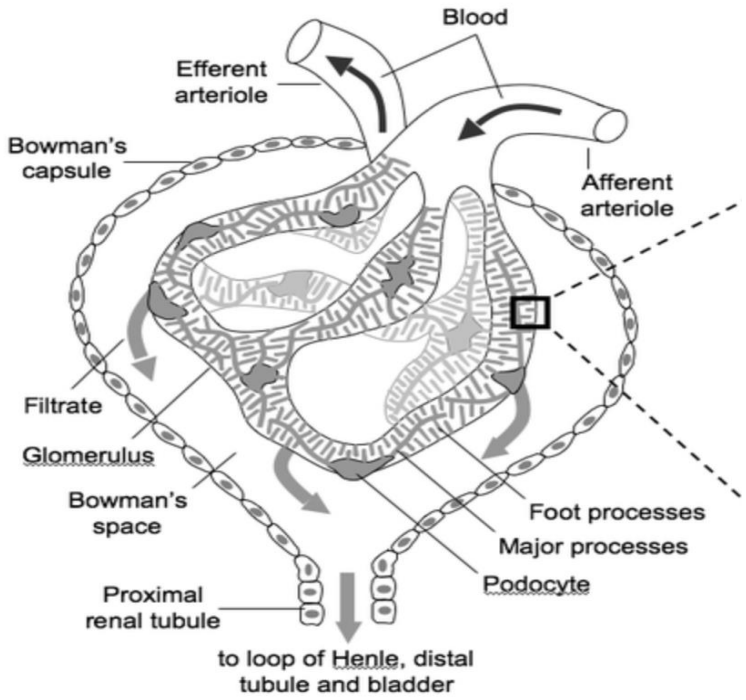
PODOCYTO-PATHIES

M.Hakemi, M.D.
Nephrology Ward,
Shariati Hospital
1400-04-10



Orchid Pharmed

NANO ALVAND

WEBINAR

Role of CNIs in the treatment of Glomerulonephritis

Speaker (Moderator) (CNIs and podocytes)

Dr.M.Hakemi 10:00 - 10:20

- Nephrologist

Speaker (CNIs in the treatment of Lupus nephritis)

Dr.T.Soleimanian 10:20 - 10:40

- Nephrologist

Speaker (CNIs in the treatment of IgA nephropathy)

Dr.F.Yaghoubi 10:40 - 11:00

- Nephrologist

Speaker (CNIs in the treatment of MCD/FSGS)

Dr.F.Tavakoli 11:00 - 11:20

- Nephrologist

Speaker (CNIs in the treatment of MGN)

Dr.E.Abdollahpour 11:20 - 11:40

- Nephrologist

Q&A 11:40 - 12:00

همراه با امتیاز بازآموزی

Jul 1 Thursday

تیر ۱۰

2021

10:00 -12:00 (IRST)

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Outline

1- Podocyte structure and function

2- Podocyte injury

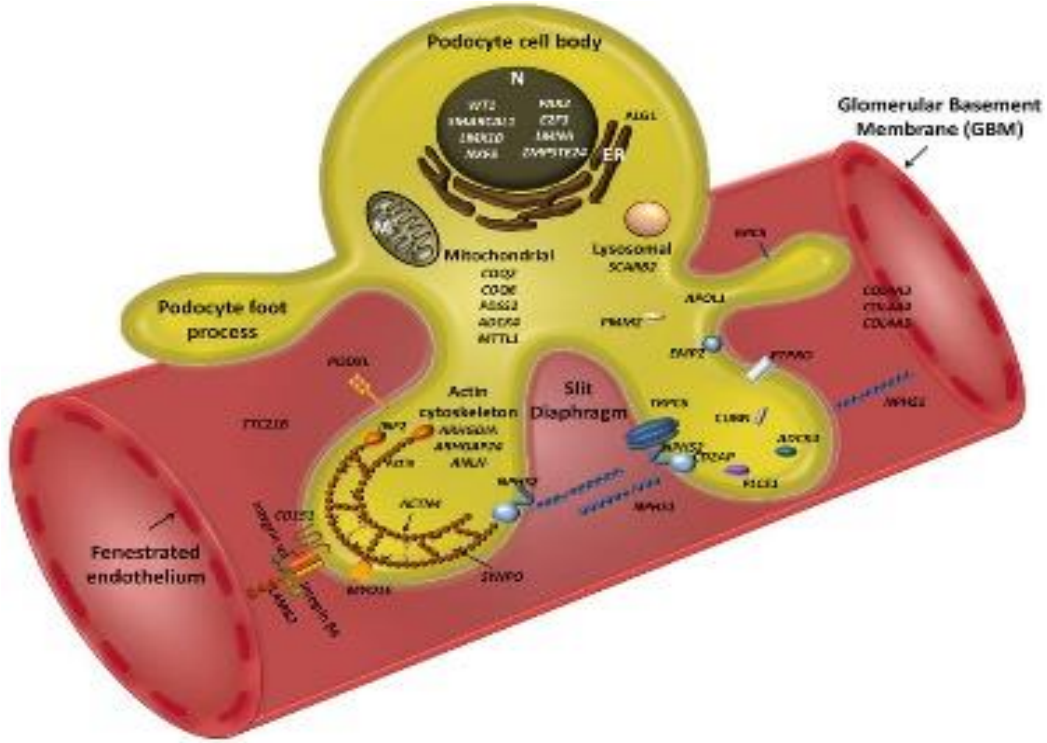
3- New classification of podocytopathies

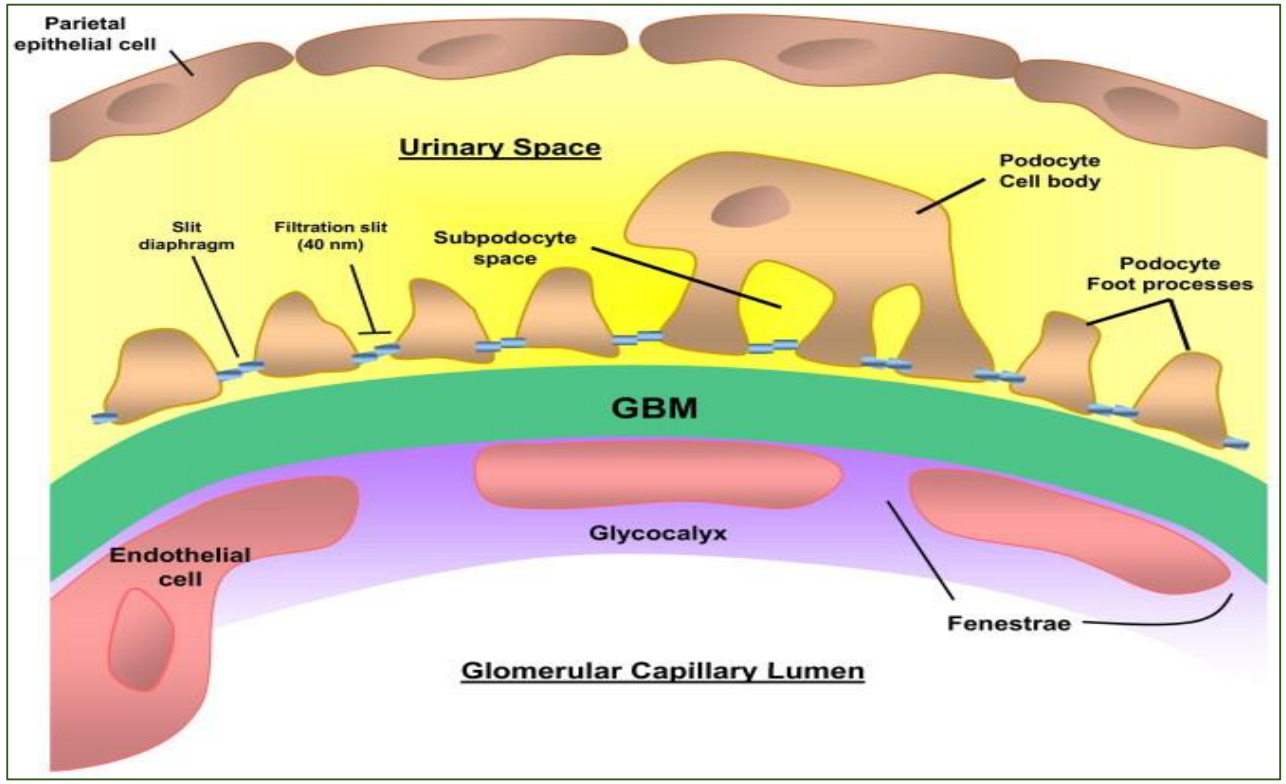
4- Immunologic and non- immunologic treatment

5- Role of CNIs

Normal Structure of the Podocyte

The podocyte consists of a **large cell body** (soma) in the urinary space Connects to the underlying glomerular basement membrane (GBM) of the capillary loop by major cellular extensions from the soma. Extensions terminate as **foot processes** on the GBM that interdigitate with those from adjacent podocytes. Podocyte foot processes are anchored to the GBM and between foot processes, the filtration slit is bridged by a 40-nm wide zipper-like slit diaphragm.

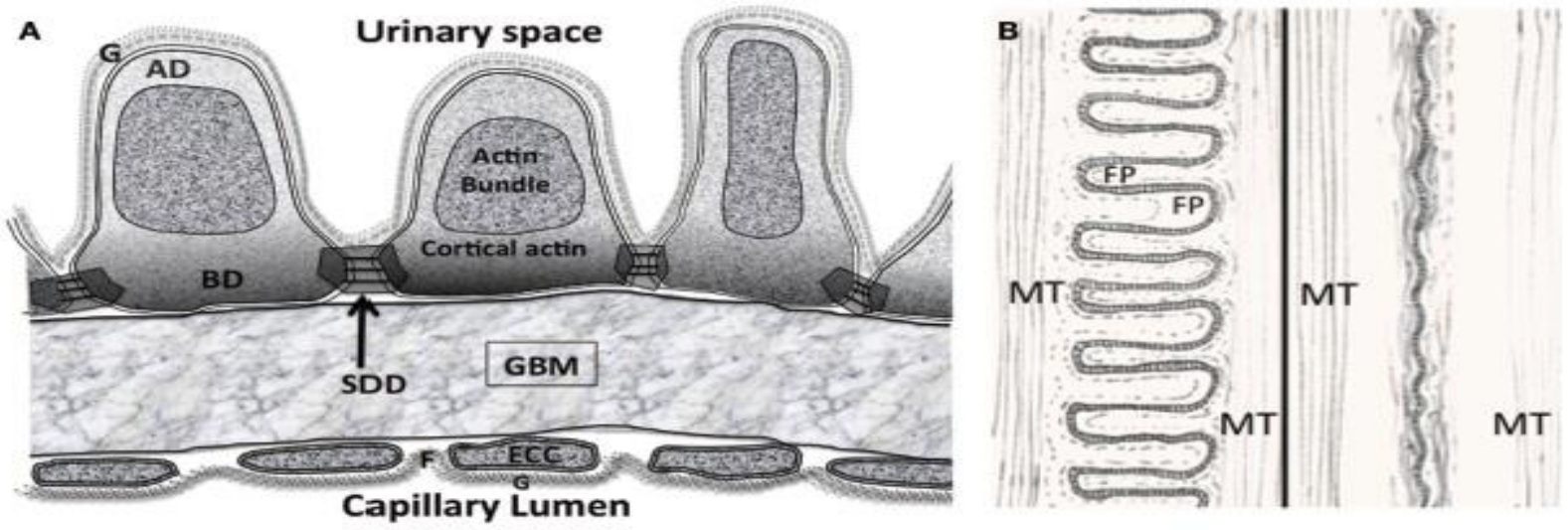




The **podocyte** has an intrinsic part to play in forming and maintaining the glomerular filtration barrier (**GFB**), but the relevance of the various structural components of the GFB in disease is complex.

For instance, the glomerular basement mem-brane (GBM) not only serves as a barrier to protein *in vivo* but also requires the slit diaphragm (**SD**) to prevent albumin passage from the capillary lumen into urinary space.

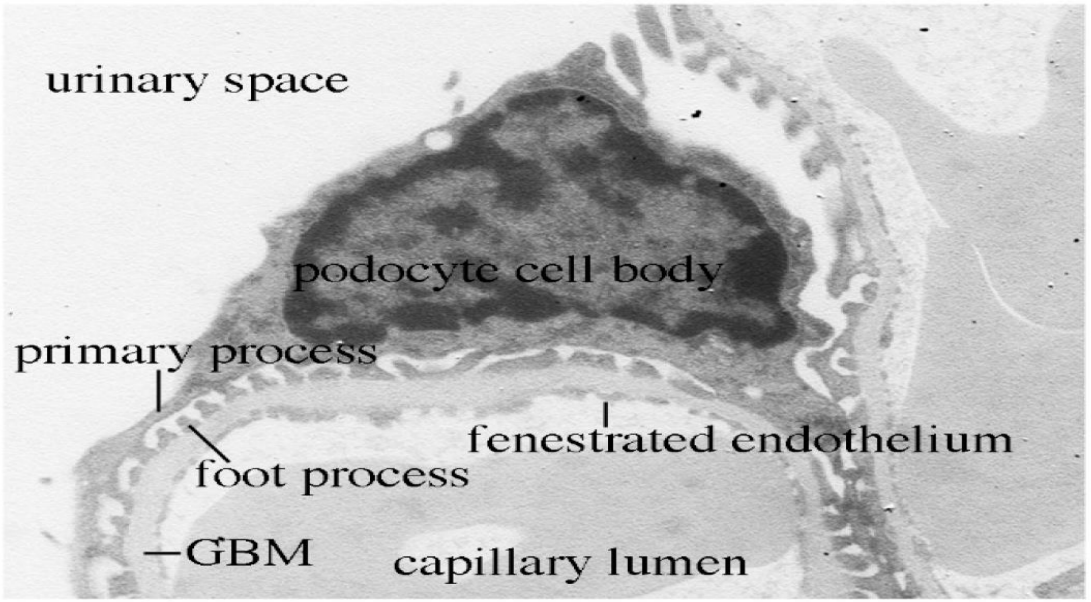
In addition to SDs, the **glycocalyx** overlying the endothelial cells restricts macromolecular passage and ensures that plasma albumin is largely excluded from the GFB.



Podocyte is a visceral epithelial cell which is standing or sitting on top of the capillaries and it is the core component of filtration barrier.

There is a number of molecules located in the slit diaphragm which adjust the shape of podocyte.

In the **podocytopathies**, the orderly structure of the podocytes and the foot process interlinked by SD is lost(foot process effacement).



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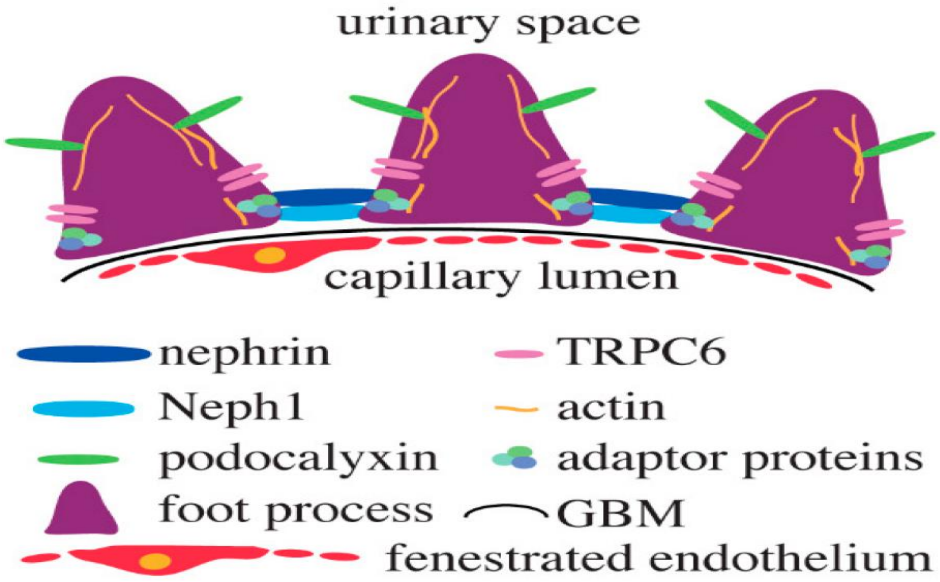

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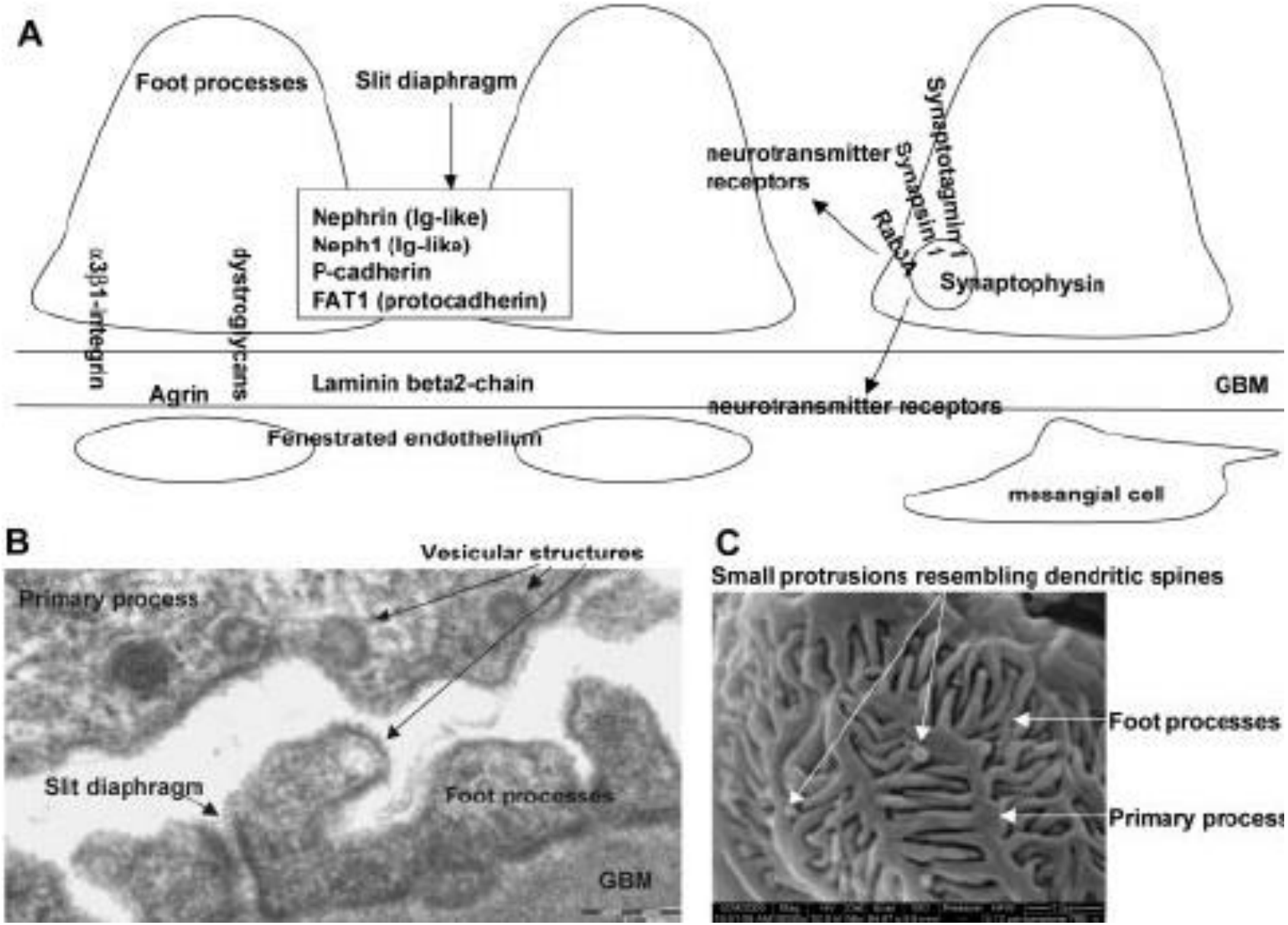
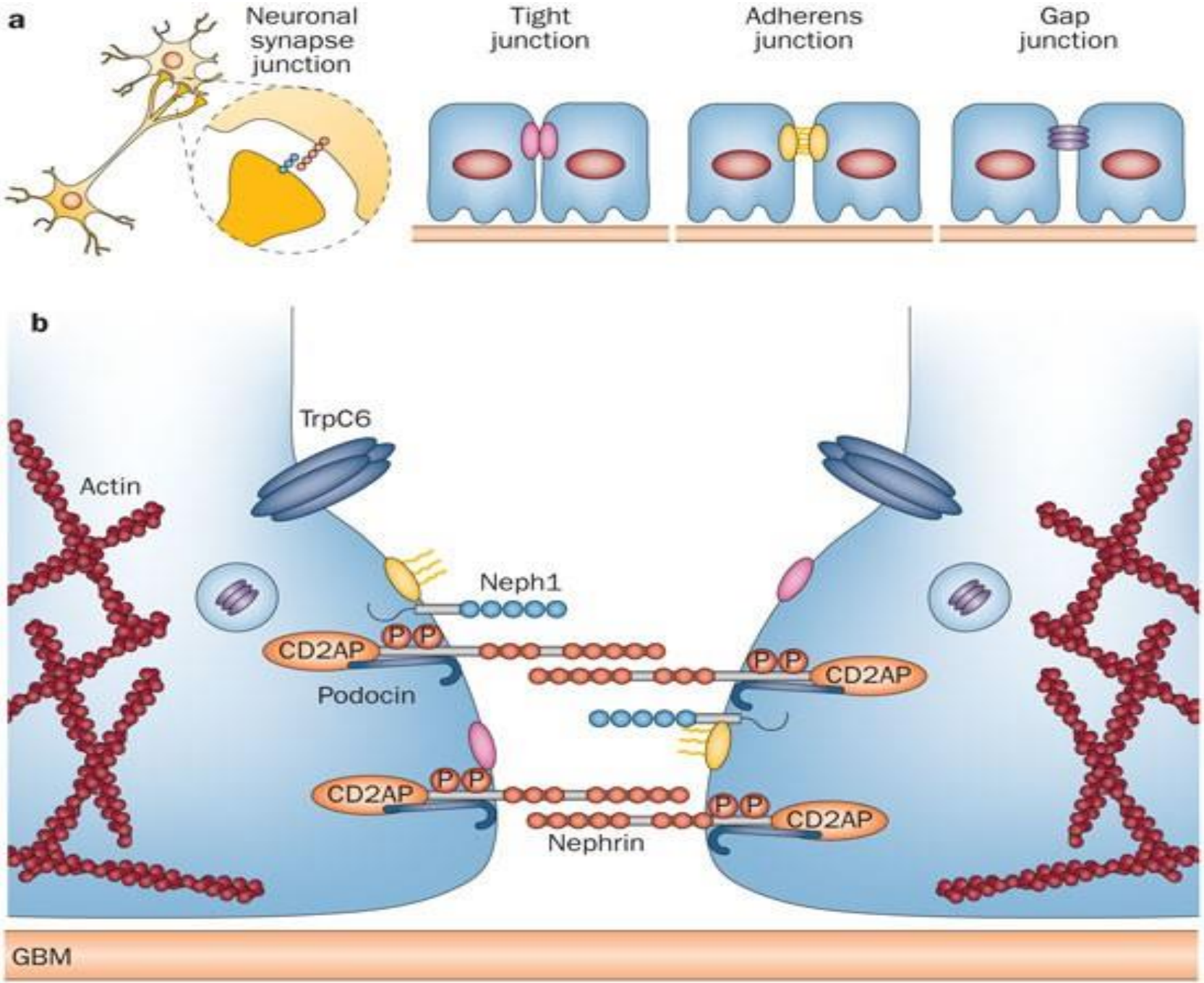

A
Foot processes
Slit diaphragm
Nephrin (Ig-like)
Neph1 (Ig-like)
P-cadherin
FAT1 (protocadherin)
α3β1-integrin
dystroglycans
Agrin
Laminin beta2-chain
Fenestrated endothelium
neurotransmitter receptors
Synaptotagmin 1
Synapsin 1
Rab3A
Synaptophysin
GBM
neurotransmitter receptors
mesangial cell
B
Vesicular structures
Primary process
Slit diaphragm
Foot processes
GBM
C
Small protrusions resembling dendritic spines
Foot processes
Primary process

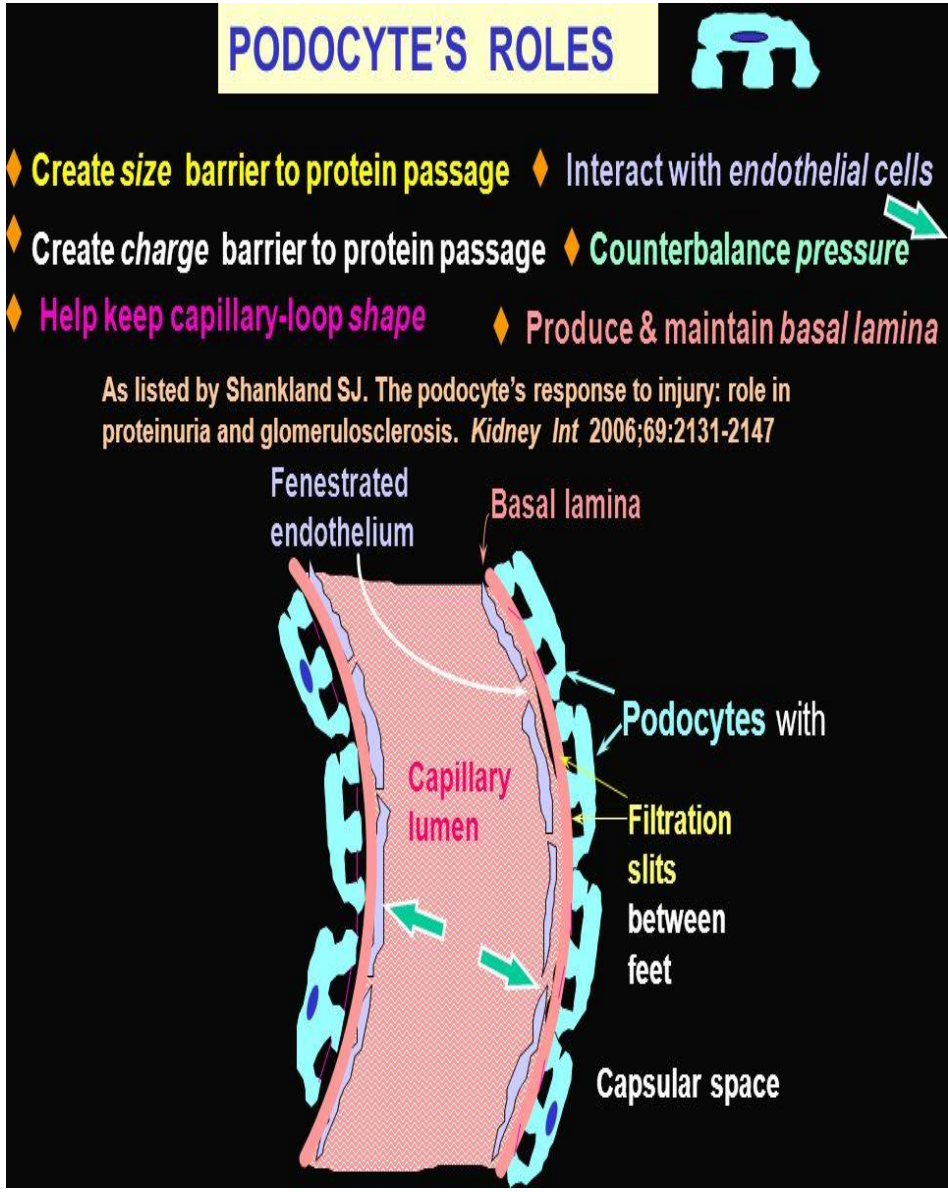

a
Neuronal synapse junction
Tight junction
Adherens junction
Gap junction
b
TrpC6
Actin
Neph1
CD2AP
Podocin
CD2AP
CD2AP
CD2AP
Nephrin
GBM

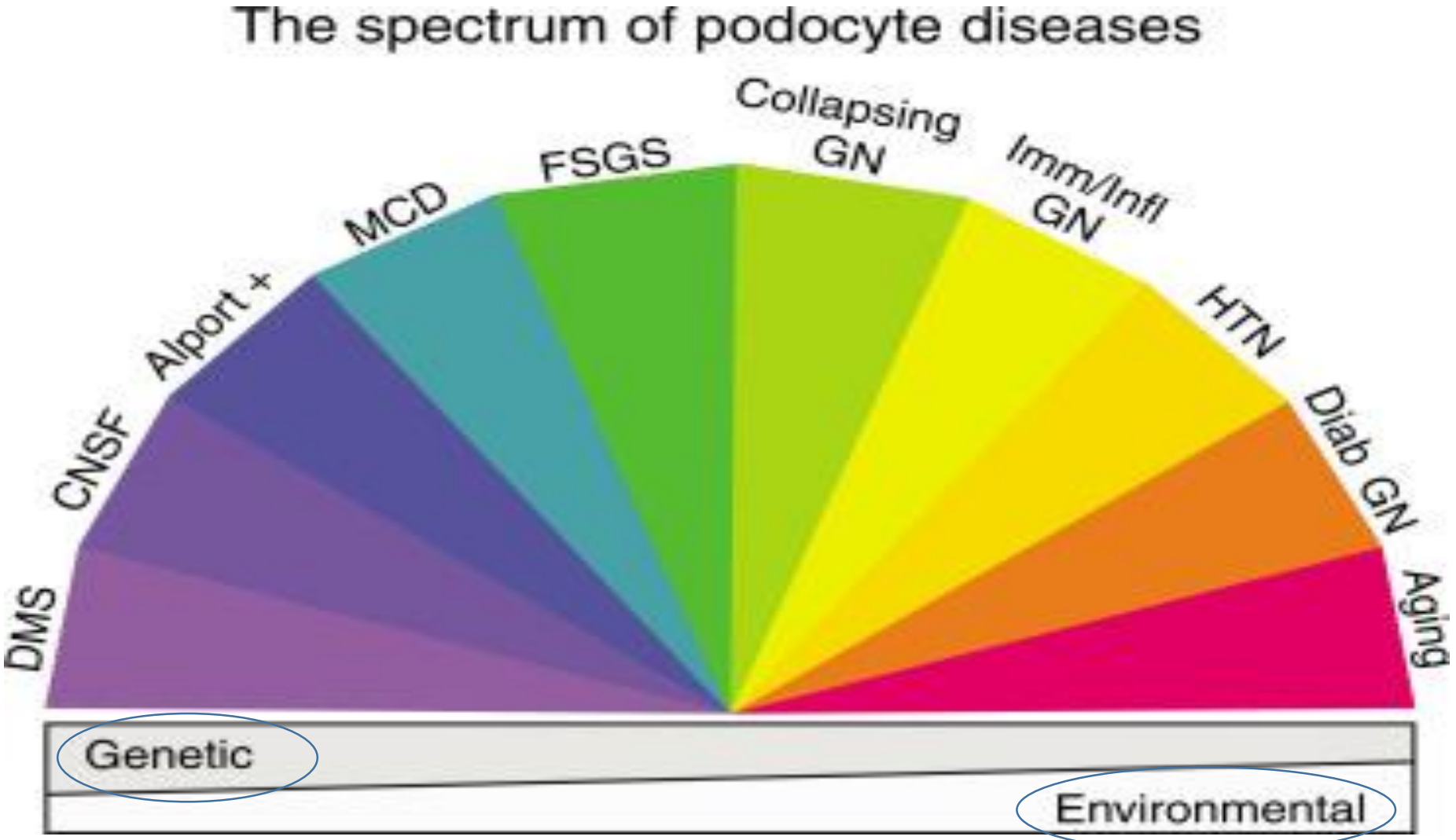
Major Functions of the Podocyte

- Structural support of the capillary loop
- Major component of glomerular filtration barrier (GFB) to proteins
- Synthesis and repair of the GBM
- Production of growth factors (VEGF) traverses the GBM against the flow of glomerular filtration

- Acts on VEGF receptors on glomerular endothelial cells
- Effect is to maintain a healthy fenestrated endothelium
- Platelet-derived growth factors (PDGFs) critical for the development and migration of mesangial cells into the mesangium
- Immunologic function

Podocytes may be a component of the innate immune system. Possibly have a surveillance role for pathogens or abnormal proteins in Bowman space




The spectrum of podocyte diseases
DMS
CNSF
Alport +
MCD
FSGS
Collapsing GN
Imm/Infl GN
HTN
Diab GN
Aging
Genetic
Environmental

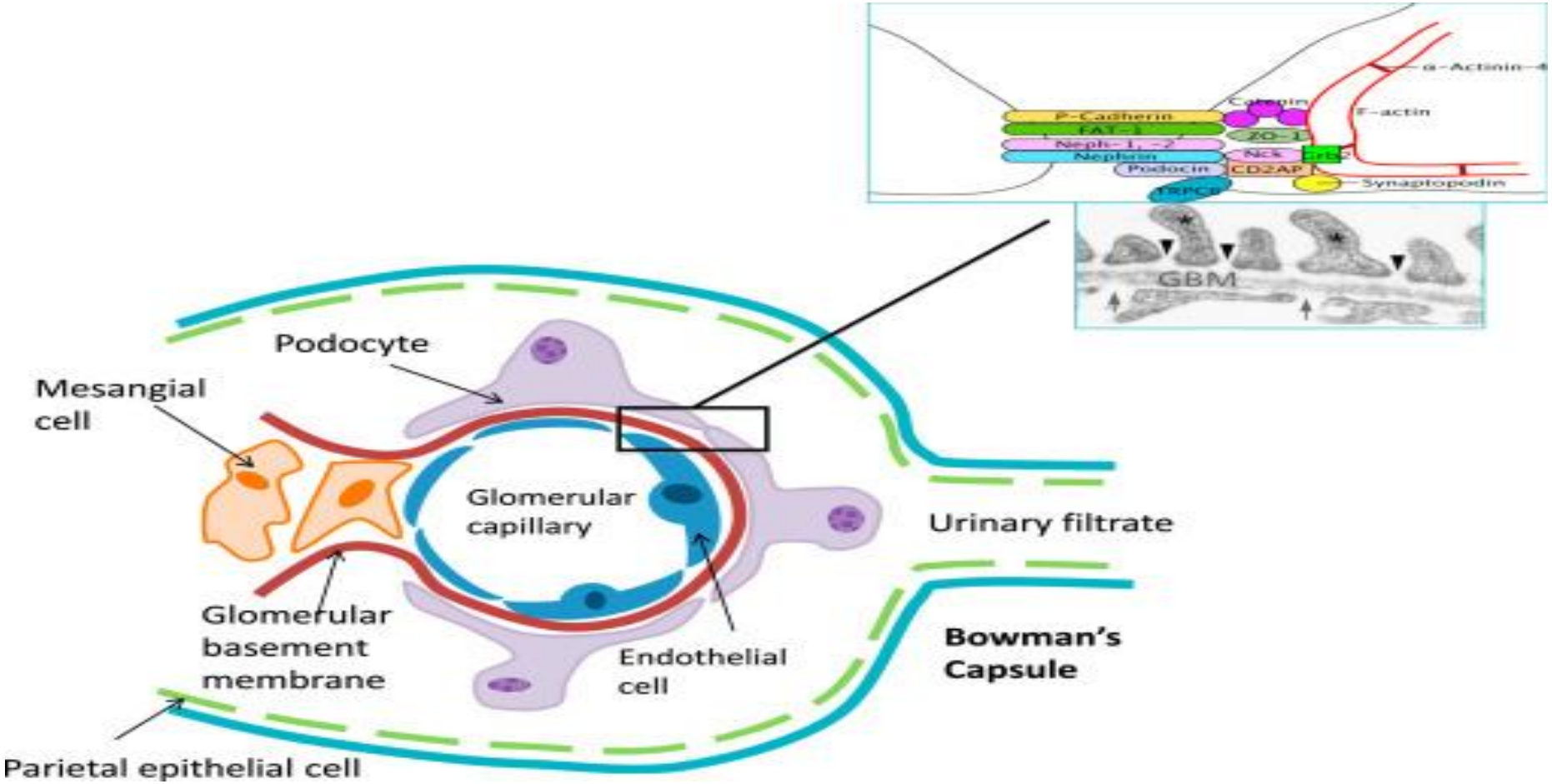
PRIMER

NATURE REVIEWS | DISEASE PRIMERS | Article citation ID: (2020)6:68

Check for updates

Podocytopathies

Jeffrey B. Kopp[1], Hans-Joachim Anders[2], Katalin Susztak[3,4], Manuel A. Podestà[5], Giuseppe Remuzzi[6], Friedhelm Hildebrandt[7,8] and Paola Romagnani[9,10]



Abstract | Podocytopathies are kidney diseases in which direct or indirect podocyte injury drives proteinuria or nephrotic syndrome. In children and young adults, genetic variants in >50 podocyte-expressed genes, syndromal non-podocyte-specific genes and phenocopies with other underlying genetic abnormalities cause podocytopathies associated with steroid-resistant nephrotic syndrome or severe proteinuria. A variety of genetic variants likely contribute to disease development. Among genes with non-Mendelian inheritance, variants in *APOL1* have the largest effect size. In addition to genetic variants, environmental triggers such as immune-related, infection-related, toxic and haemodynamic factors and obesity are also important causes of podocyte injury and frequently combine to cause various degrees of proteinuria in children and adults. Typical manifestations on kidney biopsy are minimal change lesions and focal segmental glomerulosclerosis lesions. Standard treatment for primary podocytopathies manifesting with focal segmental glomerulosclerosis lesions includes glucocorticoids and other immunosuppressive drugs; individuals not responding with a resolution of proteinuria have a poor renal prognosis. Renin–angiotensin system antagonists help to control proteinuria and slow the progression of fibrosis. Symptomatic management may include the use of diuretics, statins, infection prophylaxis and anticoagulation. This Primer discusses a shift in paradigm from patient stratification based on kidney biopsy findings towards personalized management based on clinical, morphological and genetic data as well as pathophysiological understanding.

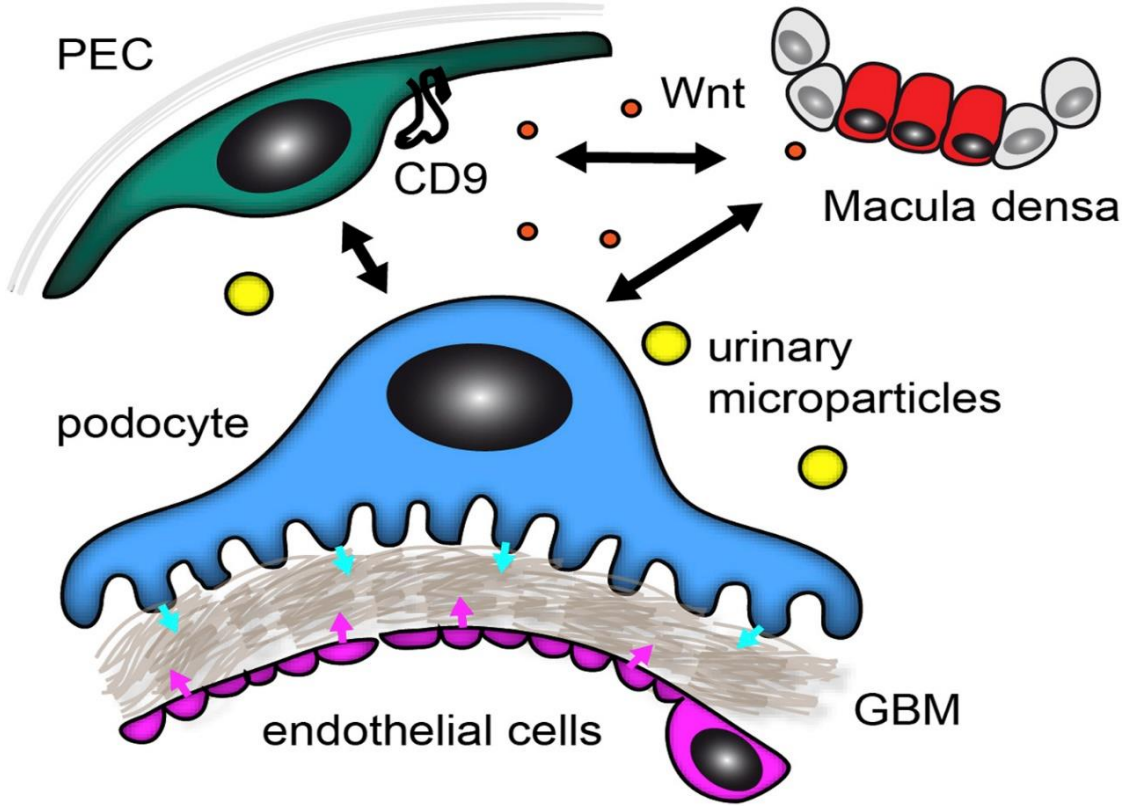
Podocyte injury

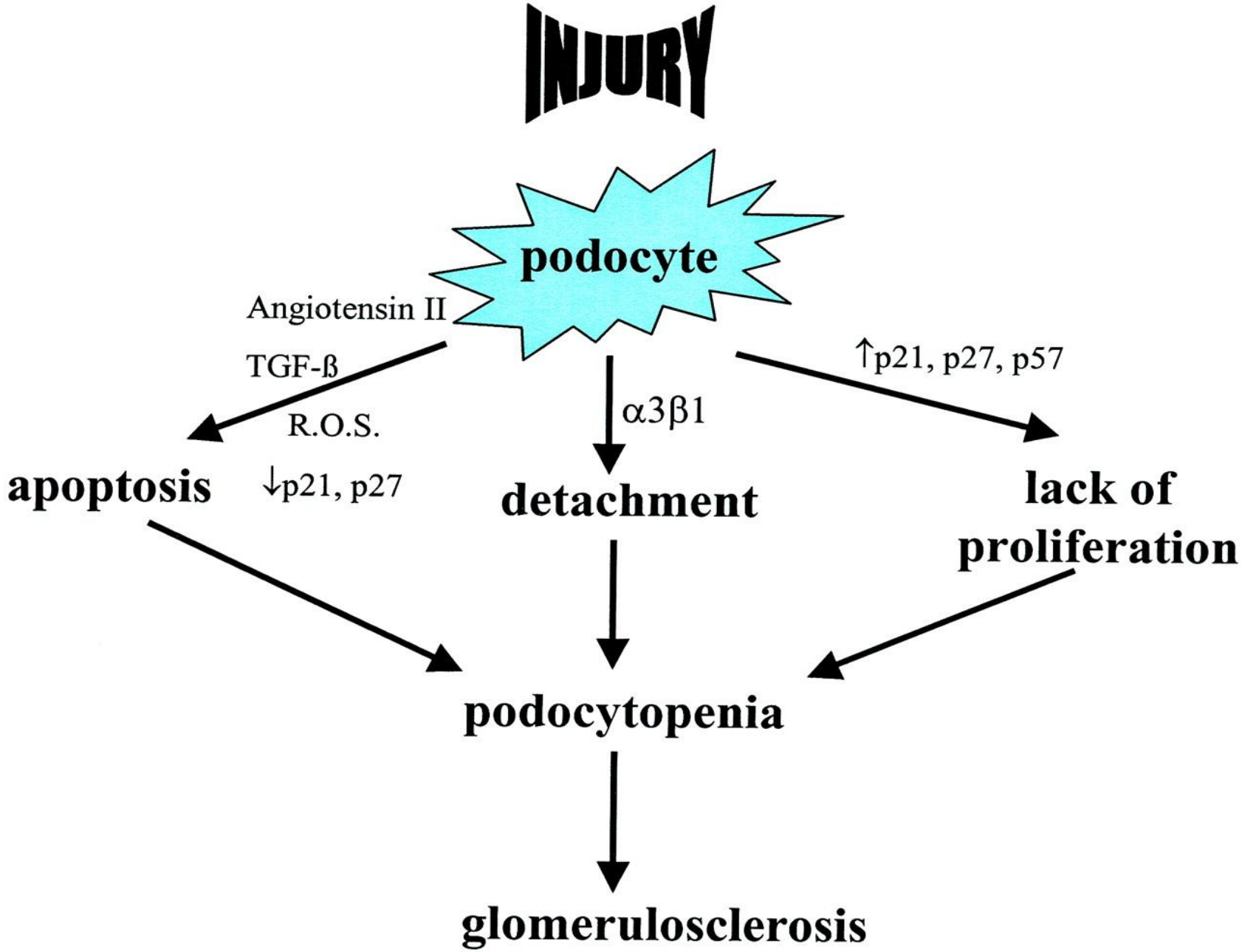
FPE

PC detachment & loss

New PC formation

Although FPE is potentially reversible, podocyte detachment or death implies irreversible podocyte loss.

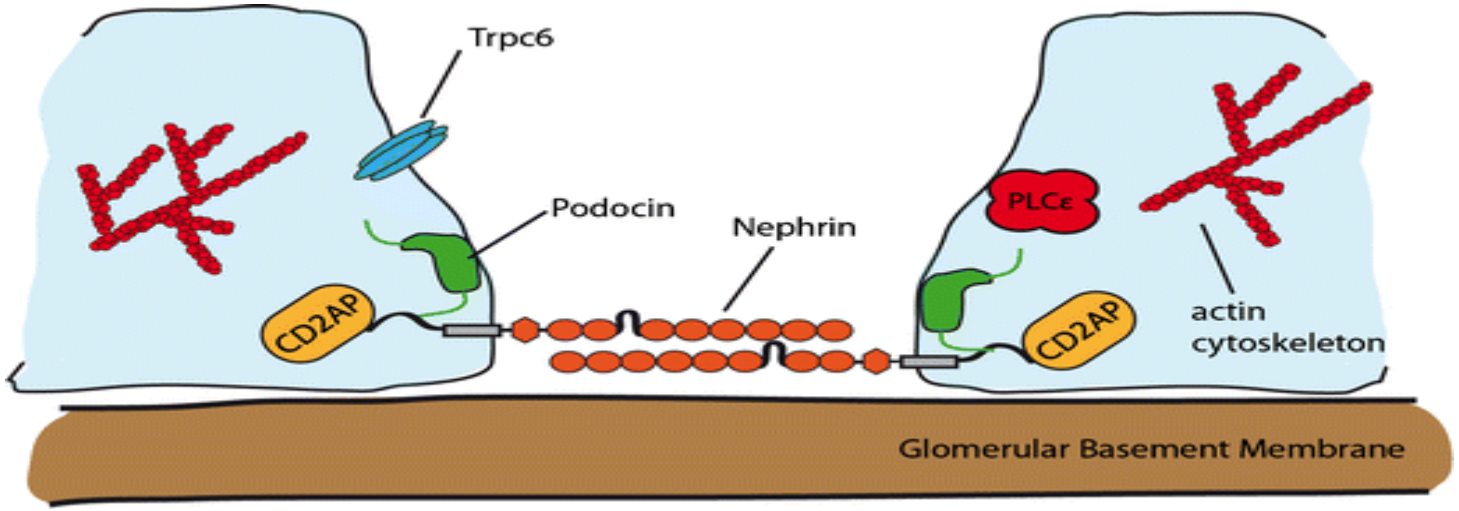


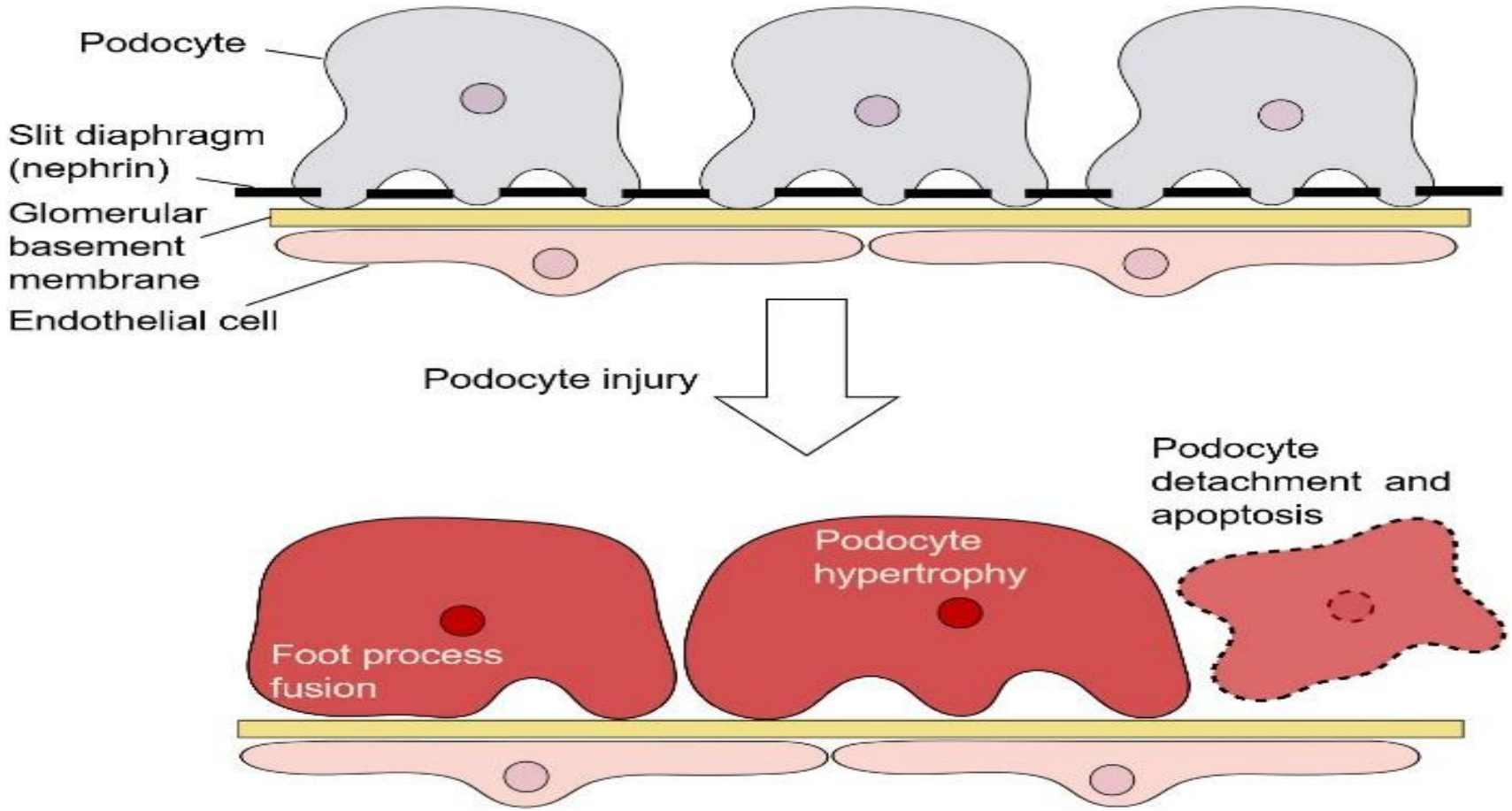

INJURY
podocyte
Angiotensin II
TGF-ß
R.O.S.
↓p21, p27
α3β1
↑p21, p27, p57
apoptosis
detachment
lack of proliferation
podocytopenia
glomerulosclerosis

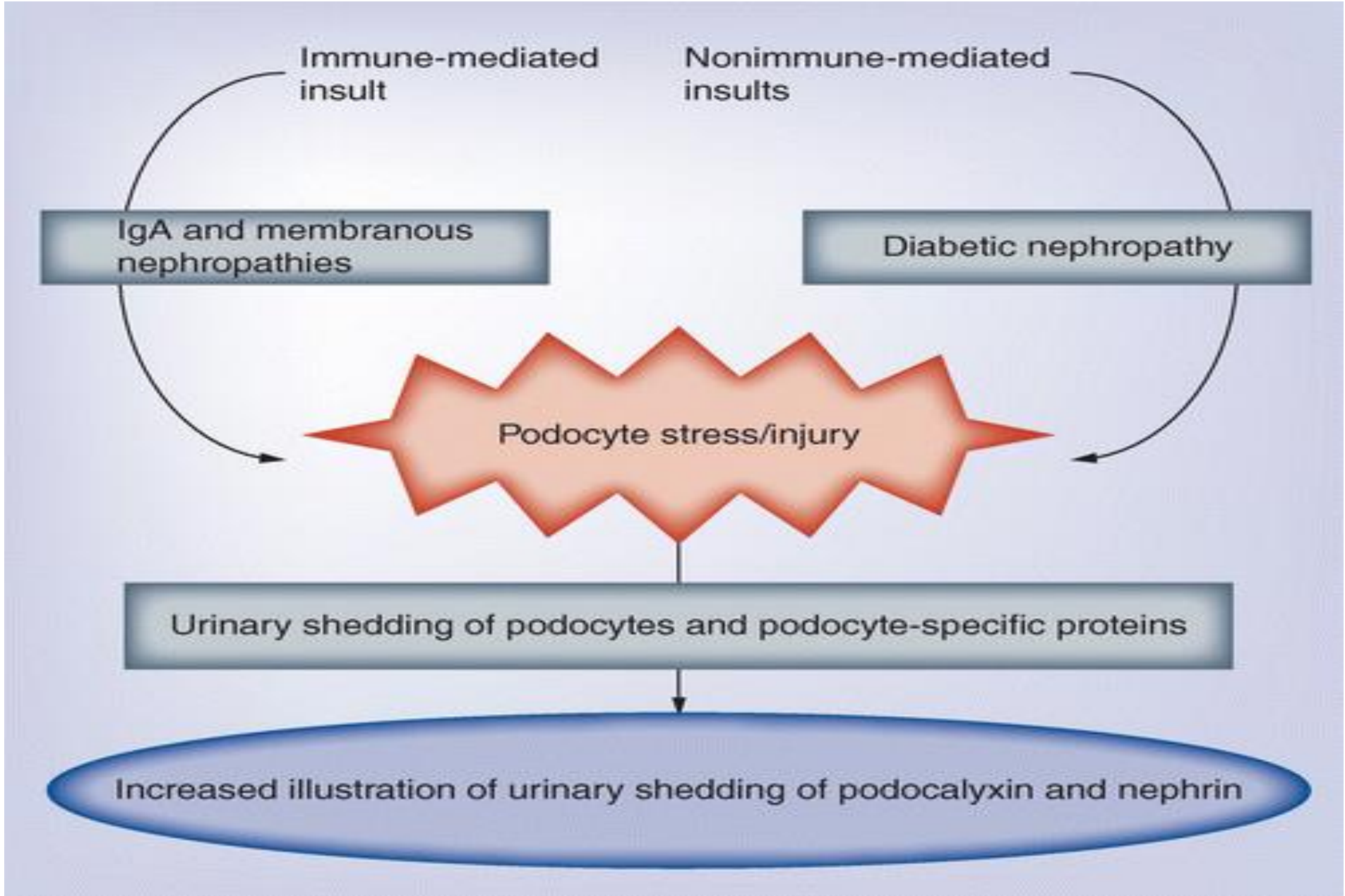
The architectural design of our kidneys is amazingly complex, and culminates in the 3D structure of the glomerular filter.

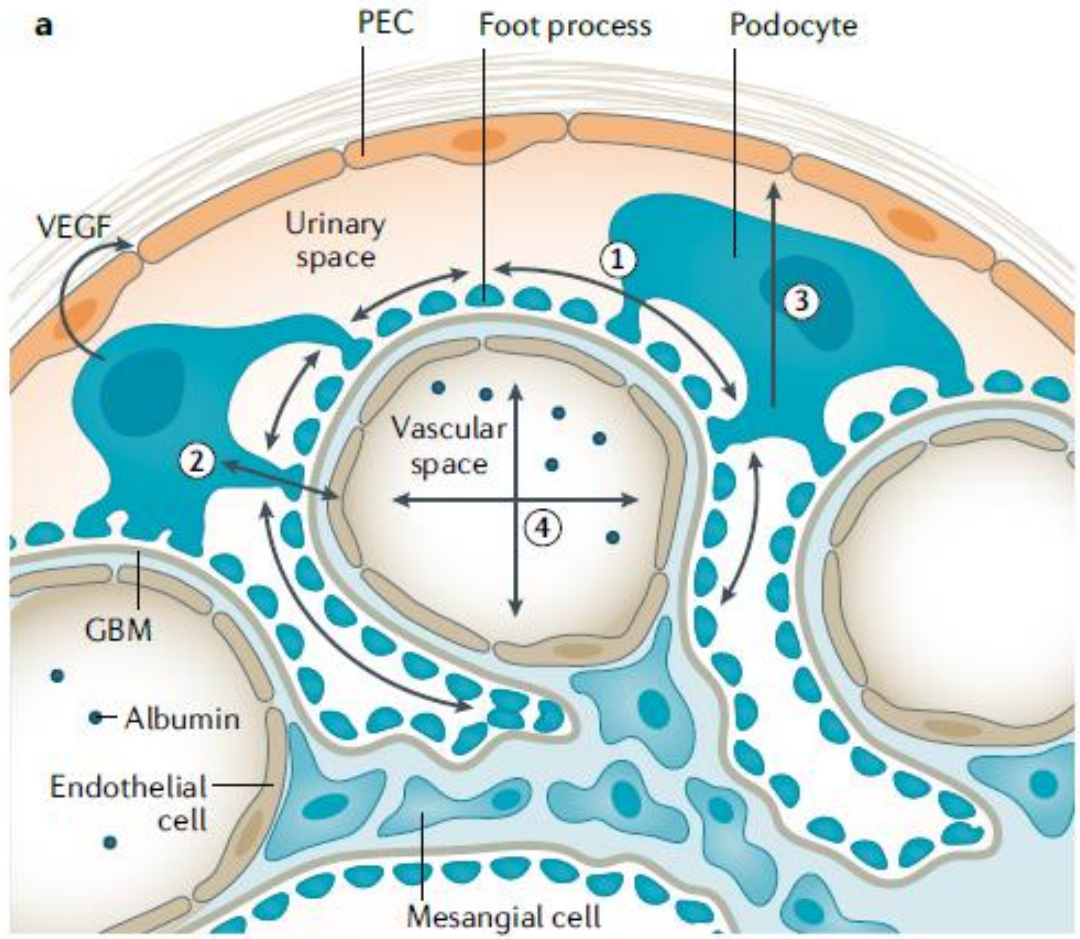
During filtration, plasma passes through a sieve consisting of a fenestrated endothelium and a broad basement membrane before it reaches the most unique part, **the slit diaphragm**, **a specialized type of intercellular junction** that connects neighbouring podocyte foot processes.

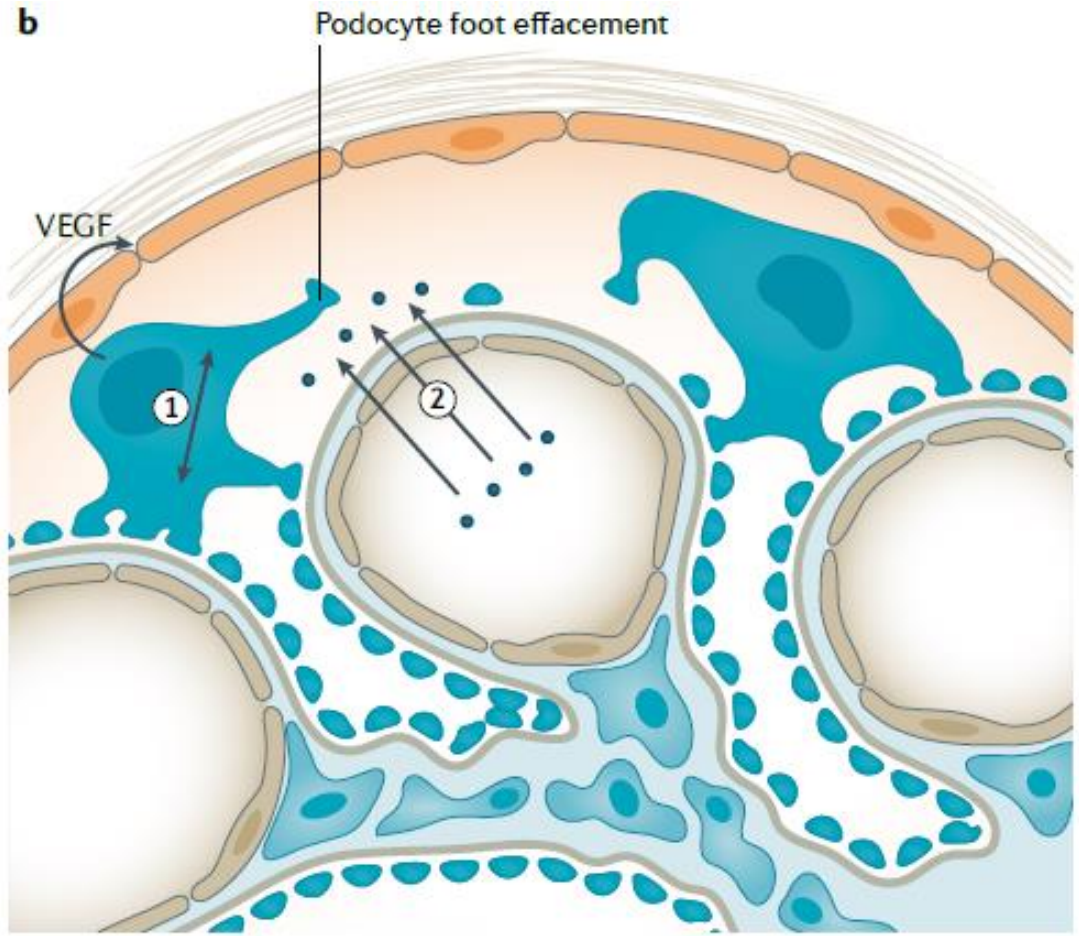
When **podocytes become stressed**, irrespective of the causative stimulus, they undergo foot process effacement and loss of slit diaphragms—two key steps leading to proteinuria. Thus, proteinuria is the unifying denominator of a broad spectrum of podocytopathies.

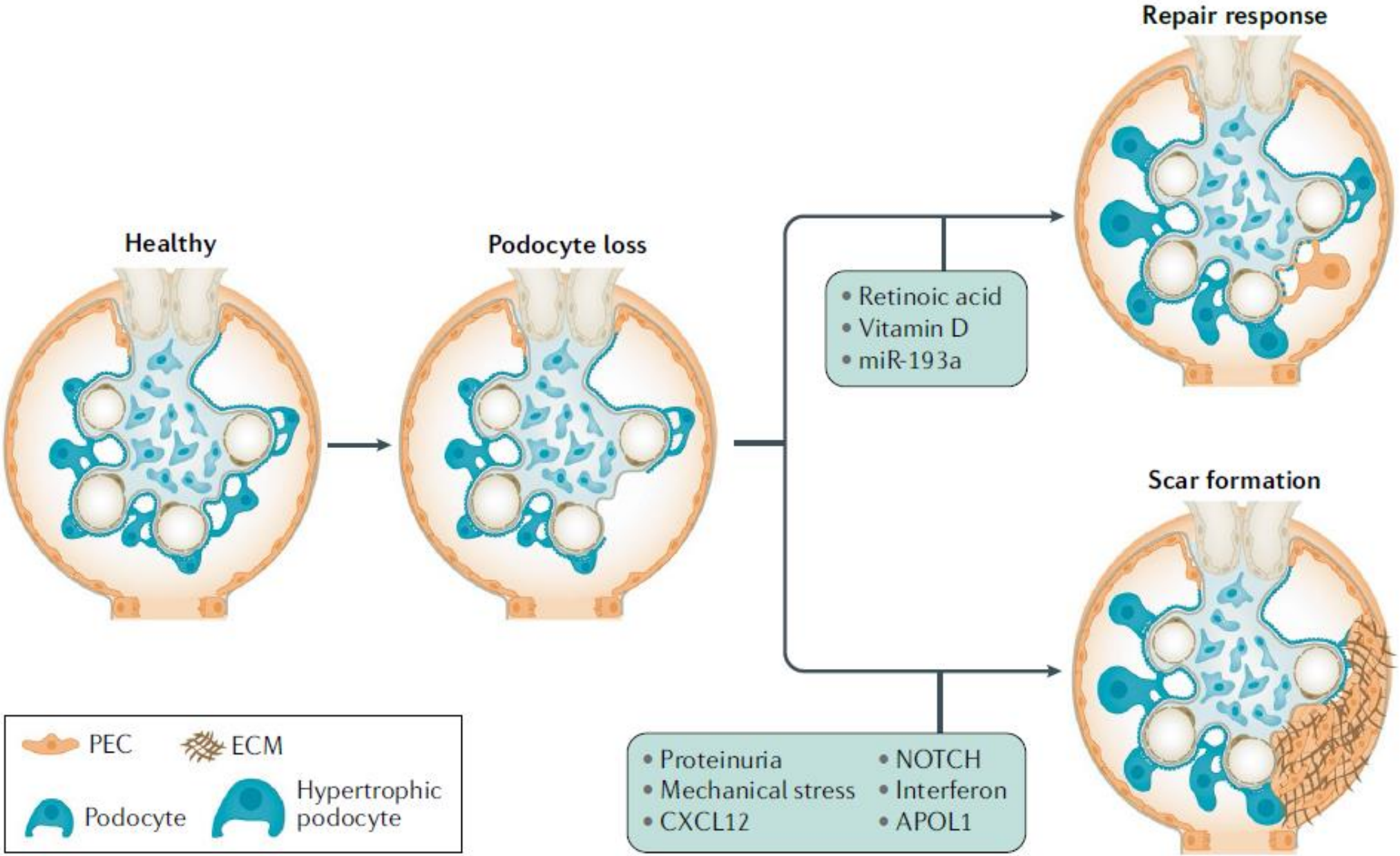


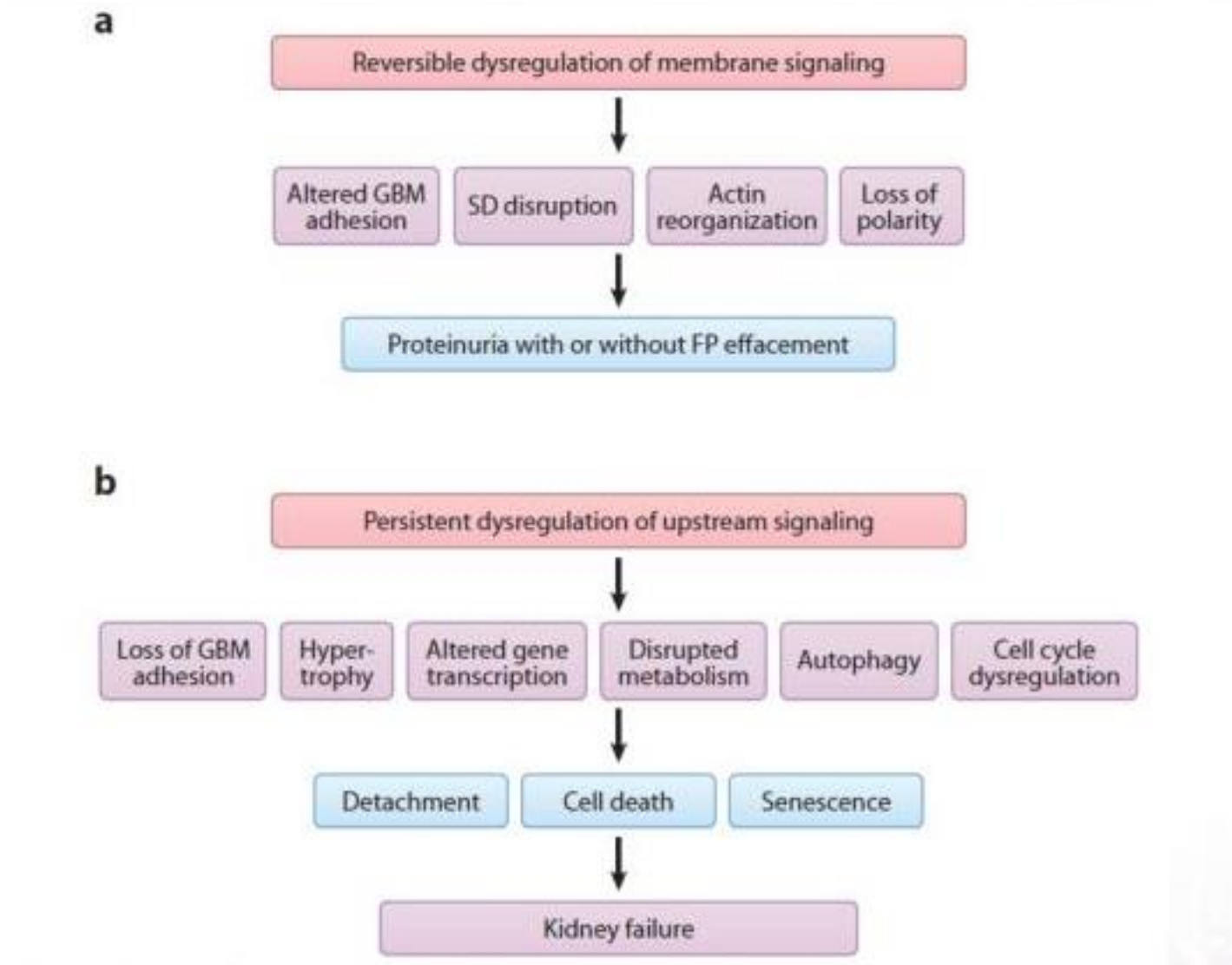

Podocyte
Slit diaphragm
(nephrin)
Glomerular
basement
membrane
Endothelial cell
Podocyte injury
Podocyte
detachment and
apoptosis
Podocyte
hypertrophy
Foot process
fusion


Immune-mediated insult
Nonimmune-mediated insults
IgA and membranous nephropathies
Diabetic nephropathy
Podocyte stress/injury
Urinary shedding of podocytes and podocyte-specific proteins
Increased illustration of urinary shedding of podocalyxin and nephrin


a
PEC
Foot process
Podocyte
VEGF
Urinary space
1
3
Vascular space
2
4
GBM
Albumin
Endothelial cell
Mesangial cell


b
Podocyte foot effacement
VEGF
1
2


Repair response
Healthy
Podocyte loss
• Retinoic acid
• Vitamin D
• miR-193a
Scar formation
• Proteinuria
• Mechanical stress
• CXCL12
• NOTCH
• Interferon
• APOL1
PEC
ECM
Podocyte
Hypertrophic podocyte

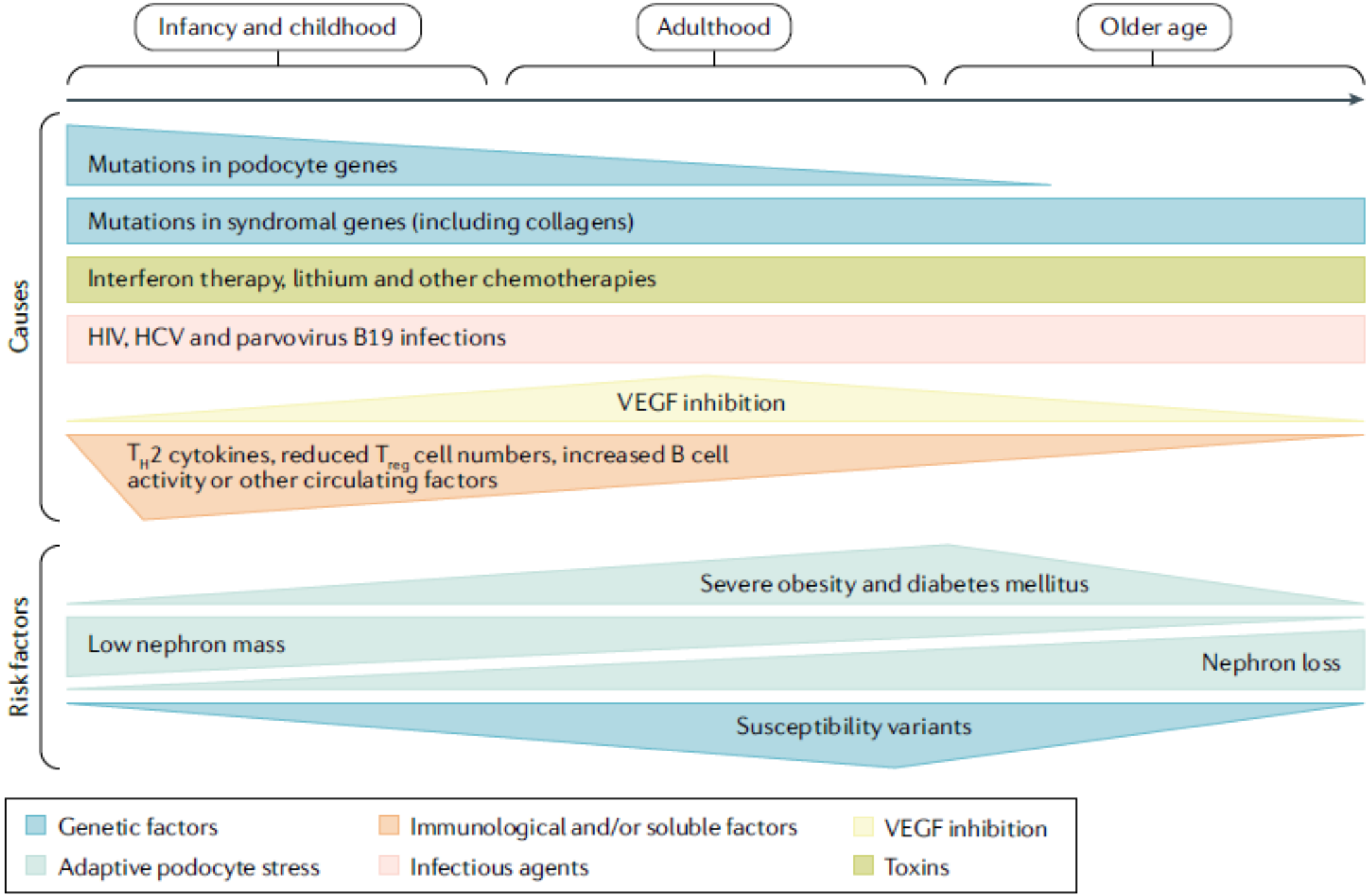

a
Reversible dysregulation of membrane signaling
Altered GBM adhesion
SD disruption
Actin reorganization
Loss of polarity
Proteinuria with or without FP effacement
b
Persistent dysregulation of upstream signaling
Loss of GBM adhesion
Hyper-trophy
Altered gene transcription
Disrupted metabolism
Autophagy
Cell cycle dysregulation
Detachment
Cell death
Senescence
Kidney failure

- ✓ Patient **age and sex** are associated with an increased probability of different types of podocytopathies related to different causes or risk factors that can frequently even combine in the same patient.

For example, **genetic causes** are more frequent in children and young adults, whereas immunological causes are more frequent in male children.

- ✓ On the other hand, podocytopathies related to inhibition of vascular endothelial growth factor (VEGF) are observed during pre-eclampsia and are, therefore, more prevalent in pregnant women.

- ✓ Major risk factors for the development of a podocytopathy, such as **increased single-nephron glomerular filtration rate** for obesity or diabetes, are more frequently observed in adult middle-age patients, whereas a **low nephron mass** endowment can cause a **podocytopathy** during adolescence or early adulthood.


Infancy and childhood
Adulthood
Older age
Causes
Mutations in podocyte genes
Mutations in syndromal genes (including collagens)
Interferon therapy, lithium and other chemotherapies
HIV, HCV and parvovirus B19 infections
VEGF inhibition
T_H2 cytokines, reduced T_{reg} cell numbers, increased B cell activity or other circulating factors
Risk factors
Severe obesity and diabetes mellitus
Low nephron mass
Nephron loss
Susceptibility variants
Genetic factors
Adaptive podocyte stress
Immunological and/or soluble factors
Infectious agents
VEGF inhibition
Toxins

Intrinsic factors	Extrinsic factors
Transcriptional regulators: WT1, PAX-2, WTIP, LIM homeobox transcription factor 1β	**Infections:** Circulating viral protein, lipopolysaccharides
Alteration of slit diaphragm complex: Nephrin, podocin, CD2AP, FAT-1, FAT-2, ZO-1 Cytoskeletal abnormality: ACTN-4 mutation	**Toxic:** Medication (pamidronate, interferon), toxin (puromycin aminonucleoside, adriamycin)
Luminal and abluminal proteins: α-β dystroglycans, podocalyxin, TRPC6	**Lymphokine or other host protein:** IFN-α, IFN-β, FSGS permeability factor, TGF-β
Cytoplasmic proteins: PLCε1 Mitochondria: tRNA mutation, COQ2 mutation	**Mechanical:** Obesity, hyperfiltration, acute ischemia associated with thrombotic microangiopathy
Metabolic: Fabry's, SCARB2/ LIMP-2	**Immunologic:** Lupus, IgA nephropathy, membranous nephropathy
Extracellular matrix: LAMB2	**Metabolic:** Diabetes Miscellaneous: Stress induced induction of CD80

WT1: Wilms tumor 1, WTIP: Wilms tumor 1 interacting protein, TGF-β: Transforming growth factor beta, FSGS: Focal segmental glomerulosclerosis, IFN-α: Interferon-alpha, IFN-β: Interferon-beta, PLCε1: Phospholipase Cε1, LAMB2: Laminin beta 2, LIMP-2: Lysosomal integral membrane protein type 2, TRPC6: Transient receptor potential cation channel 6, ZO-1: Zonula occludens 1

Approach to Diagnosis and Management of Primary Glomerular Diseases Due to Podocytopathies in Adults: Core Curriculum 2020

Wooin Ahn and Andrew S. Bomback

Podocyte injury is the initiating step in the pathway toward clinically evident forms of nephrotic syndrome known as podocytopathies, represented as either minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS). There are hallmark differences in the histologic appearances of MCD and FSGS, which in turn represent distinct pathogenic models after initial podocyte injury (eg, no change in podocyte number in MCD vs podocyte detachment and death in FSGS). However, MCD and FSGS also share a number of common causes, supporting the theory that these diseases lie along a shared podocytopathy spectrum. In this installment of *AJKD*'s Core Curriculum in Nephrology, we demonstrate how the podocytopathies can be classified according to pathogenesis and treatment response as an alternative to histologic description. Using case examples, we show how these alternative classification schemes can assist not only diagnosis, but also long-term management of podocytopathies.

Complete author and article information provided at end of article.

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doi: 10.1053/j.ajkd.2019.12.019

New Classification of podocytopathy

1- Pathogenesis- based
2- Histopathology- based
3- Treatment response- based

Pathogenesis based classification

1- Permeability factor
2- Genetic
3- Toxic
4- Hyperfiltration

Type of Podocytopathy	Causes and Pathogenesis	Pathology	Clinical Manifestation	Treatment	Recurrence After Transplantation
Permeability factor–mediated	Circulating factor causing podocyte injury	MCD, FSGS with extensive FPE	Sudden-onset nephrotic syndrome	Immunosuppression, plasma exchange	Common; sometimes immediate
Toxic	Direct toxicity or cytokine mediated ± APOL1 overexpression	MCD, FSGS (frequently collapsing) ± endothelial tubuloreticular inclusions	Variable clinical course; slowly progressing CKD or nephrotic syndrome	Removal of toxic injury	Possible; usually several months later
Genetic	Mutation causing structural or functional abnormalities of podocytes	MCD, MesGN, FSGS	Steroid-resistant nephrotic syndrome	RAS inhibitors	Rare
Hyperfiltration-mediated	Adaptive changes due to excessive nephron workload	FSGS (frequently perihilar) with glomerulomegaly and segmental FPE	Slowly progressive proteinuria without edema and hypoalbuminemia	RAS inhibitors	Rare

Gene (Inheritance Pattern)	Product	Clinical Manifestations
COL4A3/4/5 (AD, AR, XL)	Type IV collagen	Alport syndrome: bilateral anterior lenticonus, dot-and-fleck retinopathy, spherophakia, high-frequency sensorineural hearing loss
NPHS1 (AR)	Nephrin	Early-onset SRNS
NPHS2 (AR)	Podocin	Early- or late-onset SRNS
WT1 (AD)	Wilms tumor 1	Denys-Drash syndrome: Wilms tumor, male pseudohermaphroditism Frasier syndrome: gonadoblastoma, male pseudohermaphroditism
PLCE1 (AR)	Phospholipase Cε1	Early-onset SRNS
LAMB2 (AR)	Laminin β2	Pierson syndrome: microcoria, neuromuscular junction defects
CD2AP (AD)	CD2-associated protein	Early-onset SRNS
ACTN4 (AD)	α-Actinin 4	Early- or late-onset SRNS
TRPC6 (AD)	Transient receptor potential cation channel 6	Late-onset SRNS
INF2 (AD)	Inverted formin 2	Charcot-Marie-Tooth disease: motor and sensory nerve manifestations with distal leg weakness, foot deformities (pes cavus, hammer toes), late-onset SRNS
MT-TL1, MT-TL2, MT-TY (mitochondrial)	Mitochondrial tRNA	MELAS syndrome: mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes
LMX1B (AD)	LIM homeobox transcription factor 1-β	Nail-patella syndrome: hypoplastic patella, dystrophic nails, dysplasia of elbows Collagenofibrotic glomerulopathy
ITGB4 (AR)	β4 integrin	Epidermolysis bullosa
CD151 (AR)	Tetraspanin CD151	Epidermolysis bullosa, sensorineural hearing loss, nail dystrophy
SCARB2 (AR)	Lysosomal integral membrane protein 2	Action myoclonus-renal failure syndrome: ataxia, myoclonus
CUBN (AR)	Cubilin: intrinsic factor-cobalamin receptor	Megaloblastic anemia secondary to vitamin B_{12} deficiency, SRNS
COQ6 (AR)	Coenzyme Q6	Sensorineural hearing loss
MYH9 (AD)	Nonmuscle myosin 11a	Bleeding diathesis, macrothrombocytopenia, progressive sensorineural deafness, ↑ liver enzyme, cataract
SMARCAL1 (AR)	SMARCA-like protein	Schimke immune-osseous dysplasia

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; SRNS, steroid-resistant nephrotic syndrome; tRNA, transfer RNA; XL, X-linked.

Intrinsic factors	Extrinsic factors
Transcriptional regulators: WT1, PAX-2, WTIP, LIM homeobox transcription factor 1β	**Infections:** Circulating viral protein, lipopolysaccharides
Alteration of slit diaphragm complex: Nephrin, podocin, CD2AP, FAT-1, FAT-2, ZO-1 Cytoskeletal abnormality: ACTN-4 mutation	**Toxic:** Medication (pamidronate, interferon), toxin (puromycin aminonucleoside, adriamycin)
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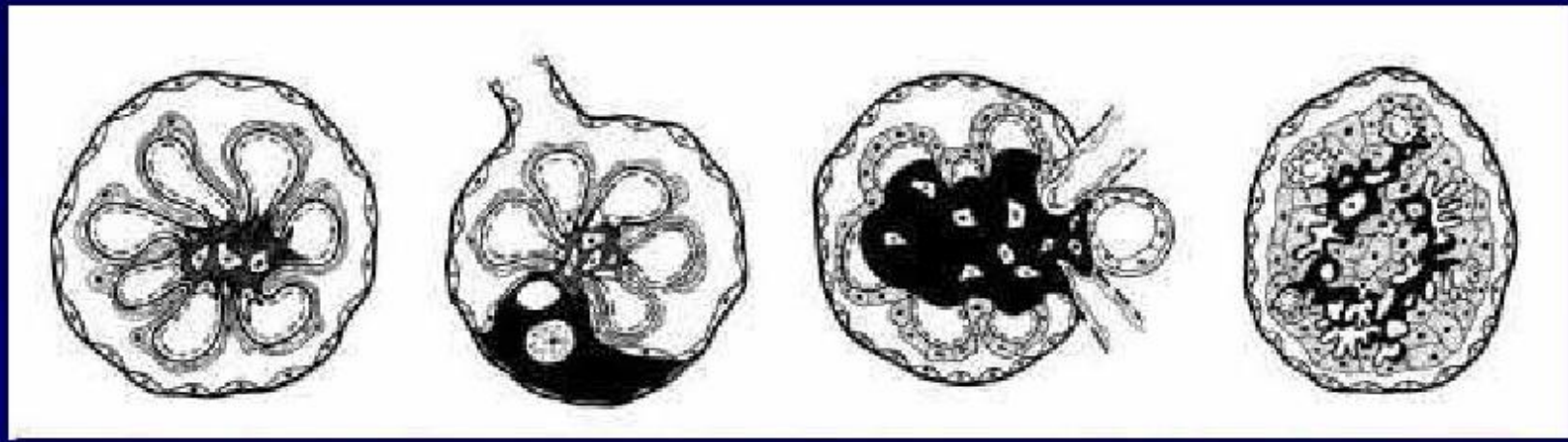
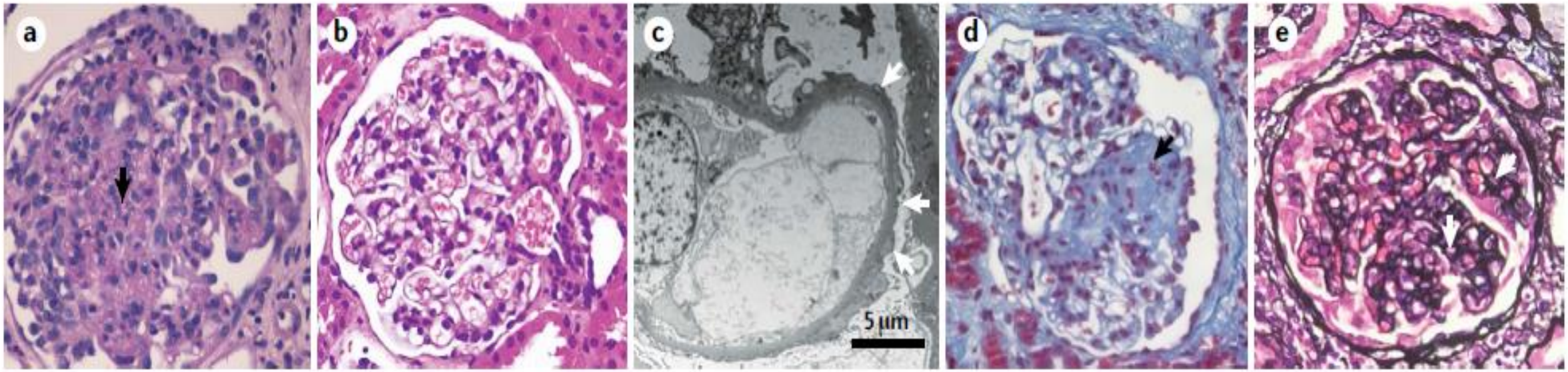
Histopathology based classification

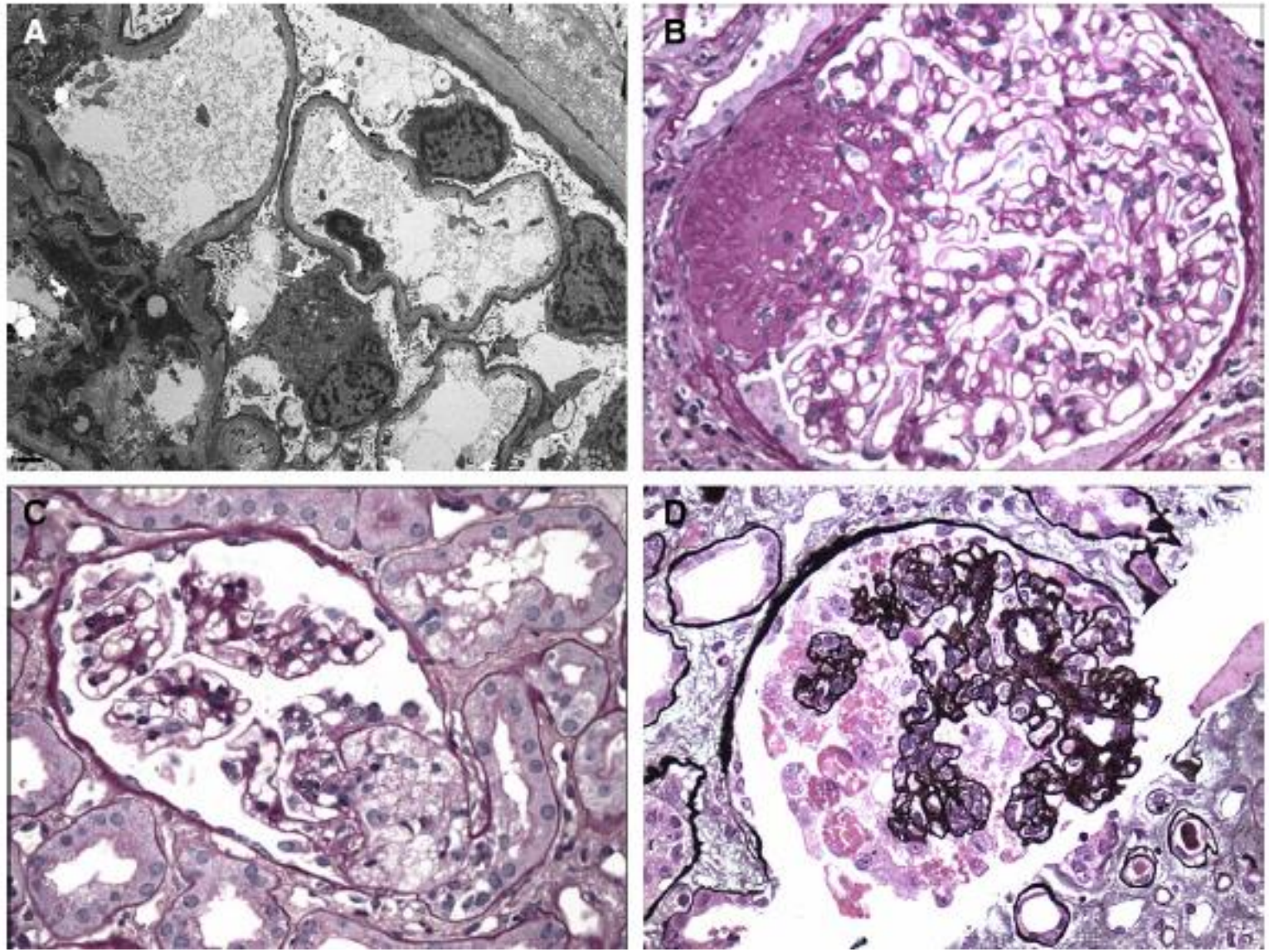
1- MCD
2- FSGS
3- DMS
4- CG

Podocytopathies:
4 morphologic patterns of glomerular injury

Normal Histology	Segmental Sclerosis	Mesangial Sclerosis	Collapse of the GBM
MCN	FSGS	DMS	CG




a
b
c
5 µm
d
e


A
B
C
D

Treatment response based classification

1-SSNS
2-SRNS
3-SD
4-FR
5-Infrequent relapse
6-Remission

Steroid-sensitive nephrotic syndrome (SSNS): nephrotic syndrome that had remission with prednisone, 1 mg/kg, daily or 2 mg/kg, every other day use within 4 mo

Steroid-resistant nephrotic syndrome (SRNS): nephrotic syndrome that failed to achieve remission with prednisone, 1 mg/kg, daily or 2 mg/kg, every other day use for 4 mo

Steroid dependence (SD): 2 consecutive relapses during steroid therapy or within 2 wk of ceasing therapy

Frequent relapse (FR): ≥2 relapses within 6 mo of initial response or 4+ relapses within any 12-mo period

Infrequent relapse: 1 relapse within 6 mo of initial response, or 1-3 relapses in any 12-mo period and treated with steroids

Remission: reduction of proteinuria to < 3.5 g/d with stable serum creatinine level (change < 25%)

- ✓ Adult podocytopathies may take up to 4 months to remit and therefore **steroid resistance** should not be declared until after 4 months of steroid use.

- ✓ In adults, classification by steroid responsiveness is also used when describing histopathologic diagnosis (eg, steroid-resistant FSGS) because classification by pathogenesis is often not possible in the absence of genetic testing.

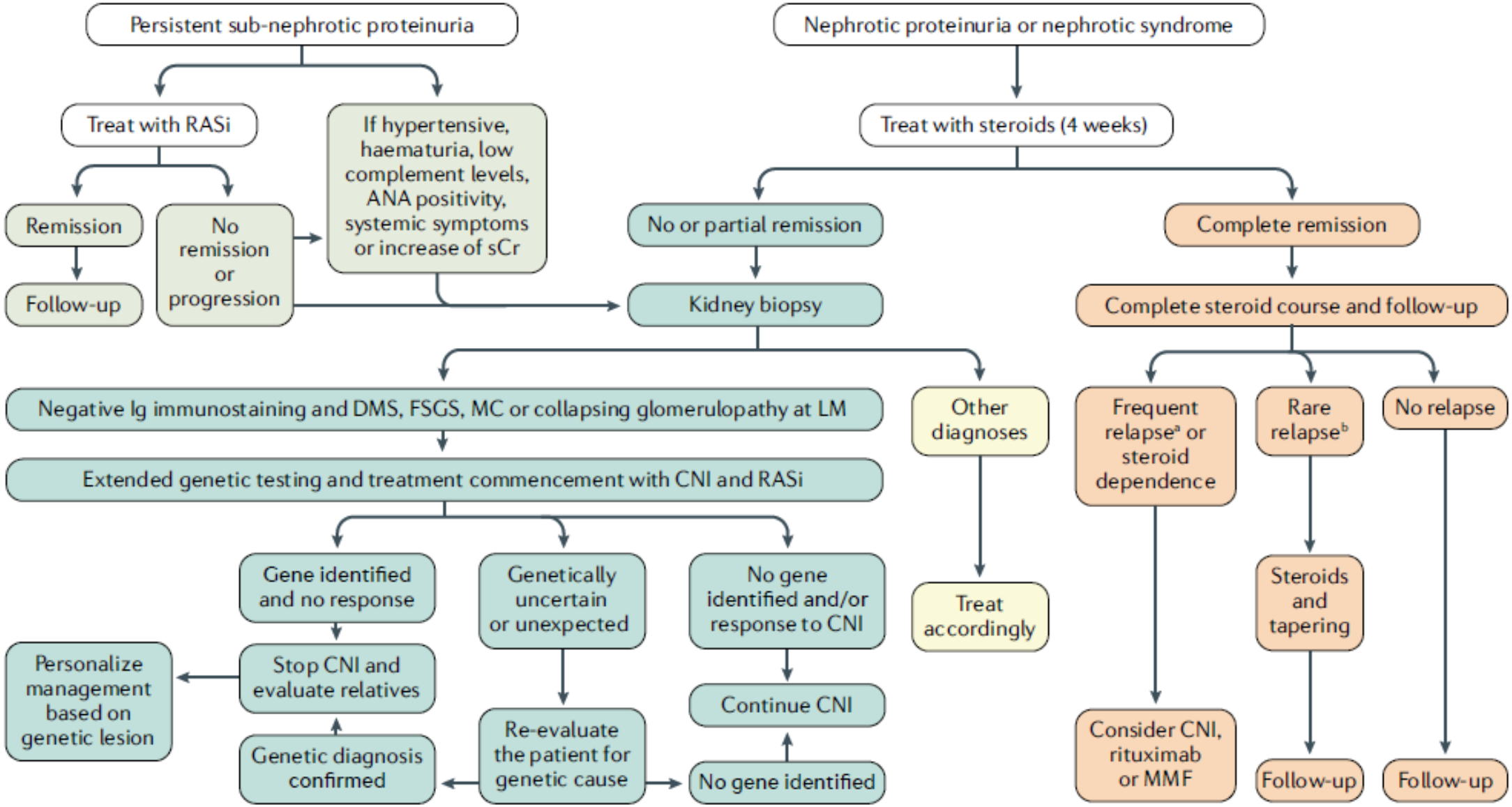
- ✓ **Genetic podocytopathies** always manifest as SRNS, but **SRNS** is not always due to a genetic problem. For example, permeability-mediated podocytopathy may present as SSNS or SRNS.

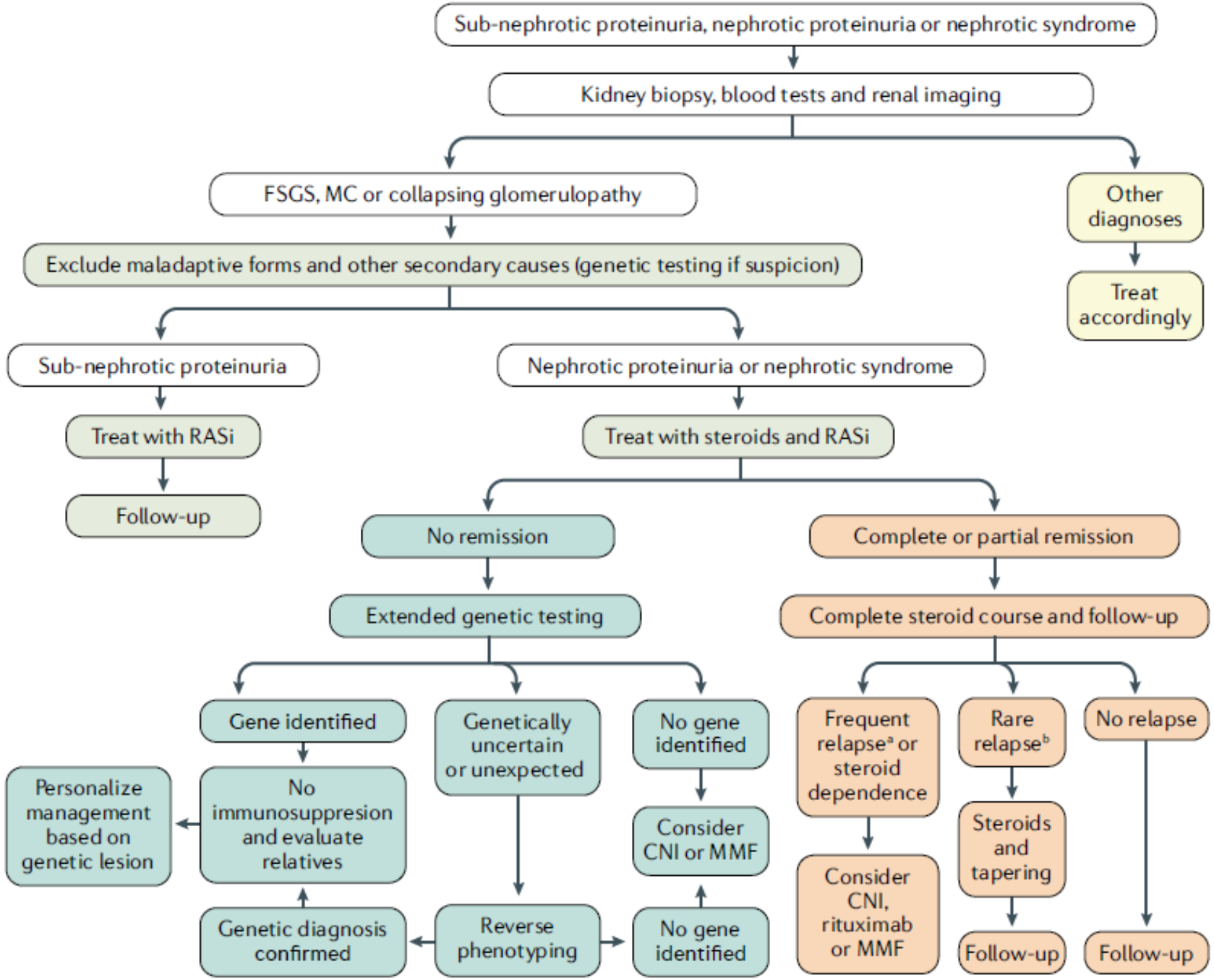
- ✓ In addition, **SSNS** can progress to **SRNS**, which may reflect progression from FSGS to **diffuse global glomerulosclerosis**.

A substantial proportion of patients with **SRNS** may have genetic podocytopathies or podocyte injuries that cannot be reversed by immunosuppressive therapy.

The **steroid-dependent and frequently relapsing** nephrotic phenotypes require alternative steroid sparing treatment to reduce the adverse effects of long term glucocorticoid use.

- **CNI**
- **RTX**
- **Alkylating agents**


Persistent sub-nephrotic proteinuria
Treat with RASi
Remission
Follow-up
No remission or progression
If hypertensive, haematuria, low complement levels, ANA positivity, systemic symptoms or increase of sCr
Nephrotic proteinuria or nephrotic syndrome
Treat with steroids (4 weeks)
No or partial remission
Complete remission
Kidney biopsy
Complete steroid course and follow-up
Negative Ig immunostaining and DMS, FSGS, MC or collapsing glomerulopathy at LM
Other diagnoses
Extended genetic testing and treatment commencement with CNI and RASi
Treat accordingly
Frequent relapse[a] or steroid dependence
Rare relapse[b]
No relapse
Gene identified and no response
Genetically uncertain or unexpected
No gene identified and/or response to CNI
Steroids and tapering
Personalize management based on genetic lesion
Stop CNI and evaluate relatives
Continue CNI
Consider CNI, rituximab or MMF
Genetic diagnosis confirmed
Re-evaluate the patient for genetic cause
No gene identified
Follow-up
Follow-up


Sub-nephrotic proteinuria, nephrotic proteinuria or nephrotic syndrome
Kidney biopsy, blood tests and renal imaging
FSGS, MC or collapsing glomerulopathy
Other diagnoses
Treat accordingly
Exclude maladaptive forms and other secondary causes (genetic testing if suspicion)
Sub-nephrotic proteinuria
Nephrotic proteinuria or nephrotic syndrome
Treat with RASi
Follow-up
Treat with steroids and RASi
No remission
Complete or partial remission
Extended genetic testing
Complete steroid course and follow-up
Gene identified
Genetically uncertain or unexpected
No gene identified
Frequent relapse[a] or steroid dependence
Rare relapse[b]
No relapse
Personalize management based on genetic lesion
No immunosuppresion and evaluate relatives
Consider CNI or MMF
Steroids and tapering
Consider CNI, rituximab or MMF
Genetic diagnosis confirmed
Reverse phenotyping
No gene identified
Follow-up
Follow-up

Nephrol Dial Transplant (2011) 26: 18–24
doi: 10.1093/ndt/gfq617
Advance Access publication 11 October 2010

NDT
Nephrology Dialysis Transplantation

Editorial Reviews

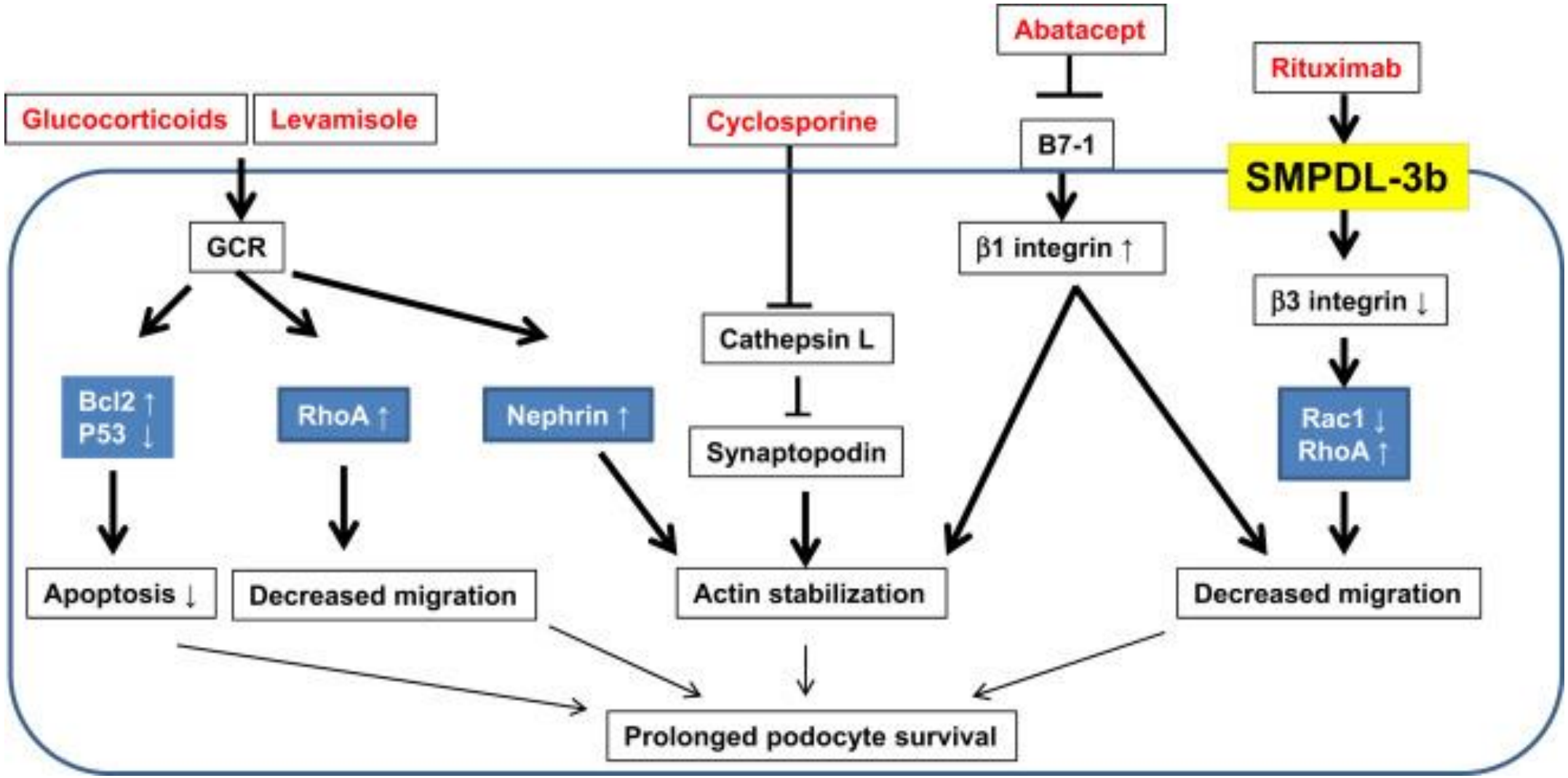
The podocyte as a direct target of immunosuppressive agents

Eva Schönenberger[1], Jochen H. Ehrich[2], Hermann Haller[1] and Mario Schiffer[1]

- The **anti-inflammatory and immunosuppressive action** of glucocorticoids, calcineurin inhibitors and mTOR inhibitors may only play a minor role in modulation of podocyte biology and promotion of glomerular repair mechanisms.

- Instead, these drugs have **direct effects on podocytes** through regulation of some cytokines and several signalling pathways relevant for cytoskeletal stability, cell maturation and survival.

- Furthermore, the expression and distribution of key components of the **slit diaphragm and the cytoskeleton** are regulated


Glucocorticoids
Levamisole
Cyclosporine
Abatacept
Rituximab
B7-1
SMPDL-3b
GCR
β1 integrin ↑
β3 integrin ↓
Cathepsin L
Bcl2 ↑
P53 ↓
RhoA ↑
Nephrin ↑
Rac1 ↓
RhoA ↑
Synaptopodin
Apoptosis ↓
Decreased migration
Actin stabilization
Decreased migration
Prolonged podocyte survival

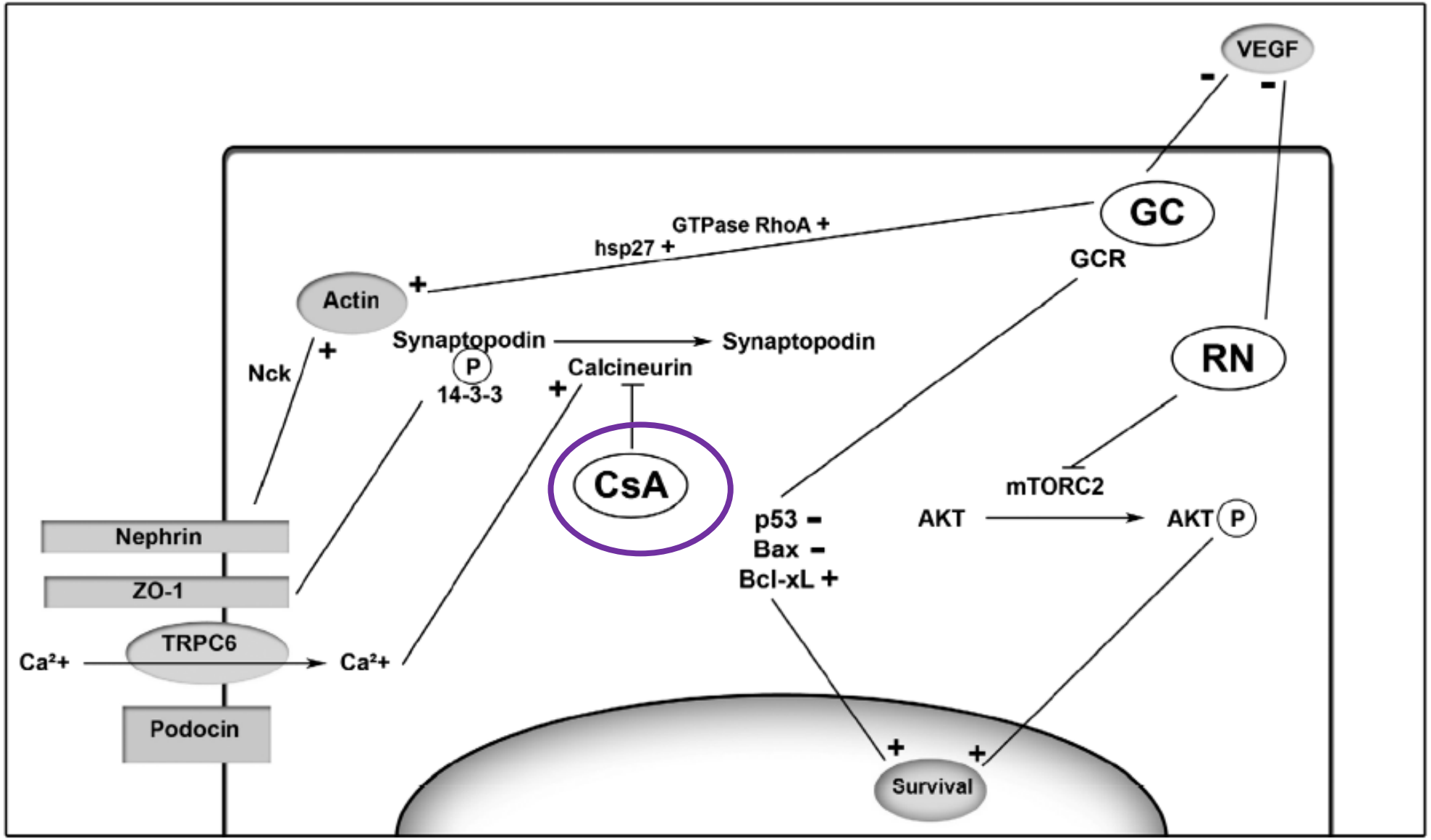
CNIs may have important beneficial effects for both the **podocyte cytoskeleton** and **podocyte viability**.

These agents **attenuate podocyte apoptosis** as well as promote a podocyte phenotype that is resistant to the development of proteinuria.

The beneficial effects of CNIs may be mediated by mechanisms that are independent of the immune system.

Given the potential role of CN in diverse glomerular diseases, the use of **CNIs** might be useful for a broader range of kidney disorders.

CN activation destabilizes the actin cytoskeleton and causes podocyte apoptosis.



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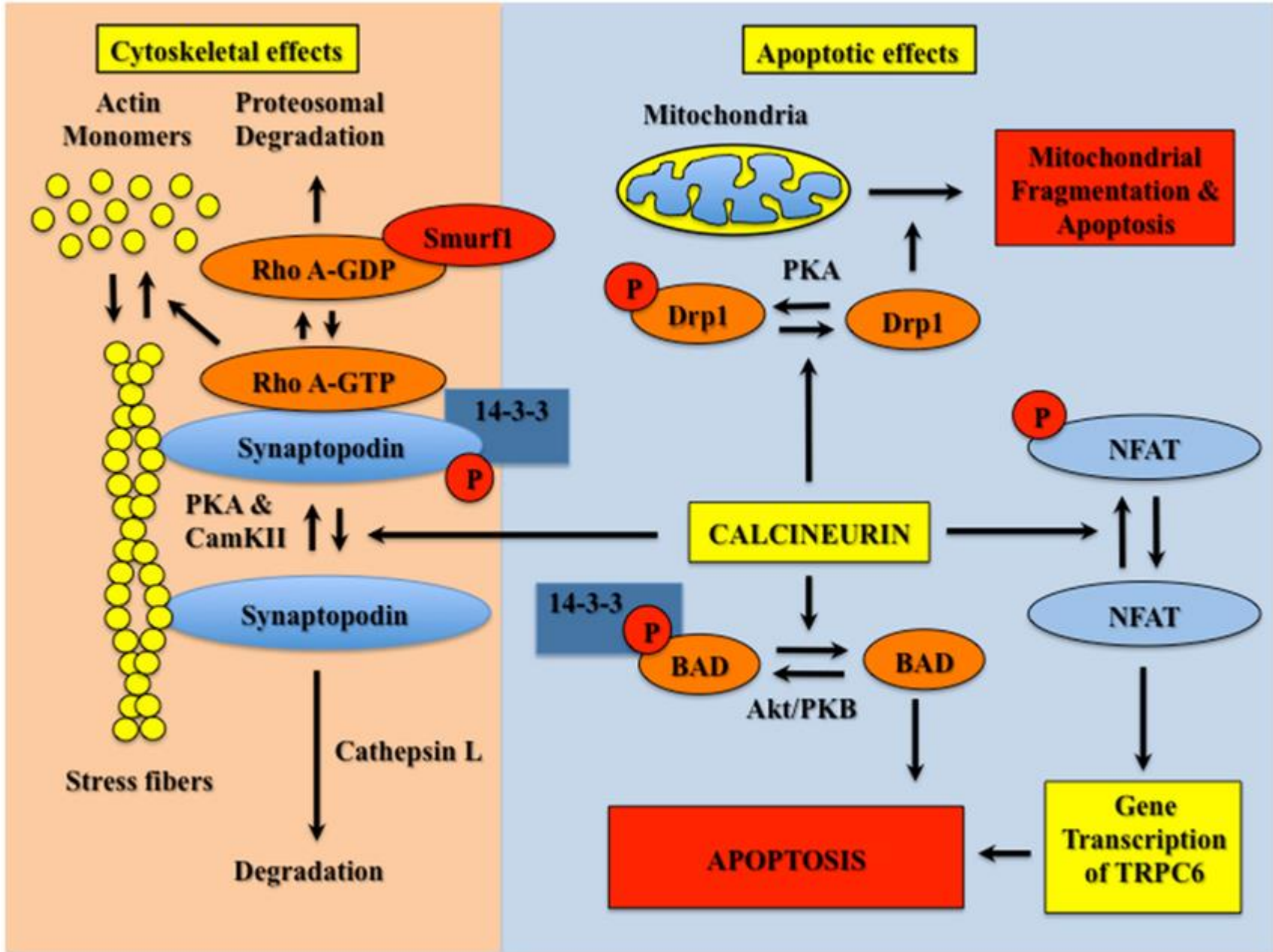
Non-immunologic actions of calcineurin inhibitors in proteinuric kidney diseases

Robert Frank Spurney*


Cytoskeletal effects
Apoptotic effects
Actin Monomers
Proteosomal Degradation
Mitochondria
Mitochondrial Fragmentation & Apoptosis
Smurf1
Rho A-GDP
PKA
P
Drp1
Drp1
Rho A-GTP
14-3-3
Synaptopodin
P
P
NFAT
PKA & CamKII
CALCINEURIN
Synaptopodin
14-3-3
P
BAD
BAD
NFAT
Akt/PKB
Cathepsin L
Stress fibers
Degradation
APOPTOSIS
Gene Transcription of TRPC6

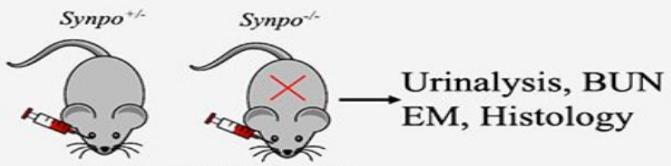
Synaptopodin is dispensable for normal podocyte homeostasis but is protective in the context of acute podocyte injury

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

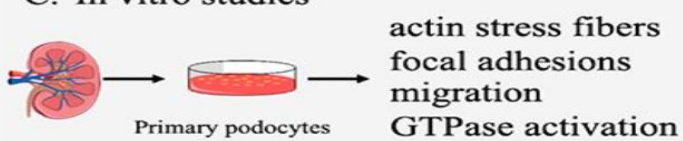
METHODS

A. Gene Editing

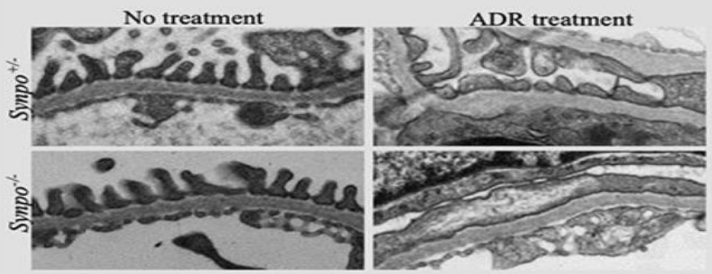
B. In vivo studies

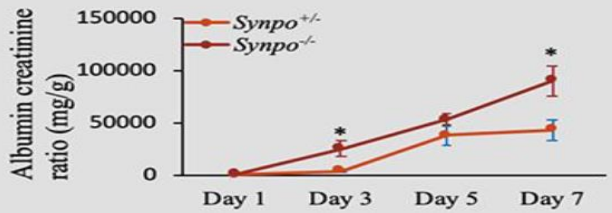


C. In vitro studies

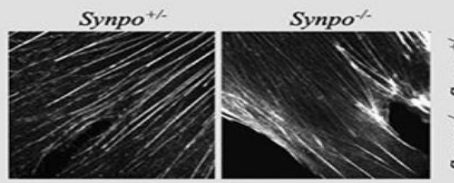


OUTCOME

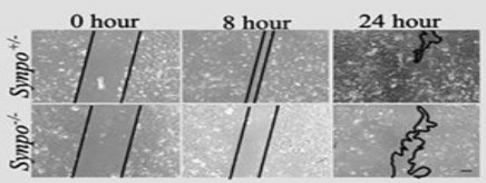




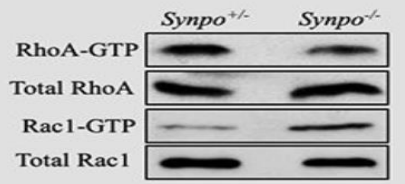
The complete lack of synaptopodin caused no obvious phenotype but resulted in increased susceptibility to Adriamycin nephropathy.



Synpo deficiency affects stress fibers.



The absence of Synpo impairs cell motility.



Reduced active RhoA and increased active Rac1 in *Synpo*$^{-/-}$ podocytes

Conclusion

Podocytes function normally in vivo in the absence of all Synpo isoforms. Synpo plays a protective role in the context of podocyte injury through its involvement in actin reorganization and focal adhesion dynamics.

doi: 10.1681/ASN.2020050572

Summary

- ✓ **The pivotal role of podocytes** on proteinuria in many different forms of glomerular diseases.

- ✓ The **anti-inflammatory and immunosuppressive action** of glucocorticoids, calcineurin inhibitors and mTOR inhibitors may only play a minor role in modulation of podocyte biology and promotion of glomerular repair mechanisms.

- ✓ Instead, these drugs have **direct effects on podocytes** through regulation of some cytokines and several signaling pathways relevant for cytoskeletal stability, cell maturation and survival.

- ✓ **CNIs** may have important beneficial effects for both the **podocyte cytoskeleton and podocyte viability** by mechanisms that are **independent of the immune system**.

- ✓ New therapies???