorganization and FPE [13] and subsequently increases podocyte cell motility in different disease models of podocyte injury in vivo [14].

Due to disease causing human mutations, TRPC6 is the most extensively studied channel in the context of Ca^{2+} signaling in podocytes [15–19]. TRPC6 is located in the podocyte foot processes at or near the site of the SD and contributes to the proposed mechanosensing function of the SD, whereby TRPC6 tightly regulates Ca^{2+} currents and cytoskeletal rearrangement of podocytes [20]. TRPC6 can be activated by an increase in $[Ca^{2+}]_i$ from the extracellular space (receptor-operated Ca^{2+} entry, ROCE) or from intracellular stores (store-operated Ca^{2+} entry, SOCE) [21–23]. During ROCE, phospholipase C [24] is activated by a G-protein-coupled receptor [25, 26]. The subsequently released diacyl-glycerol directly activates TRPC6 channels to trigger downstream calcium signaling [24, 25]. During SOCE, Ca^{2+} levels in the ER are depleted, which result in the activation of the ER-resident stromal interaction protein 1 [27]. This stimulates calcium-release-activated calcium channel protein 1 (Orai1), allowing Ca^{2+} influx into the cell, which directly activates TRPC channels and promotes the trafficking and the insertion of TRPC channels into the plasma membrane. Importantly, additional evidence supports and highlights the importance of TRPC channels as a critical regulator of calcium signaling in podocytes: ANG II activates ROCE to induce TRPC6-mediated Ca^{2+} influx in podocytes under hyperglycemic condition modelling diabetes [28], ANG II-induced albuminuria is reduced in TRPC6 knockout mice [29] and the inhibition of ANGII by losartan blocks calcium signaling in podocytes [6]. However, the strongest evidence for the pathophysiological relevance of TRPC6 remains the development of FSGS and consequent kidney failure in human patients with a gain of function mutation [9, 30].

TRPC5, calcium-activated potassium channels (BKs; KCa1.1) and store-operated channels (SOCs) have also been implicated in glomerular disease development [31–33]. Furthermore, the ionotropic N-methyl-D-aspartate receptor and purinergic P2X receptors are ligand-gated ion channels that are also thought to play a role in the pathogenesis of glomerular disease [34, 35]. Additionally, the IP_3 receptor also regulates glomerular shape and podocyte foot process formation through SOCE [36]. Further details can be found in the informative review by Tu et al. [37]. Taken together, these results demonstrate the importance of calcium and related signaling pathways in the structure and function of the glomerular filtration barrier.

Actin-cytoskeleton in podocytes

Podocytopathies are characterized by an altered cytoskeletal architecture (imbalance between polymerization and depolymerization) in the actin-rich FPs of podocytes. They can alter the permeability of the filtration barrier by changing the FP morphology [38]. Signal transduction pathways at the FP that influence cytoskeletal dynamics are controlled by the Rho family of small GTPases and their regulators: Rac1 promotes cell motility, RhoA stimulates the formation of contractile actin cables in vivo or stress fibers in vitro, while Cdc42 initiates actin branching [39–42]. Several studies have closely linked the development of proteinuria with the dysregulation of actin organization in podocytes [43–45]. Mutations affecting actin-related structure, anchors, and regulator proteins in podocytes result in actin-cytoskeleton rearrangement, disrupt the filtration barrier, and subsequently lead to kidney disease [46–50]. In this context, the actin-associated regulatory protein, synaptopodin, has gained special attention: It binds directly to RhoA and thereby prevents the targeting of RhoA for proteasomal degradation and thereby induces stress fiber formation in podocytes [51–53]. Furthermore, nephrin a major component of the SD is linked to the actin cytoskeleton and regulates it *via* the nck and CD2AP adaptor proteins [54, 55]. Mutations in nephrin disturb the actin cytoskeleton [56]. Finally, myosin 1e may be important for the function of actin cables, as mutations in myosin1e are also associated with FSGS [57, 58]. Further details can be found in an excellent review by Blaine et al. [59]. Altogether, this data underlines that the proper organization and the dynamic regulation of the podocyte cytoskeleton are vital to the kidney filtration function.

Regulation of the actin-cytoskeleton via intracellular Ca^{2+} signaling

Ca^{2+} binding can trigger podocyte pathology by activating multiple downstream signal transducers such as calcineurin, calmodulin, and small GTPases. Signaling through the

Ca^{2+}-activated serine/threonine phosphatase, calcineurin, has recently emerged as an important modulator of podocyte function. Calcineurin is widely distributed across many cell types including podocytes. Its most renowned function is the activation of the nuclear factor of activated T-cells (NFAT) [60–63], which upregulates interleukin-2 and induces T-cell response [64]. Additionally, calcineurin renders the actin stabilizer synaptopodin by dephosphorylation accessible to cathepsin L-mediated degradation. This leads to modulation in Rho GTPases activity, cytoskeletal rearrangement and proteinuria [53, 65–70]. Ang II has also been shown to activate calcineurin in a TRPC5-dependent manner [69]. Taken together, calcineurin seems to be a key transducer of Ca^{2+}-activated signaling in podocyte injury.

Another important calcium sensor is calmodulin. It is a critical upstream regulator of the Ca^{2+}/calmodulin–dependent kinase (CaMK4), which activates Rac1 and suppresses synaptopodin and nephrin leading to the remodeling of the actin-cytoskeleton and a motile podocyte phenotype [71]. Podocyte-specific inhibition of CaMK4 restores synaptopodin expression and protects the actin-cytoskeleton from damage. In addition, the interaction between calmodulin and *MYO9A* is crucial to crosslink actin and to regulate RhoA activity [72]. Importantly, heterozygous loss-of-function mutations in *MYO9A* directly impairing the interaction with actin and calmodulin cause a form of human autosomal dominant FSGS. Finally, calmodulin is also involved in the Ca^{2+}-dependent inactivation of TRPC6 channels, which serves as a negative feedback regulation to prevent excess influx of Ca^{2+} [73]. Thus, the disruption of the calmodulin-bridge with TRPC6 can lead to sustained Ca^{2+} elevation, stimulation of downstream signaling cascades and filamentous actin (F-actin) rearrangements. Altogether, calmodulin plays an important role in the fine adjustment of $[Ca^{2+}]_i$ in podocytes.

It is well known that the activation and the inactivation of small GTPases are mediated by guanine nucleotide exchange factors (GEF)s, which stimulate the exchange of bound GDP by free GTP, and by GTPase-activating proteins (GAP)s, which trigger the hydrolysis of GTP to GDP [39]. Interestingly, the highly $[Ca^{2+}]_i$ dependent Rho GEF, Arhgef1, has been shown to influence vascular tone and blood pressure in vascular smooth muscle cells in vivo [74]. Moreover, Arhgap24/ FiLGAP inactivates Rac1 [75] and a mutant form of Arhgap24/FiLGAP has been associated with a familial form of FSGS [76]. Further details of the regulation of the small GTPases in podocytes can be found in an excellent review by Saleem et al. [77]. Altogether, increased $[Ca^{2+}]_i$ levels are associated with small GTPase-induced cytoskeletal rearrangements, which in turn alter podocyte motility.

In summary, the downstream signaling of Ca^{2+} converges on the actin-cytoskeleton, and Ca^{2+} is a critical regulator to mediate the dynamic remodeling of the actin-cytoskeleton and to contribute to the regulation of the podocyte motility (Table 1).

The effect of immunosuppressive agents on the Ca^{2+}-actin-cytoskeleton

Immunosuppressive agents are widely used in the therapy of proteinuric kidney diseases due to their immunotherapeutic or anti-inflammatory therapeutic effects [78]. However, there is growing evidence that these agents may additionally directly target podocytes via the Ca^{2+}-actin-cytoskeleton axis and enhance stability of actin filaments (Fig. 1; Table 2).

Glucocorticoids

For decades, glucocorticoids (GCs) have remained the primary treatment for many glomerular diseases [79]. GCs act predominantly by altering gene expression, but also have secondary non-genomic effects [79]. After binding to a cytoplasmic glucocorticoid receptor (GR), which is expressed in every cell, the complex undergoes nuclear translation to induce transcriptional responses via binding to glucocorticoid response elements. In contrast, non-genomic effects are mediated by binding to GRs located in the cytosol or by direct interaction with the cell membrane [80]. Podocytes have also been shown to express functional glucocorticoid receptors [81–83], and several studies have shown that GCs can change gene expression in podocytes in vitro, demonstrating that podocytes are responsive to GCs, as has been comprehensively summarized by *Broek et al.* [84].

It is well established that GCs can, on one hand, exert significant anti-proteinuric effects by influencing Ca^{2+} signaling: They preserve the structural and functional integrity of the SD by binding and blocking TRPC6 channels [85]. On the other hand, GCs increase actin polymerization and the stability of actin filaments [86, 87]. For example, actin structure and binding molecules have been identified as targets of GCs: They increase gene expression and phosphorylation of nephrin [88, 89], upregulate CD2-associated protein [90], induce olfactomedin-1 expression [91] and promote Krüppel-like factor 15 gene expression, which stabilize the actin cytoskeleton under stress and podocyte injury [92–94]. Furthermore, GCs protect podocytes by stabilizing the expression of α-actinin-4, an actin crosslinking protein that coordinates cytoskeletal organization [95]. Actin regulators are an additional important target group: GC treatment after exposure to proteinuria-inducing agents reduced Rac1

Table 1 Comparison of the specific alterations in various pathways/targets in relation to the effect on podocytes (injury or protection)

Signal pathway/protein	*Function in podocyte protection*	*Function in podocyte injury*
TRPC6	Balance between TRPC5 and TRPC6	Overactivation e.g. through gain-of-function mutation
Calcium-activated potassium channels (KCa1.1)		Activation enhances Ca^{2+} influx through TRPC6 activation
Store-operated channels (SOCs)		Activation triggers actin remodeling
Ionotropic NMDA receptor and purinergic P2X receptor		Activation enhances Ca^{2+} influx
Calcineurin		Facilitates cathepsin L-mediated degradation of synaptopodin
Calmodulin	Ca^{2+}-dependent inactivation of the TRPC6 channel	Through Ca^{2+}/calmodulin–dependent kinase (CaMK4) activation of Rac1 and suppression of synaptopodin and nephrin
Synaptopodin	Prevention of synaptopodin from degradation	Cathepsin L-mediated degradation of synaptopodin through calcineurin
Small GTPases	Activation of RhoA promotes stable actin cables; balance between RhoA and Rac1 activation	Overactivation of Rac1 promotes cell motility
Arhgap24/ FiLGAP	Inactivating Rac1	Mutant form of Arhgap24/FiLGAP is associated with a familial form of FSGS
Nephrin	Major component of the SD, is linked to the actin cytoskeleton and regulates it via adaptor proteins	Mutations in nephrin affect the actin cytoskeleton
Myosin1e		Pathological variants in myosin1e are associated also with FSGS

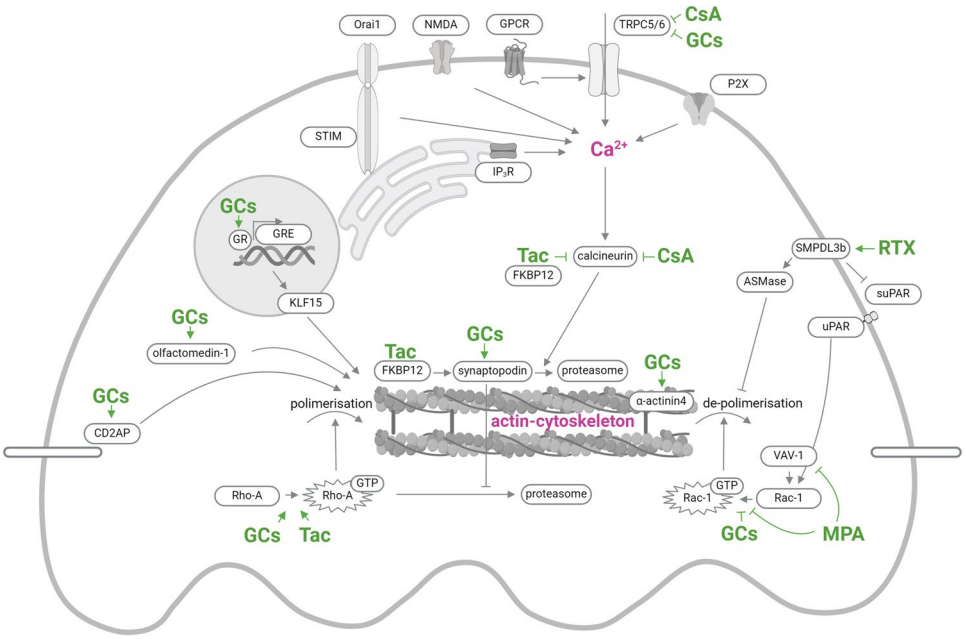

Fig. 1 Direct effects of GCs, CsA, Tac, MMF, and RTX on ion channels, actin-cytoskeleton components and regulators in podocytes. Created in BioRender.com. *CsA* cyclosporine A, *GCs* glucocorticoids, *RTX* rituximab, *MPA* mycophenolic acid, *Tac* tacrolimus

over-activity and podocyte motility [96, 97], increased the stability of actin filaments by stabile synaptopodin expression, and increased RhoA activity [98, 99]. The effects of GCs-induced changes on the actin-cytoskeleton lead to its increased stability and enhanced protection of podocytes against damage (Fig. 2A).

Cyclosporine A

Cyclosporine A (CsA) is a calcineurin inhibitor that blocks the activation of NFAT in T cells preventing the transcription of cytokines such as Il-2 and Il-4. Recent studies demonstrated that its therapeutic effects extend

Table 2 Summary of the specific molecular mechanisms of podocyte protection induced by each of the various drugs

Immunosuppressive agents	*Effect on podocytes*
Glucocorticoids	Blocking TRPC6 signaling
	Activation of the nephrin gene promoter and support of nephrin`s phosphorylation
	Upregulation of CD2AP adaptor protein
	Stabilizing the expression of actin crosslinking protein, α-actinin-4
	Prevention of synaptopodin's degradation
	Diminishing Rac1 overactivity and enhancing RhoA activity
	Promoting Krüppel-like factor 15 gene expression
	Inducing olfactomedin-1 expression
Cyclosporine A	Preventing synaptopodin's dephosphorylation and degradation
	Decreasing TRPC6 gene expression
Tacrolimus	Preventing the degradation of synaptopodin
	Increasing the activation of RhoA
Mycophenolate-mofetil	Reducing podocyte's $[Ca^{2+}]_i$
	Stabilizing stress fiber formation
	Reducing the expression levels of Vav1 and Rac1 activity
Rituximab	Preventing acid-sphingomyelinase down-regulation
	Upregulation of ASMase expression and activity
	Binding soluble urokinase-type plasminogen activator

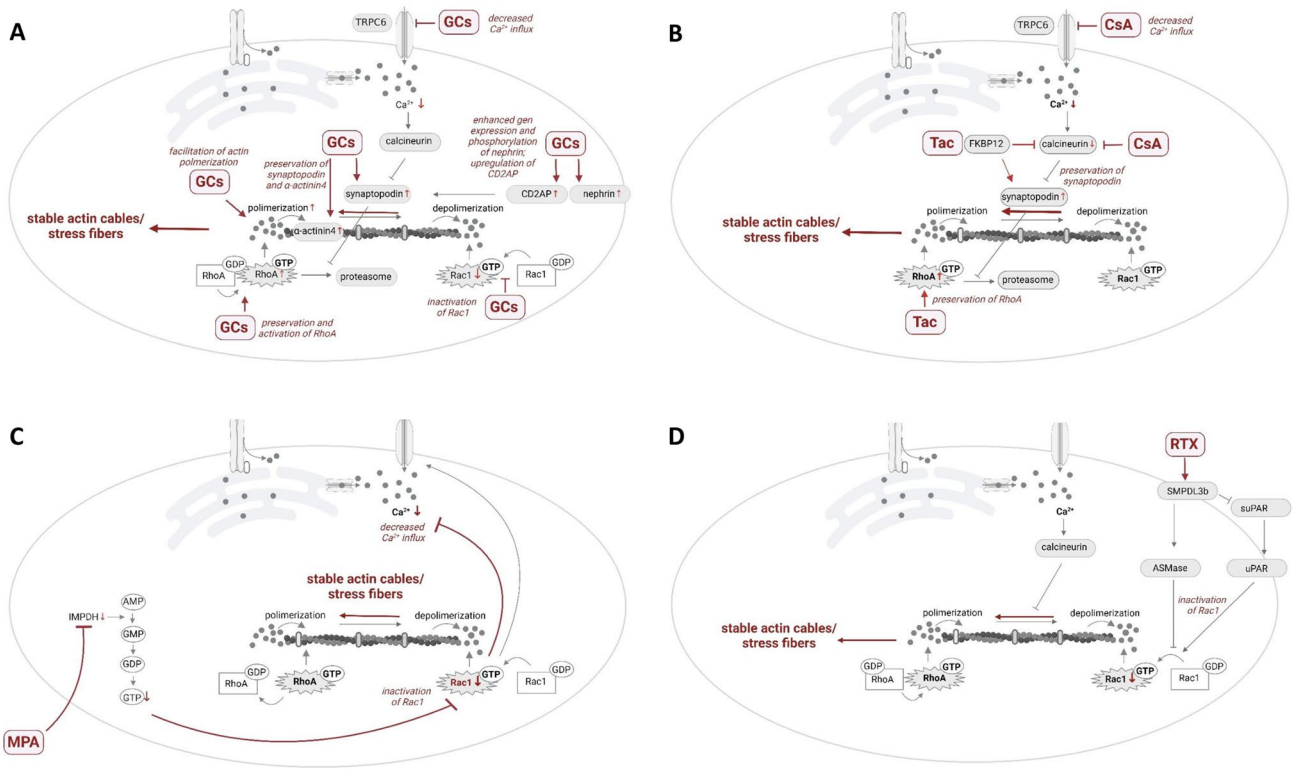

Fig. 2 Direct effects of GCs, CsA, Tac, MMF, and RTX on ion channels, actin-cytoskeleton components, and regulators in podocytes. Panels focus on the relevant mechanisms of action of each of the drugs: GCs (**A**), CsA (**B**), Tac (**B**), MMF (**C**), and RTX (**D**). Created in BioRender.com. *CsA* cyclosporine A, *GCs* glucocorticoids, *RTX* rituximab, *MPA* mycophenolic acid, *Tac* tacrolimus

beyond immune cells. Calcineurin dephosphorylates the actin-associated protein and Rho-GTPase-regulator synaptopodin in podocytes and increases its susceptibility to cathepsin L-mediated degradation. CsA prevents the dephosphorylation of synaptopodin by calcineurin, thereby maintaining the phosphorylation-dependent interaction of synaptopodin with −14–3-3 beta [65] and preventing the degradation of synaptopodin. Therefore, CsA stabilizes the stress fiber formation making podocytes more resistant to the development of proteinuria. Similarly, inhibition of Ca^{2+} channels by CsA as well as the cathepsin L inhibitor reduced FPE, which was induced by the treatment of isolated glomeruli with protamine-sulfate. This suggests that Ca^{2+} signaling through calcineurin- and cathepsin L-dependent cleavage of synaptopodin is essential in the initial stages of glomerular injury and can serve as a podocyte-specific therapeutic target [100]. Accordingly, pre-incubation of mouse podocytes with CsA during treatment with puromycin aminonucleoside increased the expression of synaptopodin and restored the organization of the actin-cytoskeleton [101]. Additionally, CsA decreases TRPC6 expression in doxorubicin nephropathy [102]. These findings (Fig. 2B) clearly demonstrate that the treatment response of CsA in proteinuric kidney diseases extends beyond its immunosuppressive effect and reveals the podocyte as the therapeutic target of choice for glomerular diseases [103].

Tacrolimus

Tacrolimus (Tac) is another calcineurin inhibitor, that exerts the same effect on calcineurin and downstream inhibition of NFAT activation in T-cells though it lacks clear structural similarity to CsA [61]. Its activity is mediated through the FK506 binding protein 1A (FKBP12). Importantly, FKBP12 is localized to the actin-cytoskeleton and associates with F-actin [104]. FKBP12 knockdown in podocytes leads to alterations in the structure of F-actin, highlighting the importance of FKBP12 expression and function in maintaining the integrity of the actin cytoskeleton [104]. Furthermore, Tac could restore the expression of FKBP12 and enhance the interactions between FKBP12 and synaptopodin to ameliorate FPE in injured podocytes [104]. The stabilizing effect of Tac on the synaptopodin expression is strongly supported by in vitro and in vivo studies [101, 105]. Additionally, Wu et al. investigated the calcineurin-related Ca^{2+}-actin-cytoskeleton axis and found that it was highly up-regulated in a model of depleted miR-30 and impressively blocked by Tac [106]. Tac also activates the actin-regulator RhoA [107]. Altogether, Tac seems to be able to stabilize stress fibers in podocytes mostly in a Ca^{2+}-calcineurin dependent manner, but also directly via actin-cytoskeleton (Fig. 2B).

Mycophenolate mofetil

The prodrug mycophenolate mofetil (MMF) is activated by esterases in the gut and blood to release the pharmacologically active drug moiety, mycophenolic acid (MPA), which functions as a selective non-competitive inhibitor of inosine 5′-monophosphate dehydrogenase. This is the rate-limiting enzyme in the de novo purine synthesis pathway and thereby impairs lymphocyte proliferation [108]. Importantly, direct effects on non-immune cells, including glomerular cells such as mesangial cells and podocytes, have been attributed to MMF [109]. In a lupus model, MMF reduced expression levels of Vav1 and Rac1 activity, which ameliorated stress fiber formation in podocytes [107]. This finding is further supported by our in vitro experiments, which were designed to exclude the effect of immune cells and study MPA's direct effect on podocytes: We detected a significant change in 350 genes within 24 h of MPA treatment [110], and these genes were partially related to Ca^{2+}-signaling and actin-cytoskeleton regulation. As validation, we showed that MPA treatment was able to completely block the increase in $[Ca^{2+}]_i$ induced by bovine serum albumin and subsequently stabilize the stress fiber formation. Additionally, we demonstrated in a nephrotoxic serum nephritis model in vivo an improvement of proteinuria treatment and identified a significant reduction in podocyte's $[Ca^{2+}]_i$ after MMF treatment as possible underlying mechanisms. This change resulted in a tendency towards structural stabilization of podocyte foot processes [111]. Together, these data suggest a relevant effect of MPA to directly stabilize stress fibers in podocytes (Fig. 2C).

Rituximab

Rituximab (RTX) is a B-cell depleting chimeric monoclonal IgG1 antibody targeting the CD20 receptor. B-cell destruction is mediated by the Fcγ immunoglobulin receptor, complement activation and trigger of apoptosis [112]. RTX has been shown to be effective in podocytopathies by the depletion of B-cells [113]. RTX also possesses other B-cell-independent effects: By targeting sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) in podocyte lipid rafts, RTX regulates acid-sphingomyelinase activity and stabilizes the podocyte actin-cytoskeleton [114]. The inhibition of stress fibers formation in podocytes, following incubation with sera of patients with recurrent FSGS after transplantation, was blocked by treatment with RTX. This response and podocyte viability were dependent on SMPDL-3b expression in vitro, as the knockdown of SMPDL-3b in podocytes abrogated these effects. Furthermore, SMPDL-3b

has been shown to increase the stability of the cytoskeleton by binding soluble urokinase-type plasminogen activator receptor with subsequent Rac1 inhibition [115]. No data are currently available on the direct effects of the humanized, and therefore less immunogenic, anti-CD20 antibodies, ofatumumab and obinutuzumab, or the anti-CD38 antibody daratumumab [116]. Altogether, RTX seems to possess a relevant direct effect on podocytes. However, few weeks after administration, RTX is likely no longer present in the circulation, making the duration and relevance of its direct effect on podocytes potentially less pronounced compared to other immunosuppressive agents (Fig. 2D).

Cyclophosphamide

To date, no data are available about a direct beneficial effect of cyclophosphamide on podocytes. Children with genetic proteinuric diseases also do not respond to cyclophosphamide therapy [117].

Immunosuppressive therapy in genetic nephrotic syndrome

The non-immunologic effects of the immunosuppressive drugs discussed above raise the question, whether patients with genetic steroid resistant nephrotic syndrome (SRNS) could benefit from an immunosuppressive therapy or not. In terms of CsA, there are some multicenter studies offering sparse data. In a large retrospective multicenter study of CsA treatment, none of the patients with genetic nephrotic syndrome experienced a complete remission and only two (17%) achieved a partial response [66]. In another multicenter study, 3% of patients with genetic SRNS experienced a complete remission, and 16% of patients with genetic SRNS showed a partial remission after CsA therapy [118]. The PodoNet Consortium has obtained similar results: Of 74 patients with proven genetic mutations, two patients had complete and 12 partial remissions. Thus, in this series, a total of 14/74 (19%) patients with genetic SRNS had a limited response to immunosuppression with CsA and prednisolone pulses [117]. Based on some case reports, children with *WT-1* mutation might constitute a particular group, which could show favorable response to an intensified therapy with CsA and GCs [119, 120]. Interestingly, the authors discuss the potential role of the direct effect on podocytes. In summary, most patients with genetic nephrotic syndrome do not benefit from an immunosuppressive therapy and show significantly lower response rates compared with non-genetic patients. This could be due to a direct effect stabilizing actin-binding proteins, which is missing if these proteins themselves are mutated, leading to drug-resistant damage of the actin-cytoskeleton. As genetic podocytopathies are caused by mutations in multiple distinct proteins, it is not unexpected that their response to therapies differs. The extent of nephrotoxic effect (in case of CsA and Tac) and the subsequent reduction of plasma flow is also difficult to predict. Therefore, it is generally not recommended to administer immunosuppressive drugs in genetic forms of NS. However, in the future, it could be part of an individualized therapeutic concept for patients with genetic NS.

Conclusion

Immunosuppressive drugs commonly used to treat proteinuric kidney diseases exert direct effects on ion channels, actin-cytoskeleton components, and regulators (Fig. 1) in podocytes. This explains, in conjunction with their effects on immune cells, their clinical effectiveness. In the adaptation to damage, a strict regulation of the Ca^{2+}-actin-cytoskeleton axis is crucial for the survival of podocytes. Therefore, utilizing the demonstrated direct effects of GCs, CsA, Tac, MMF, and RTX is an essential part in choosing an individual therapeutic approach. The question, to what extent the non-immune, direct drug actions contribute to sustained effects of immunosuppression, will require continued studies in the future.

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Declarations

Competing interests The authors declare no competing interests.

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