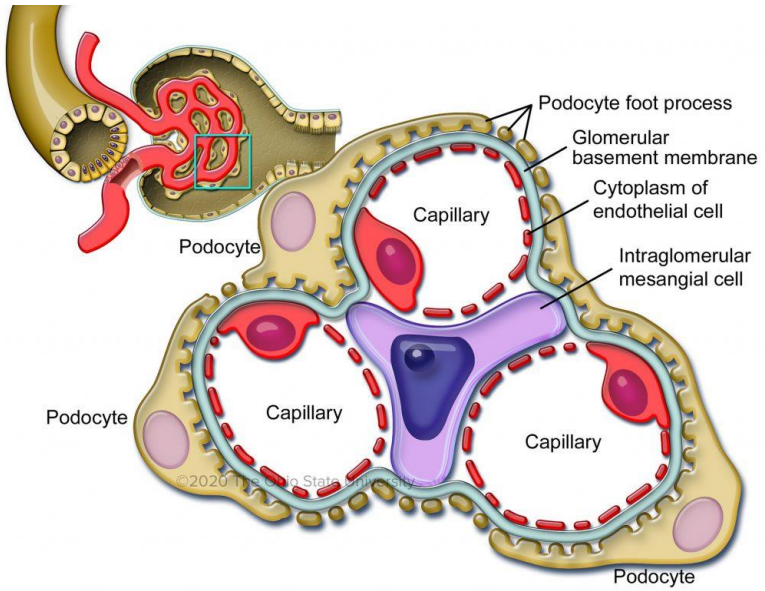
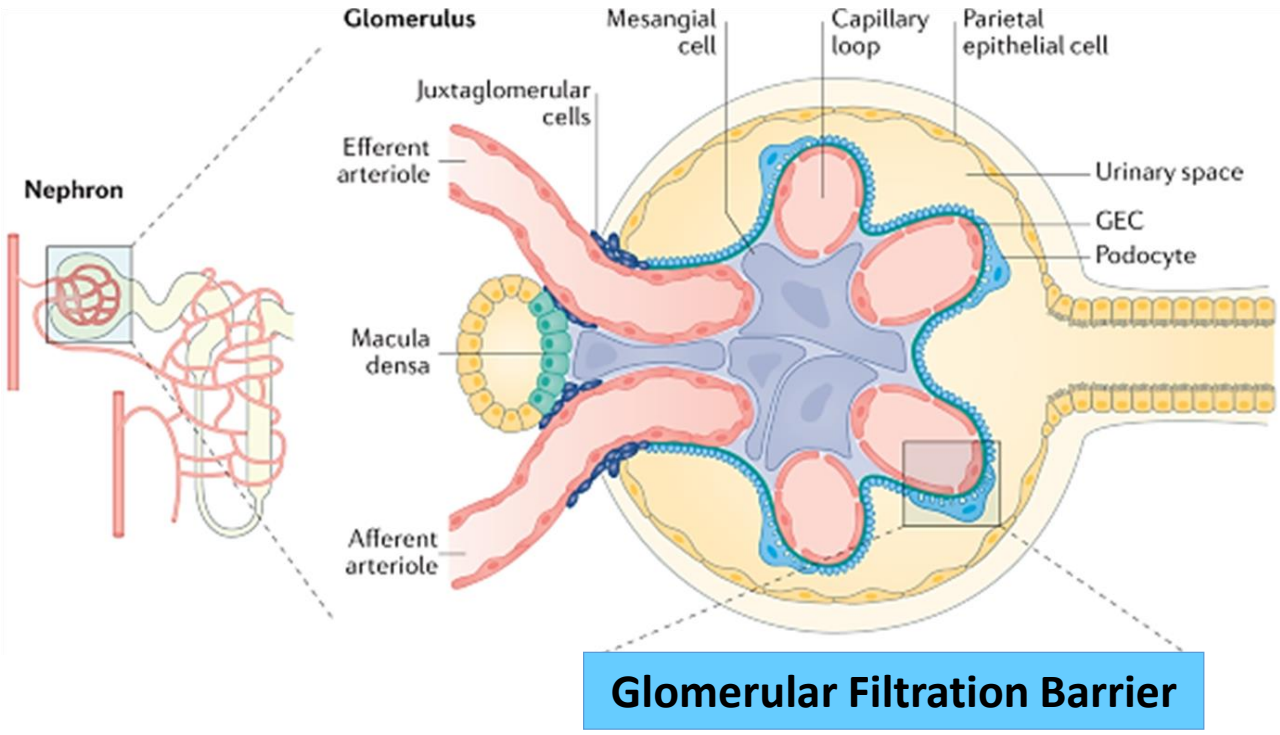

بسم الله الرحمن الرحیم

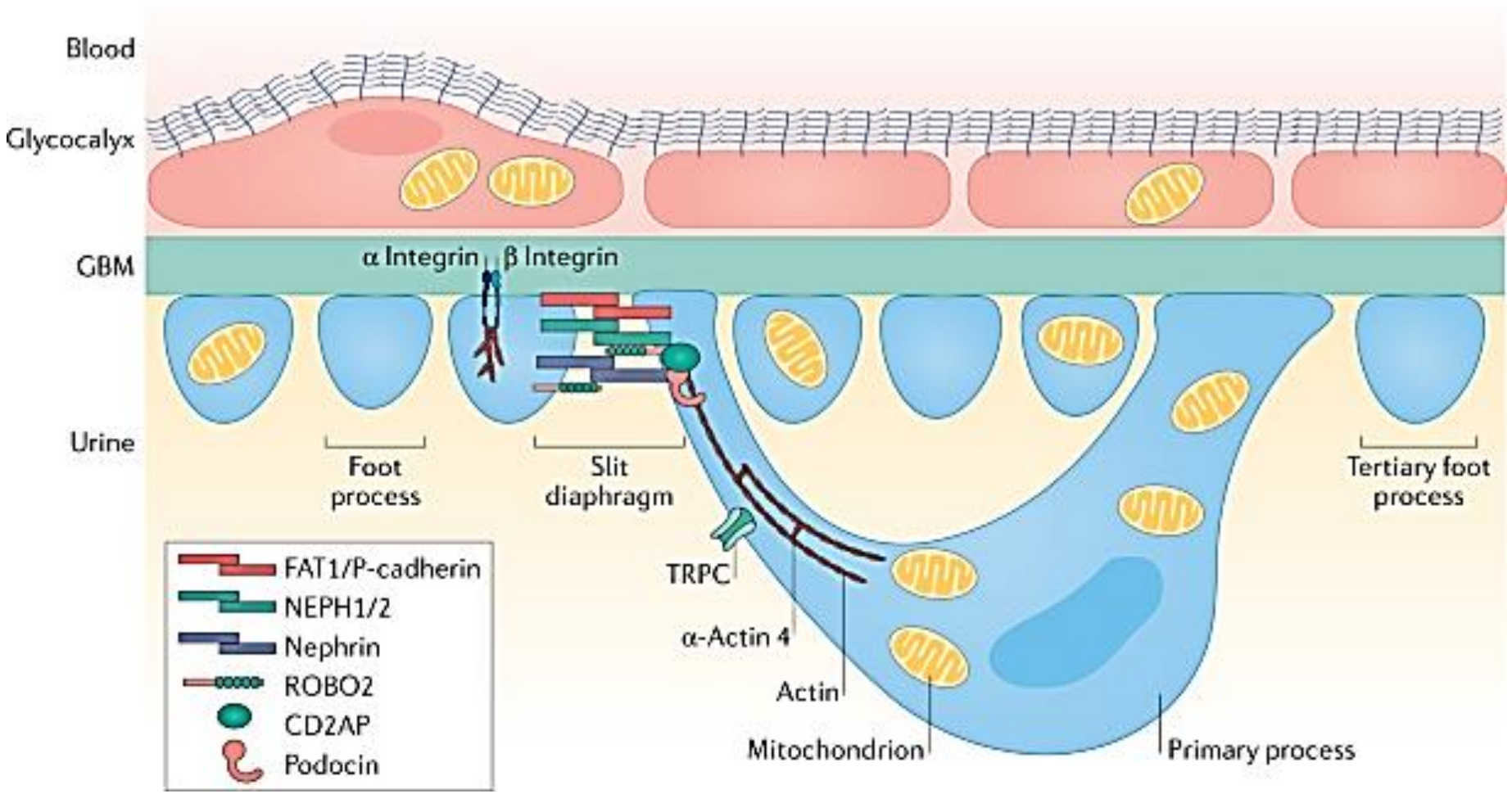
Mesangial Cells and renal function





Glomerular Filtration Barrier

Glomerular Filtration Barrier



History of Renal Mesangial cells(MCs)

Early Discovery and Anatomical Characterization

In 1933, the German anatomist Zimmerman proposed the existence of a third cell — the mesangial cell.

Functional Insights and Pathological Roles

By the 1990s, research focused on MCs' contractile properties

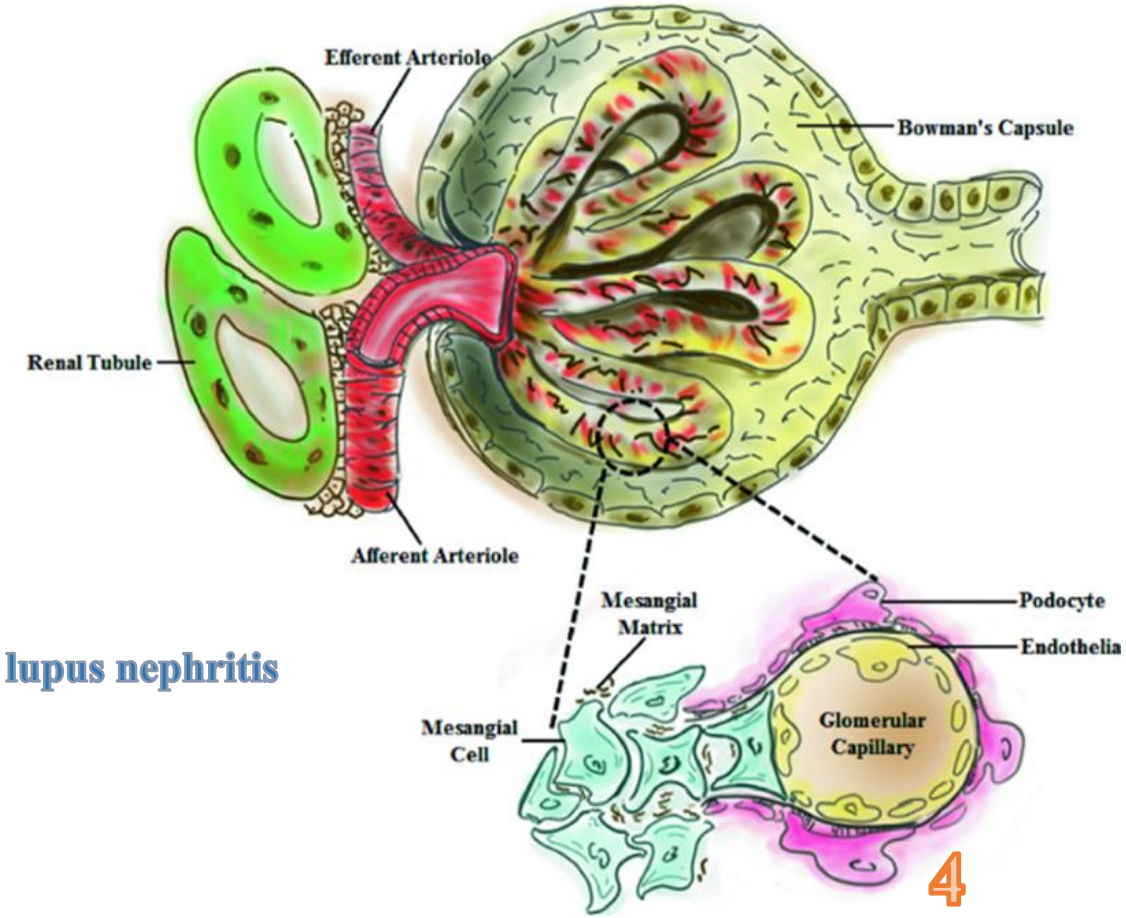
Developmental Origins and Molecular Regulation

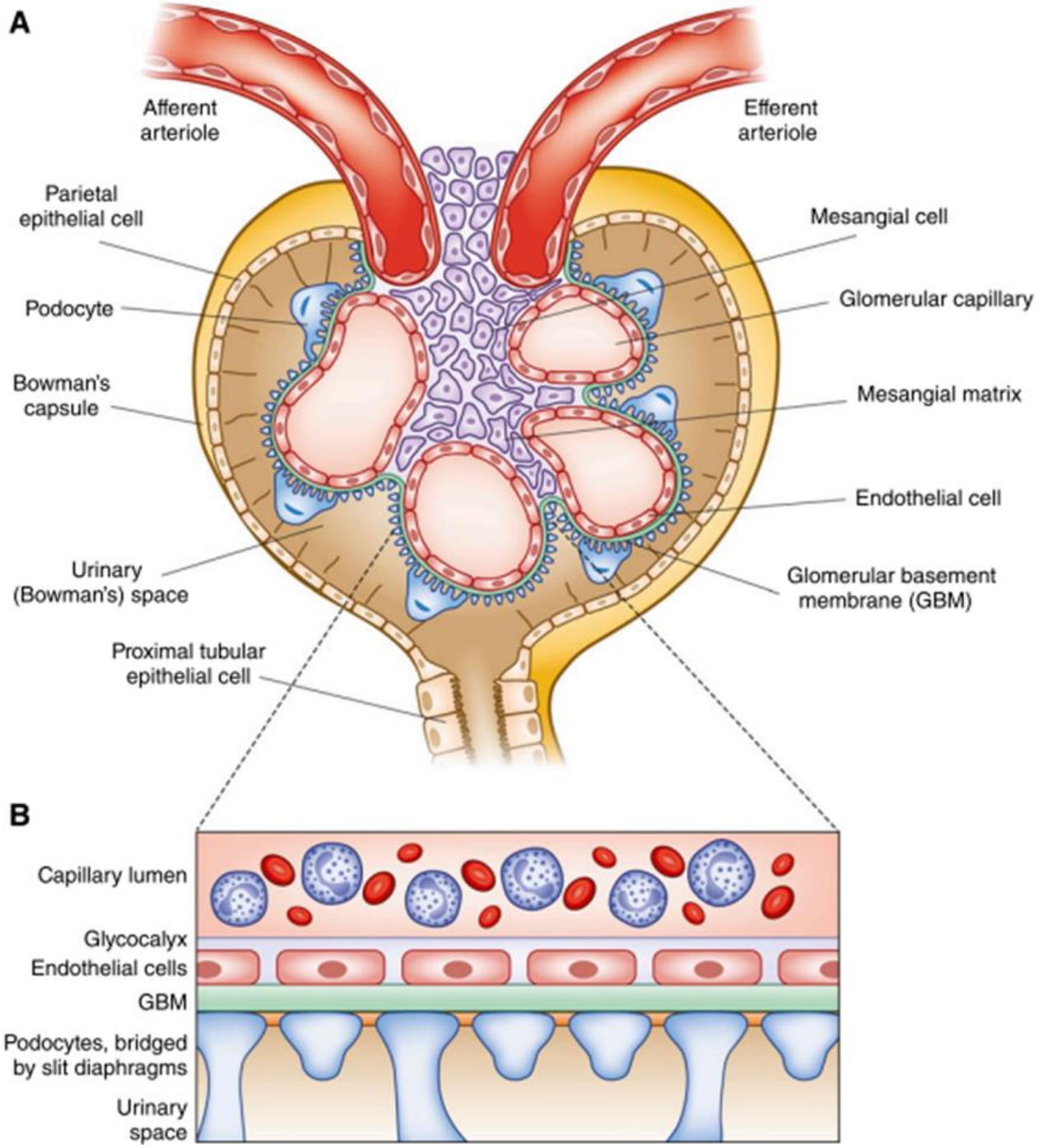
In the 2000s, MCs originate from Foxd1+ stromal mesenchyme

Modern Perspectives

MCs' roles in immune regulation and structural support particularly in lupus nephritis

Their interactions with endothelial cells and podocytes




A
Afferent arteriole
Efferent arteriole
Parietal epithelial cell
Podocyte
Bowman's capsule
Urinary (Bowman's) space
Proximal tubular epithelial cell
Mesangial cell
Glomerular capillary
Mesangial matrix
Endothelial cell
Glomerular basement membrane (GBM)
B
Capillary lumen
Glycocalyx
Endothelial cells
GBM
Podocytes, bridged by slit diaphragms
Urinary space

Mesangium, Mesangial matrix and Mesangial cells

The mesangium forms the central region of the renal glomerulus consists of:

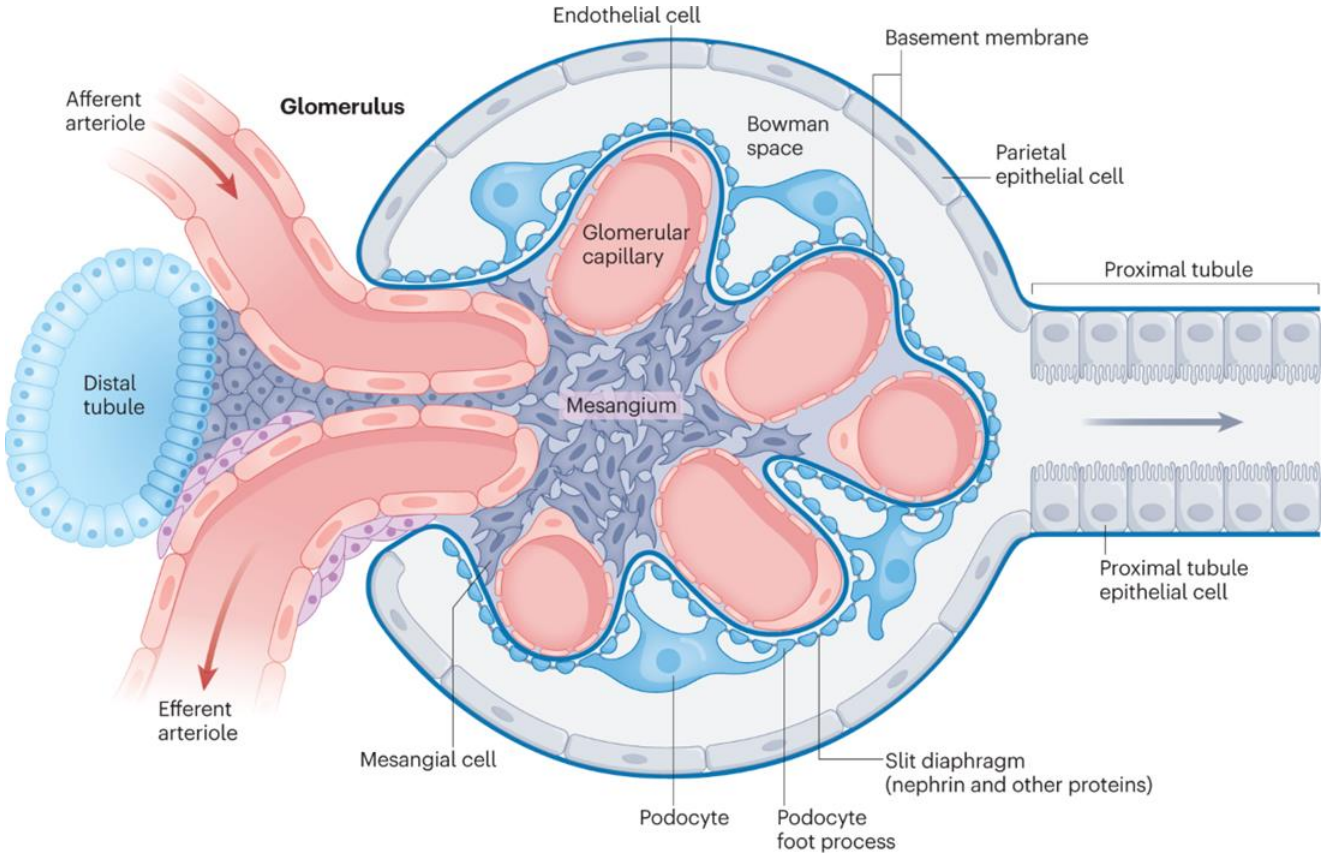
- ✓ **Mesangial cells (MCs)**

30–40% of the total glomerular cell population

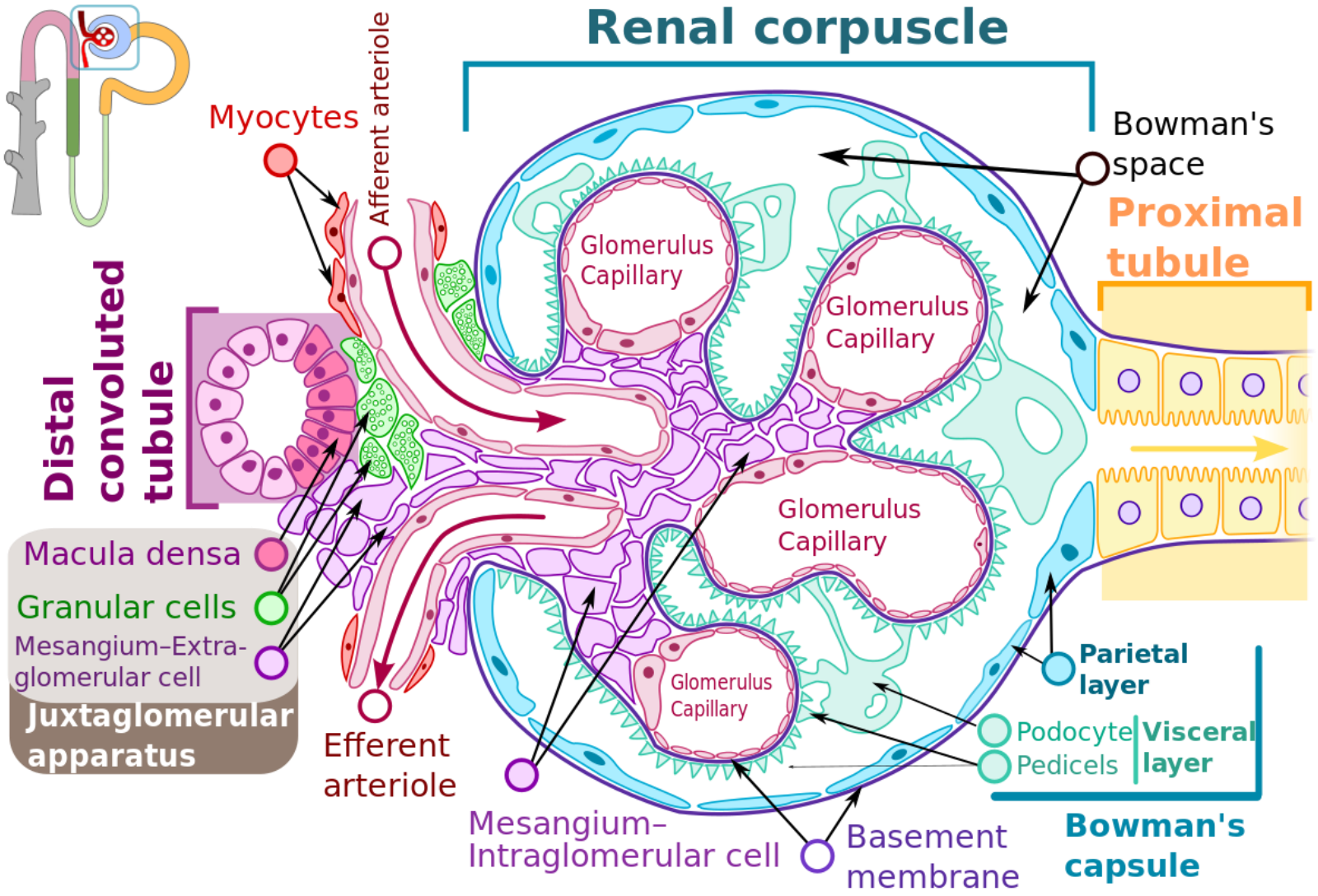
- ✓ **Extracellular matrix (ECM)**

The ECM is produced by MCs

- ✓ **Collagens type IV and V**
- ✓ **Laminin A, B1, and B2**
- ✓ **Fibronectin**
- ✓ **Proteoglycans**



The Mesangial cells



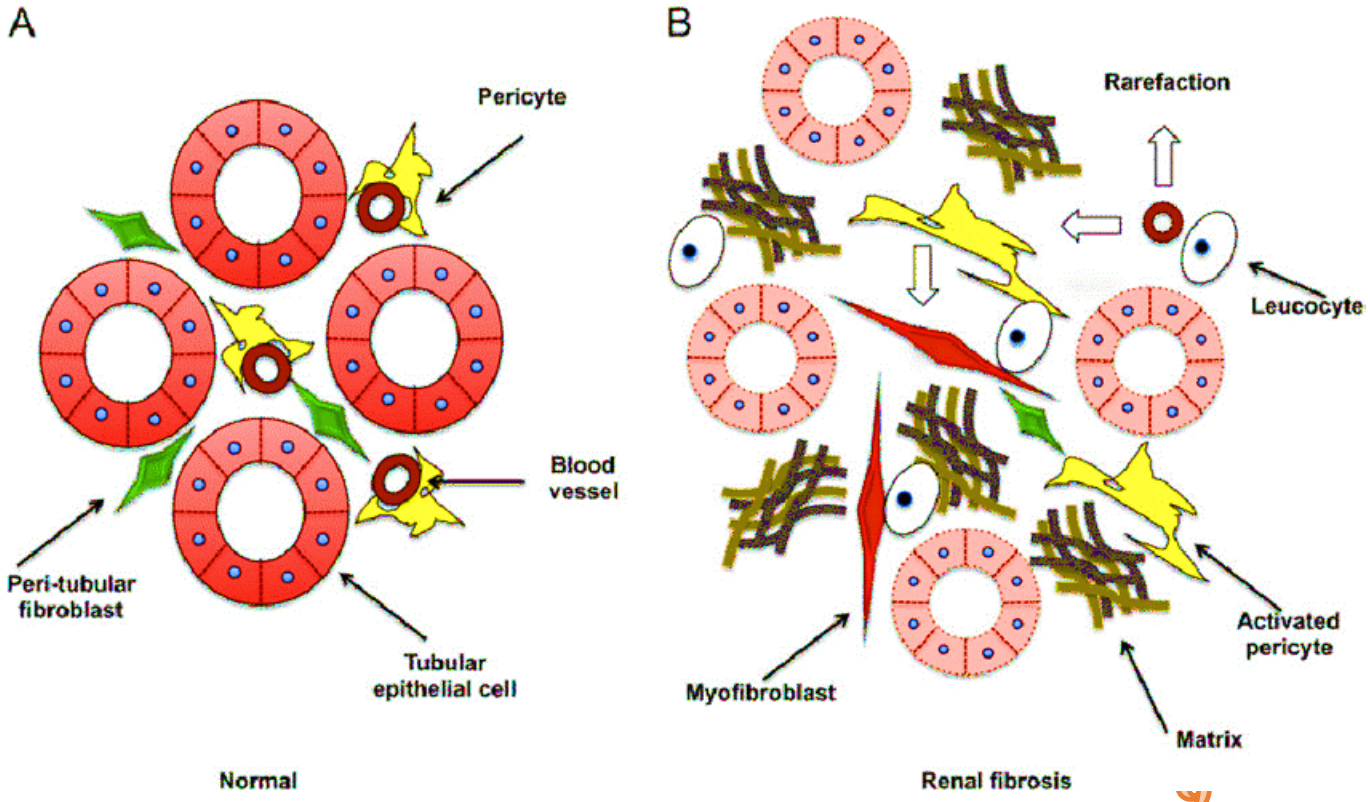
Mesangial Cells

Subtype	Location	Key Functions
Intraglomerular	Within glomerulus	Support, filtration regulation, phagocytosis Matrix production, contractility
Extraglomerular	Vascular pole, JGA	Part of juxtaglomerular apparatus Signaling, support, possible role in BP regulation

Different Types of Mesangial Cells

Three different types of MCs have been described

- **Vascular Smooth Muscle-like Mesangial Cells**
- **Pericyte-like Mesangial Cells**
- **Fibroblast-like Mesangial Cells**



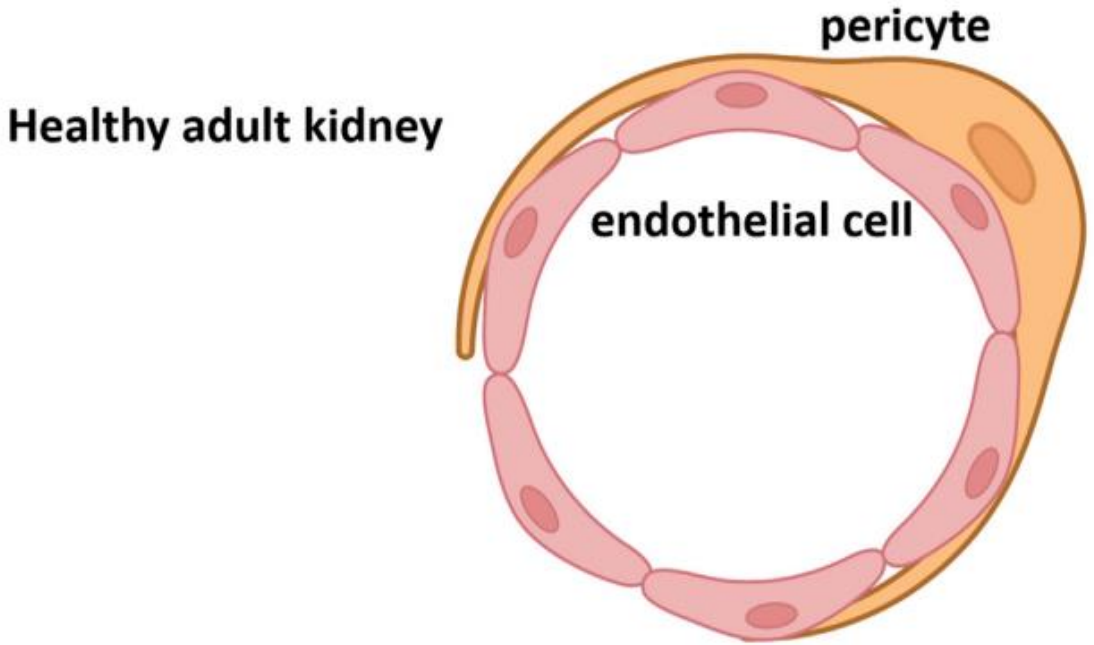
Vascular Smooth Muscle-like Mesangial Cells

Feature	Vascular Smooth Muscle-like Mesangial Cells
Location	**Glomerular mesangium and arteriolar junctions**
Developmental Origin	**Mesenchymal precursors (shared with pericytes)**
Contractile Apparatus	**Actin, myosin, and tropomyosin filaments**
Functional Roles	**Contractility Regulation** **GFR regulation** **Structural Support**
Regulation Mechanisms	**Calcium Signaling:Ca^{2+}L-type channels** **Angiotensin II(AngII)** **Endothelin** **NO/cGMP pathways limit excessive contraction**
Pathological Role	**Glomerulosclerosis like diabetic nephropathy** **Increased ECM production**

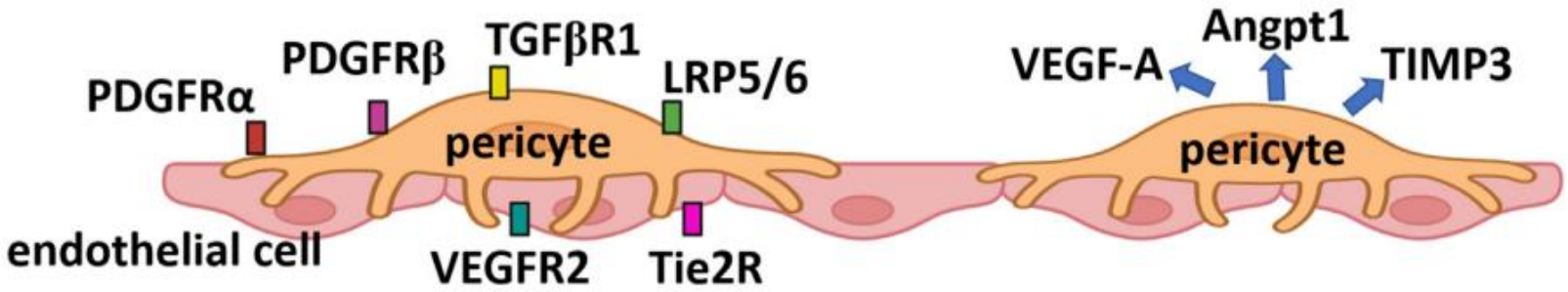
Pericyte-like Mesangial Cells

Feature	Pericyte-like Mesangial Cells
Location	Glomerular tuft (mesangium)
Morphology	Elongated, pericyte-like processes; express PDGFRβ
Functions	Contractility, matrix production, phagocytosis, immune response
Development	PDGF-B/PDGFRβ pathway dependent
Pathological Role	Proliferation and matrix expansion in glomerular diseases

Pericyte-like Mesangial Cells



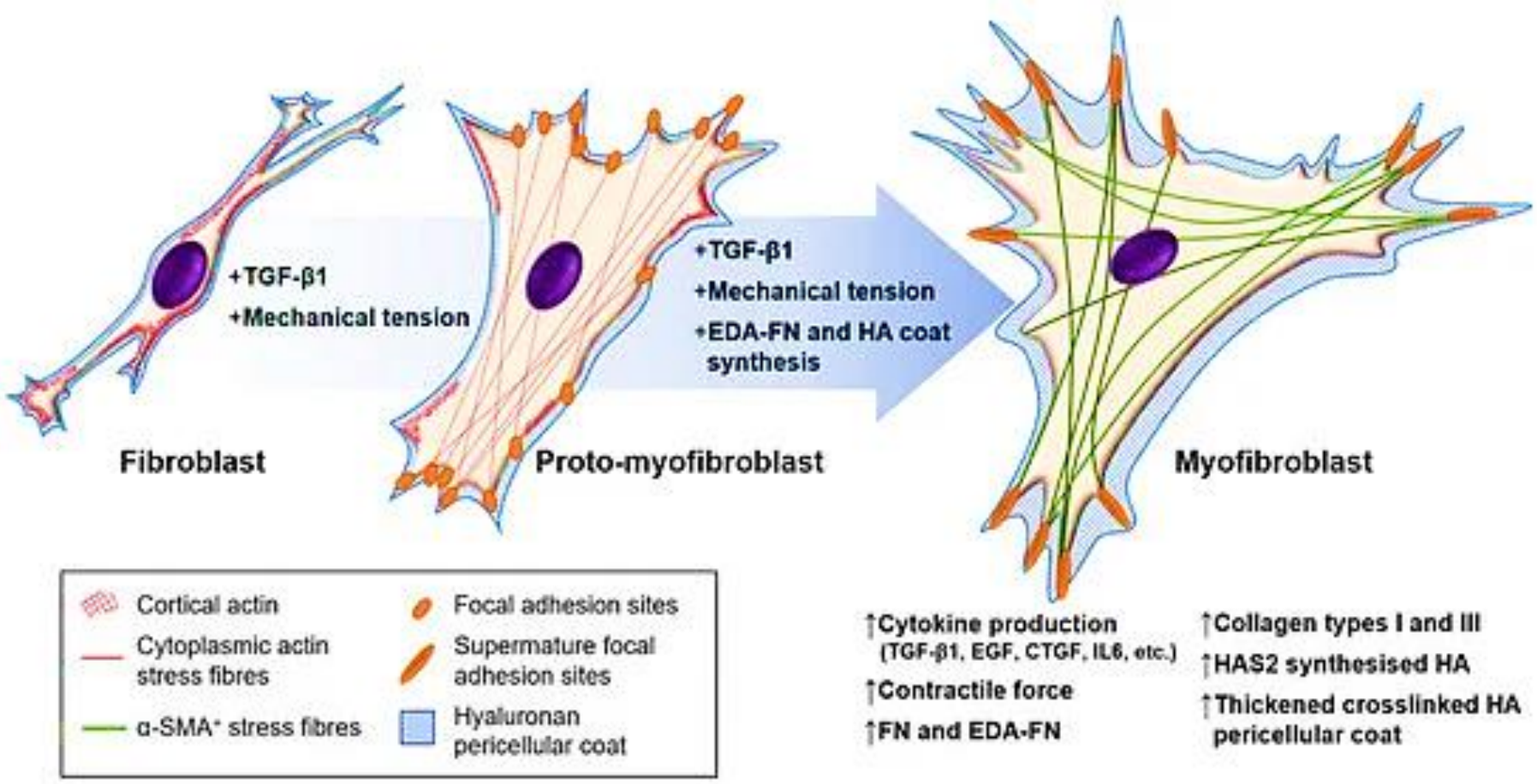
Pericyte marker	
PDGFR-β	NG2
PDGFR-α	Gli1
CD73	TNC
SMMHC	p75NTR
CD248	MYH11
KCNA5	



Fibroblast-like Mesangial Cells

Feature	Fibroblast-like Mesangial Cells
Location	**Glomerular mesangium**
Markers	***PDGFRA*, α-smooth muscle actin (α-SMA)**
Primary Function	**Matrix homeostasis**
Pathological Role	**Fibrosis** **Glomerulosclerosis** **Induced myofibroblast-like phenotype, characterized by:** • **Expression of α-SMA** • **Excessive ECM deposition** • **Proliferation driven by PDGF and other mediators**

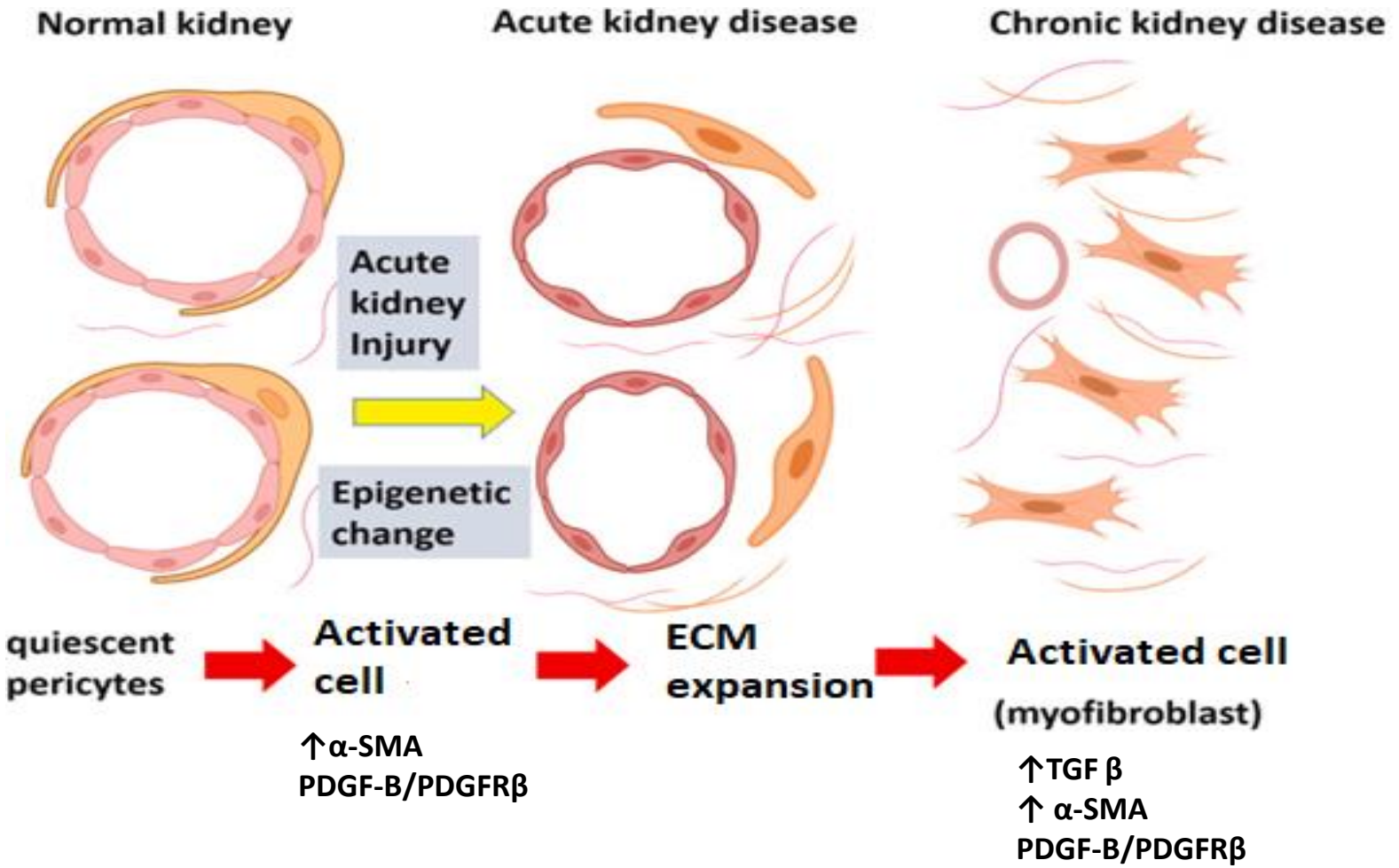
Fibroblast-like Mesangial Cells



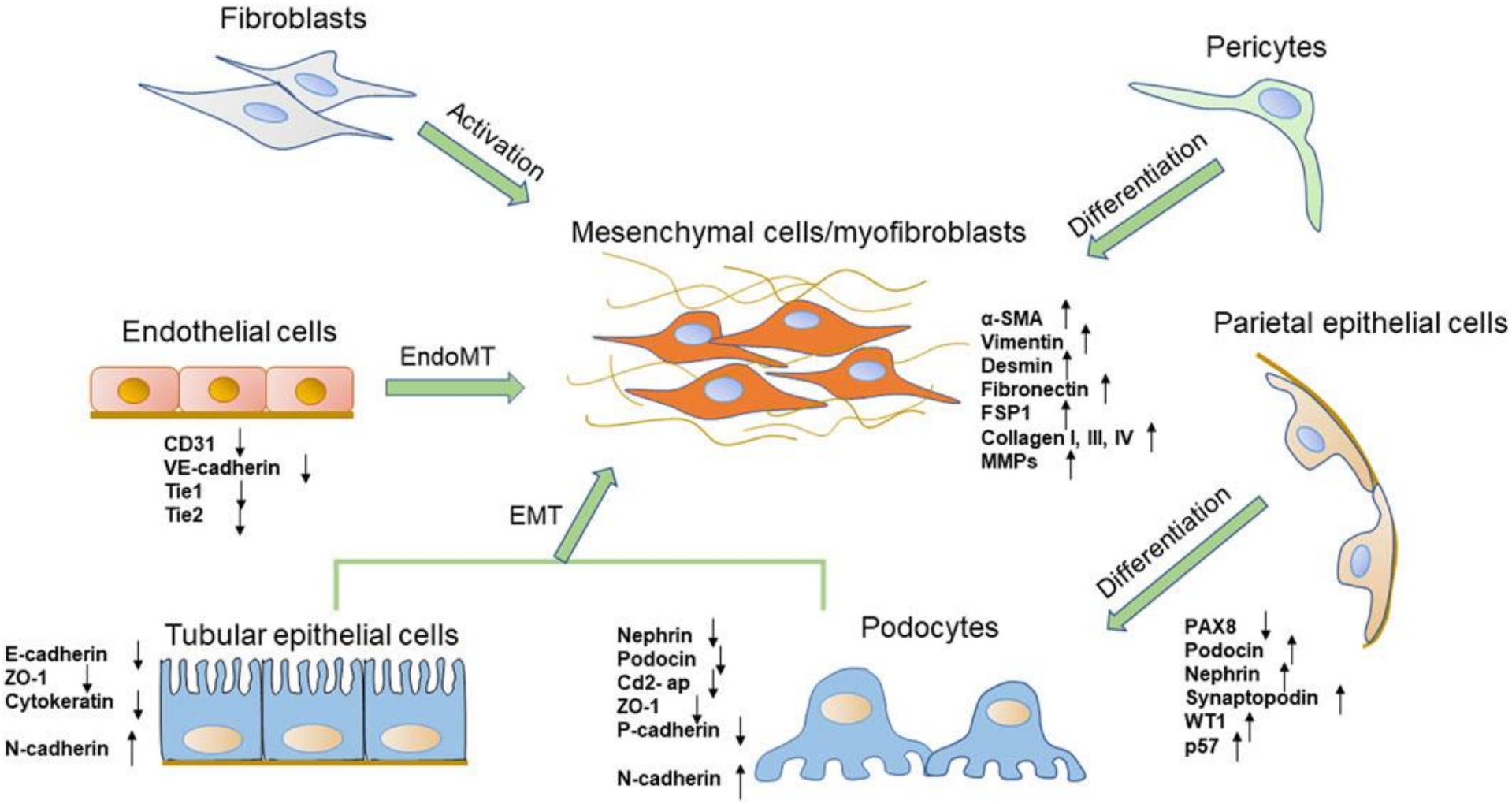
Different Mesangial Cell Phenotypes

Attribute	Quiescent MC	Activated MC	Hypertrophied MC
Proliferation rate	**Low**	**High**	**Low**
Cell shape	**Stellate**	**Elongated**	**Polygonal**
***α*-sma expression**	**None**	**Low**	**High**
Key mediators	**-**	**PDGF-*β***	**PDGF-*β*, TGF-*β***
Associated matrix proteins	**Coll IV**	**Coll I, Fibronectin**	**Coll IV,Coll I, Fibronectin**

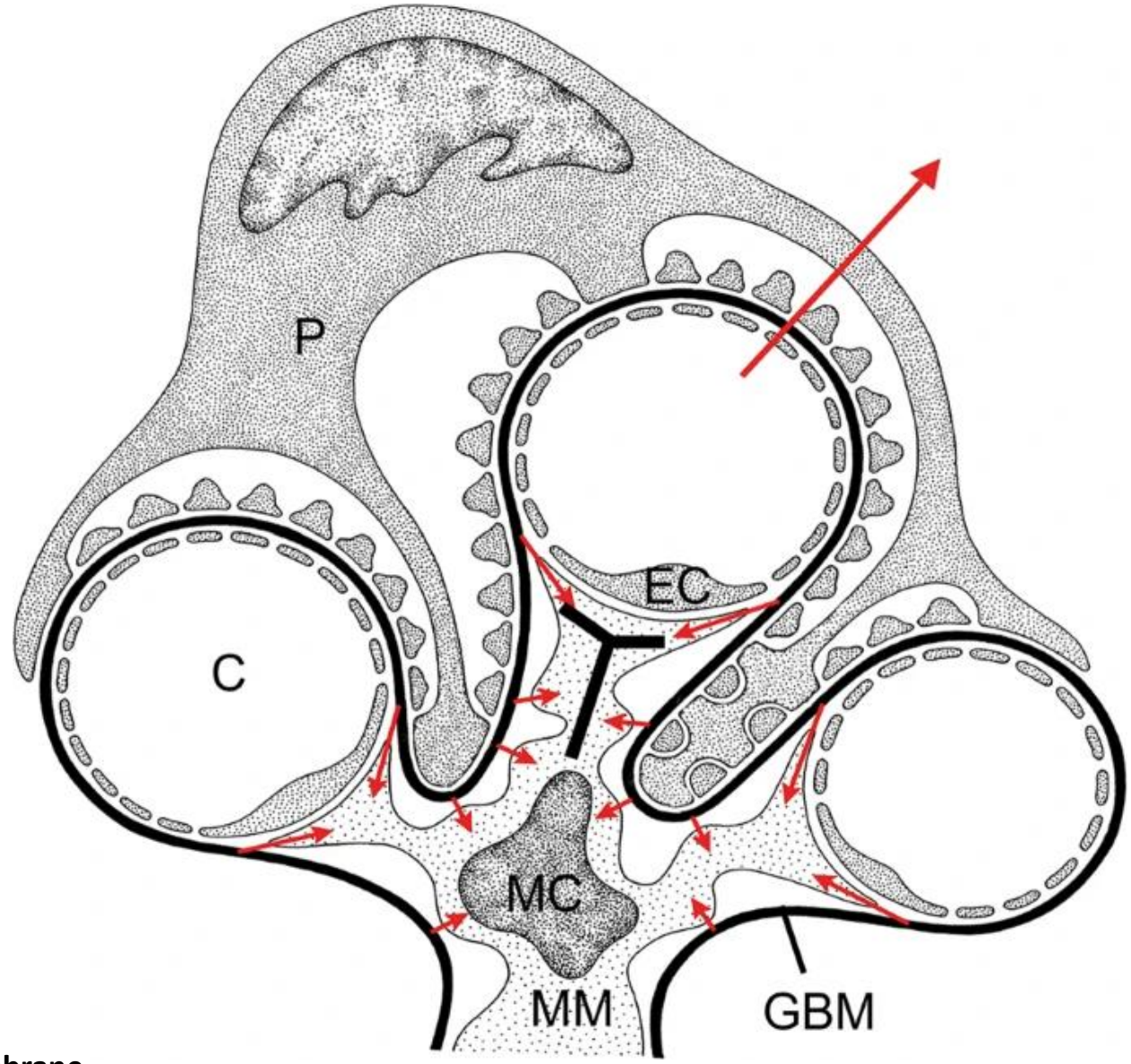
Different Mesangial Cell Phenotypes



Cellular phenotypic transitions in diabetic nephropathy



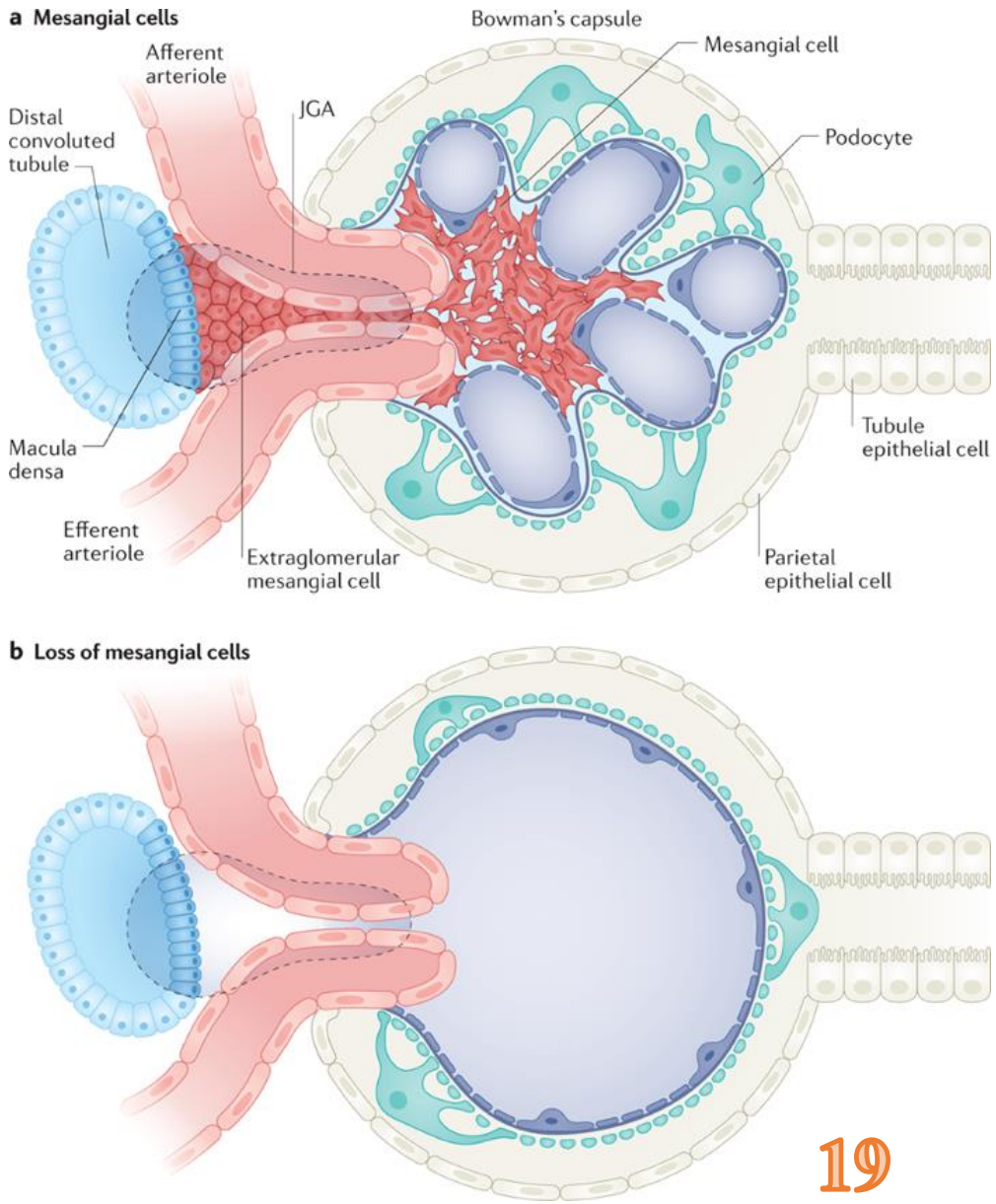
Mesangial cell structure



MC: mesangial cell
MM: mesangial matrix
P: podocytes
EC: endothelial cells
C: capillaries
GBM: glomerular basement membrane

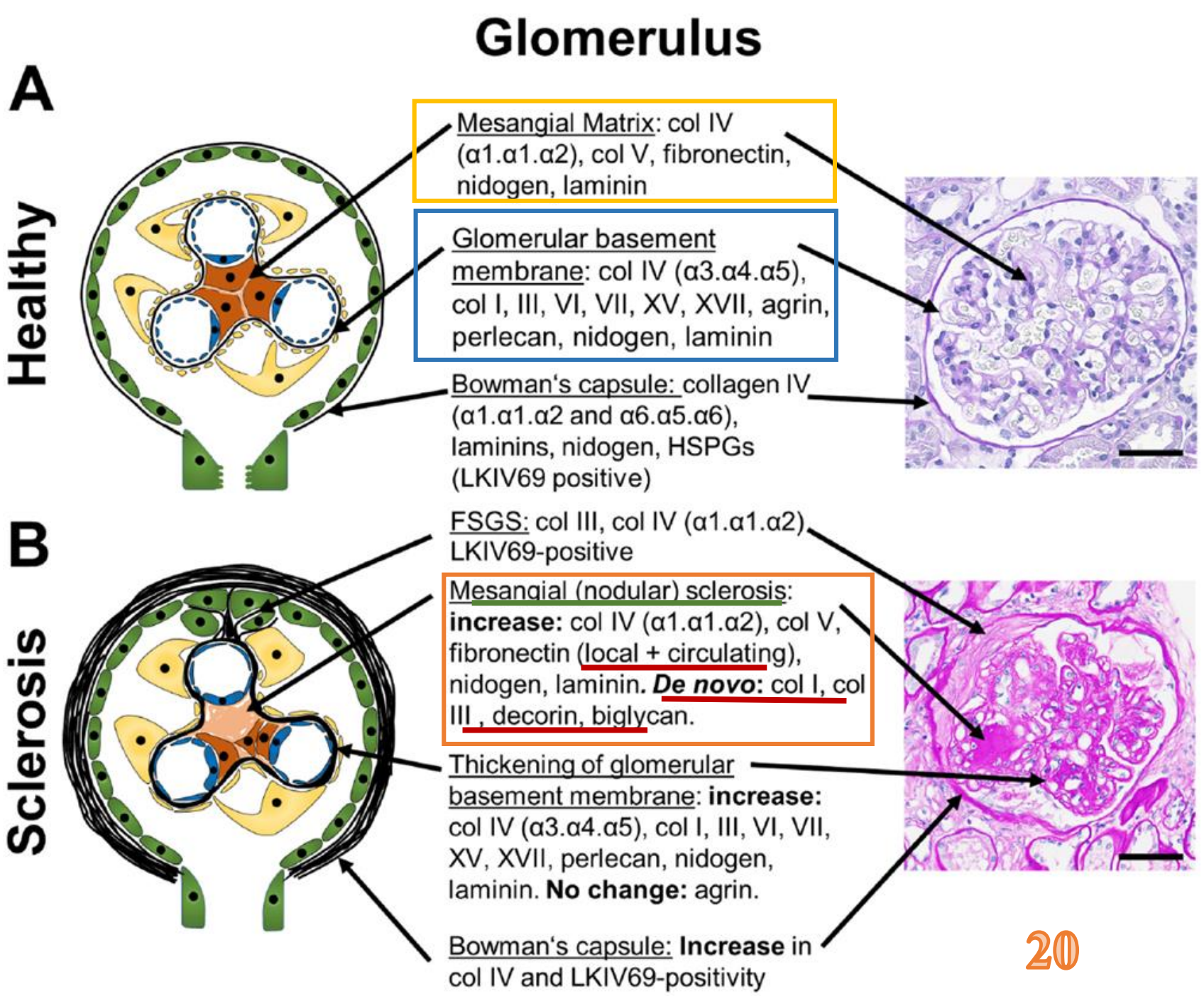
Specialized functions of mesangial cells

- Structural Support
- Biomechanical homeostasis of the glomerulus
- Regulation of Glomerular Filtration
- Controll renal blood flow
- Cell-to-Cell Communication
- They produce extracellular matrix
- Fibrosis
- Glomerular recovery after injury



ECM Regulation

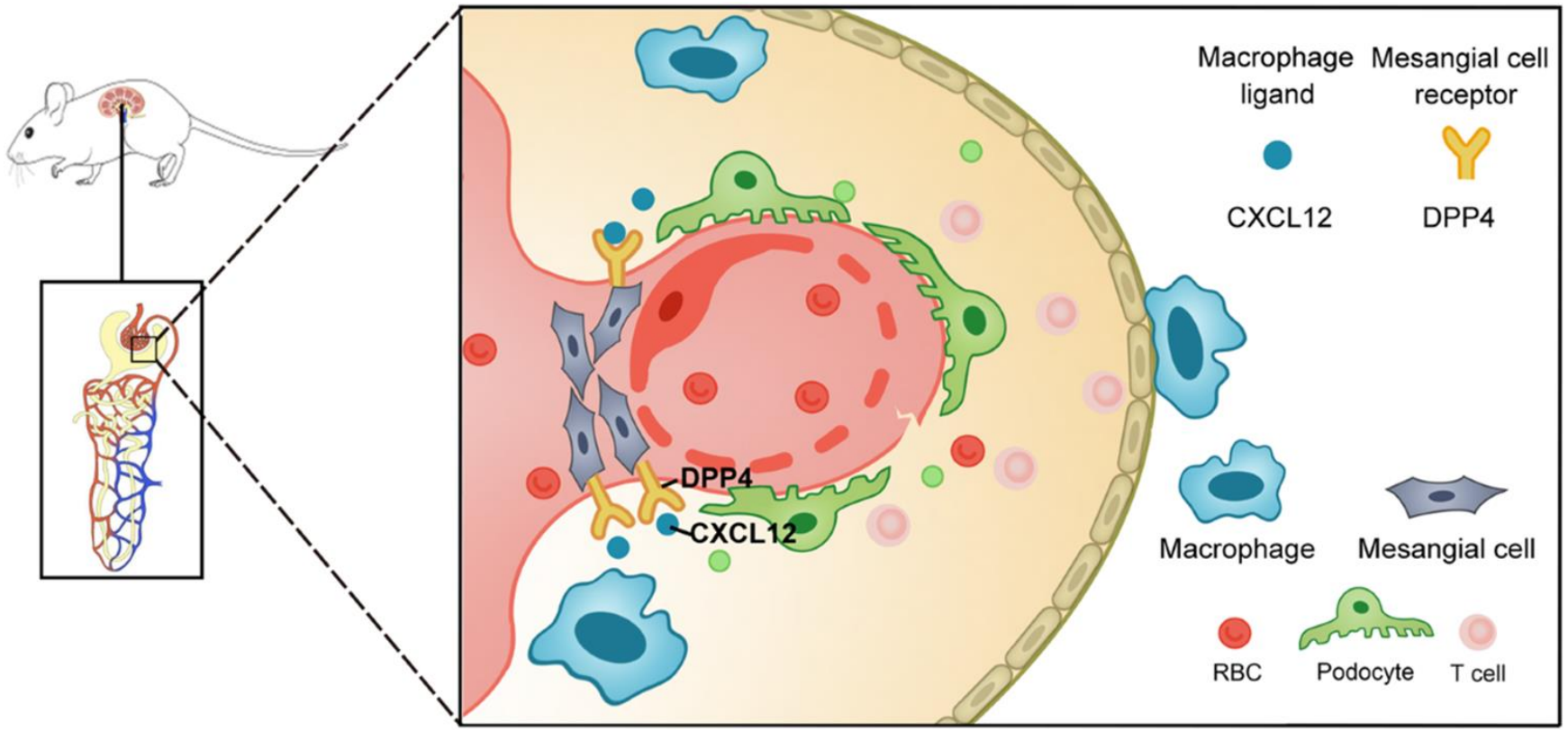
- ✓ **Facilitating the turnover of GBM**
- ✓ **Provide an environment for maintaining endothelial cell and podocyte homeostasis**



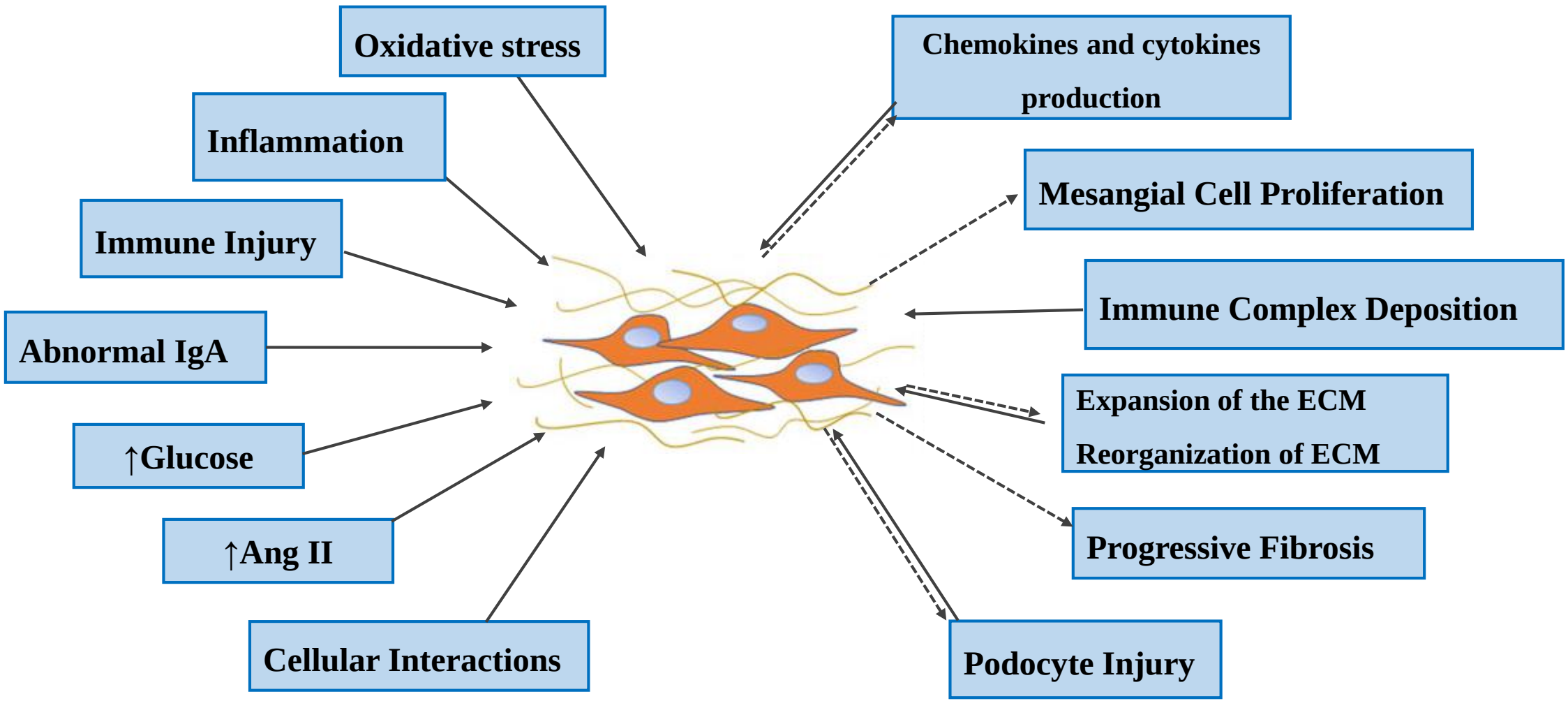
Specialised functions of mesangial cells

- Phagocytotic activity

Phagocytosis of macromolecules and immune complexes



Pathogenic Mechanisms of Mesangial Injury



Injury Patterns in Diseases Localized to the Glomerular Stalk

Injury Patterns and Diseases

- Mesangiolysis

The dissolution of mesangial cells and matrix

Characterized by high immunological activity and is often acute

- Mesangioproliferative Glomerulonephritis :

Proliferation of mesangial cells

Increase in mesangial matrix

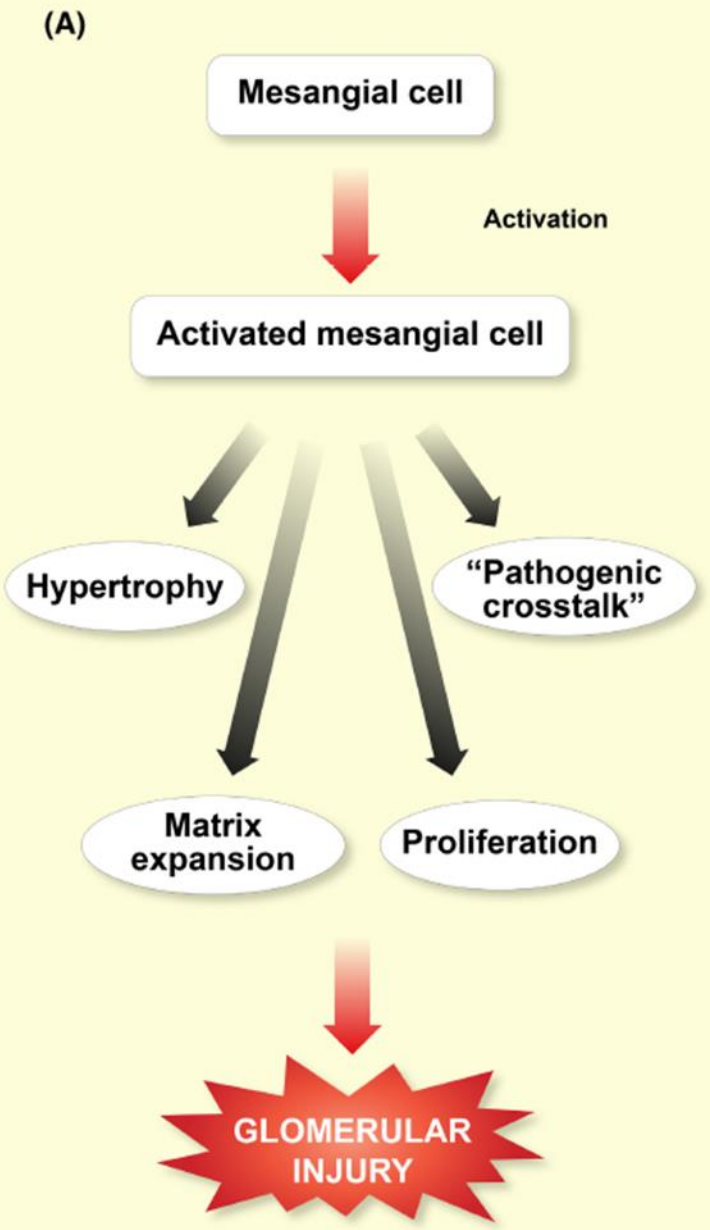
Characterized by variable immunological activity and chronicity

- Membranoproliferative Glomerulonephritis :

Affects both mesangial and podocytes

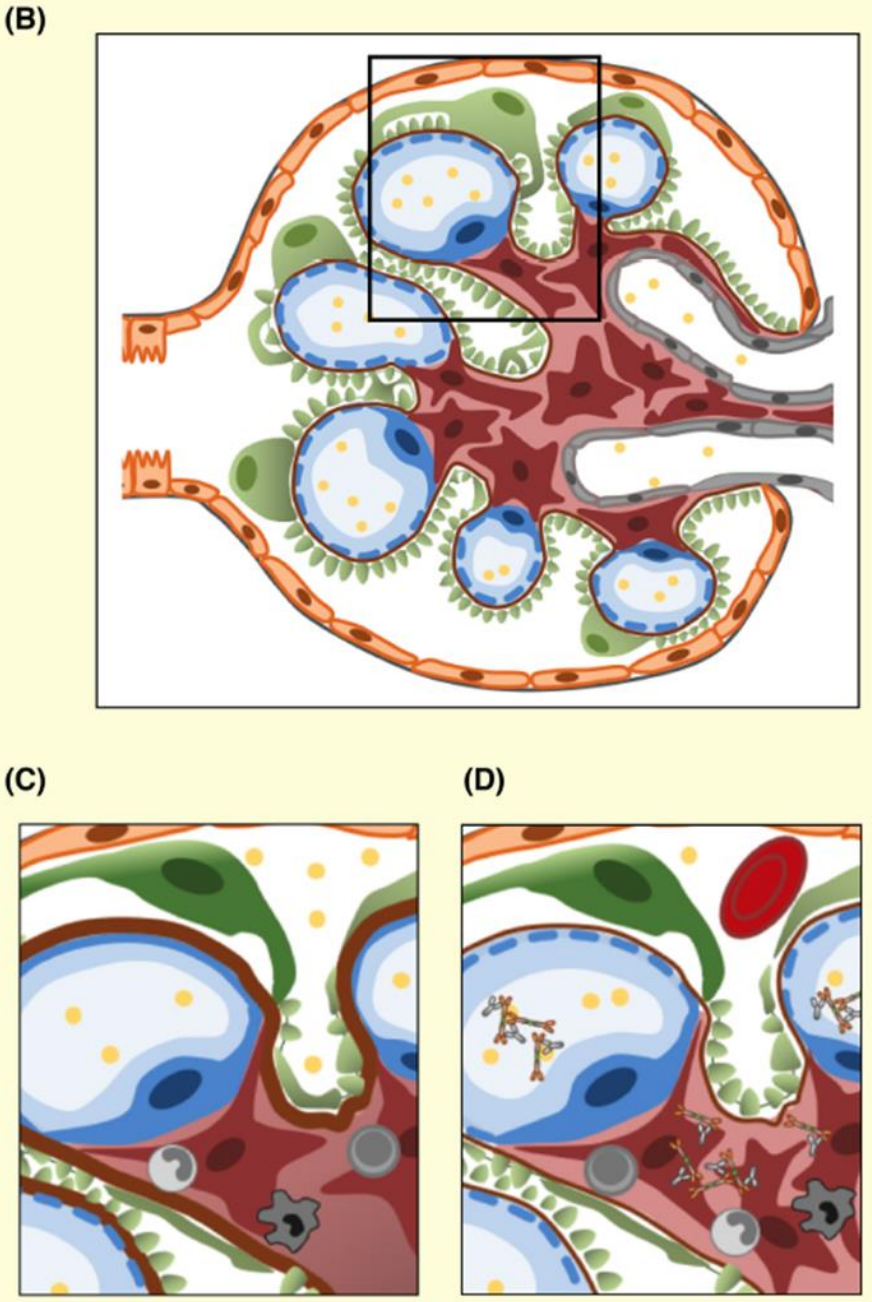
Mesangial cell proliferation and matrix expansion

Characterized by intermediate immunological activity and can be acute



Pathological Conditions that Affect Mesangial Cells

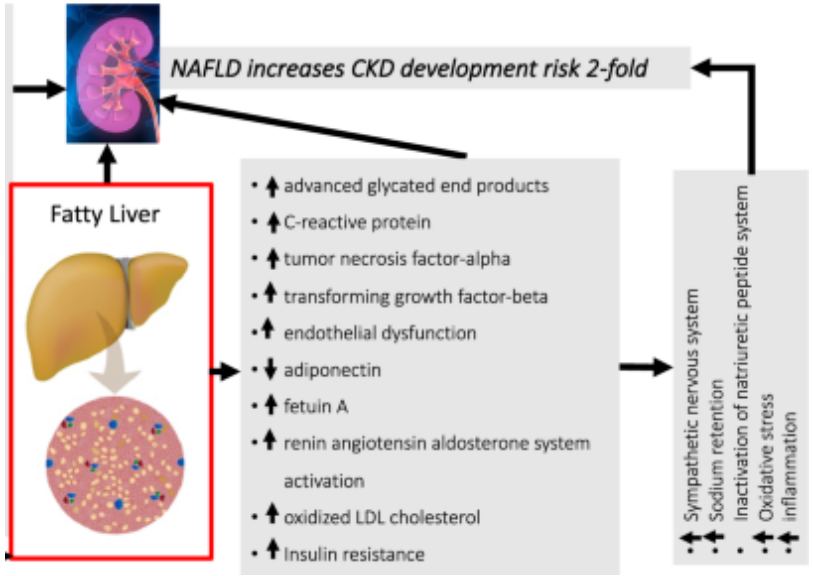
- Thrombotic microangiopathy
- Ischaemia
- Hypertension
- Lupus Glomerulonephritis
- Diabetes



Mesangial Injury Patterns in Glomerular Diseases

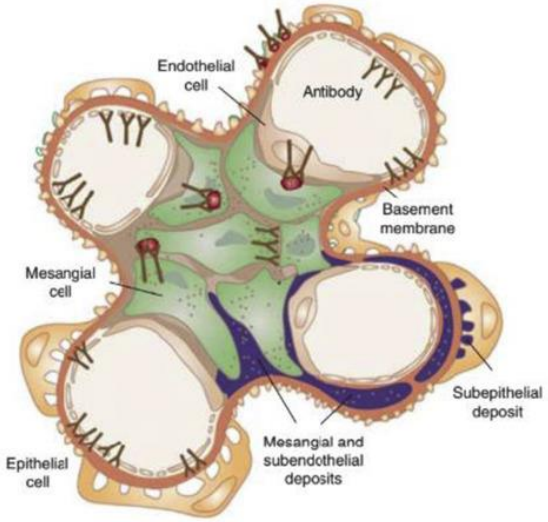
- **Cirrhotic Glomerulosclerosis**

Thickening of the glomerular mesangial stalk and capillary wall
↑ECM
IgA deposition in the glomerular mesangium



- **Lupus Mesangio-proliferative Glomerulonephritis**

↑ Mesangial size and cellularity
Inflammatory cell infiltration in the glomeruli and peri-glomerular region
Neutrophils
dendritic cells
Macrophages T cells



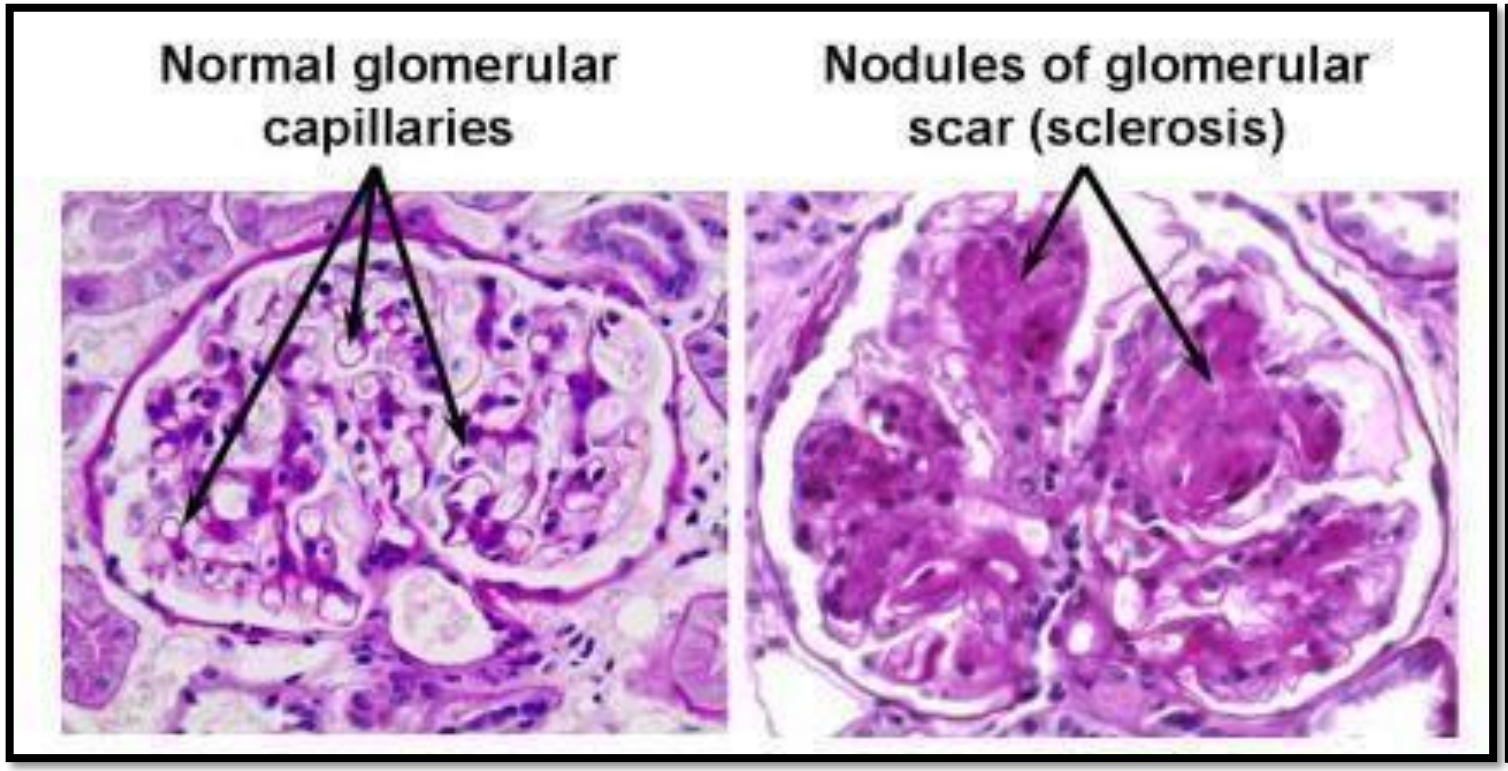
Mesangial Injury Patterns in Glomerular Diseases

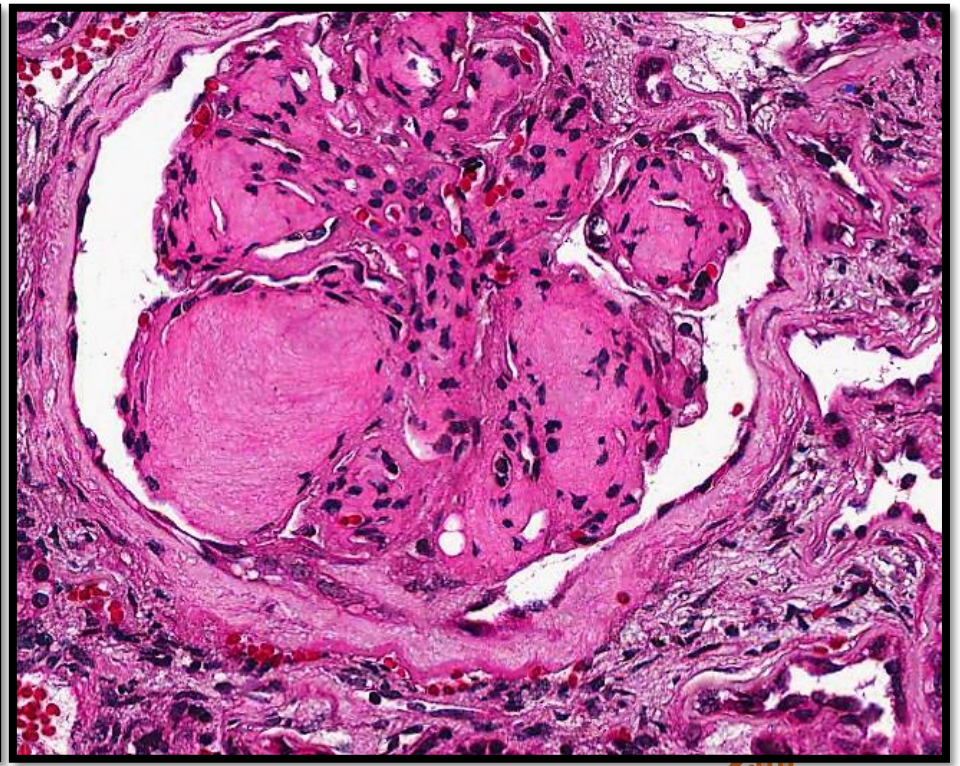
Diabetic kidney disease (DKD)

ECM Expansion

Cellular proliferation

Increased cellularity of the glomerulus (now known as Kimmelstiel– Wilson nodules)

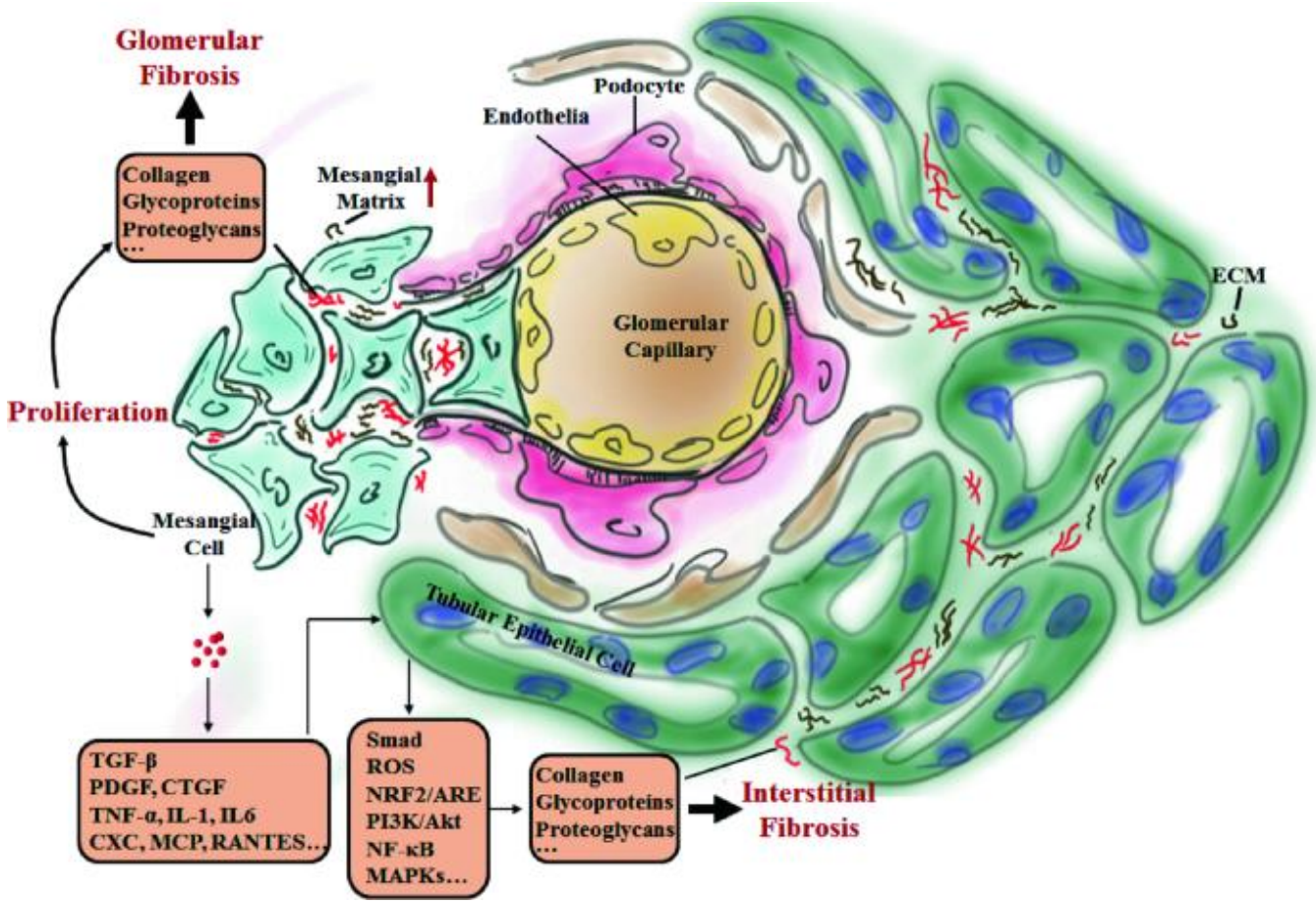




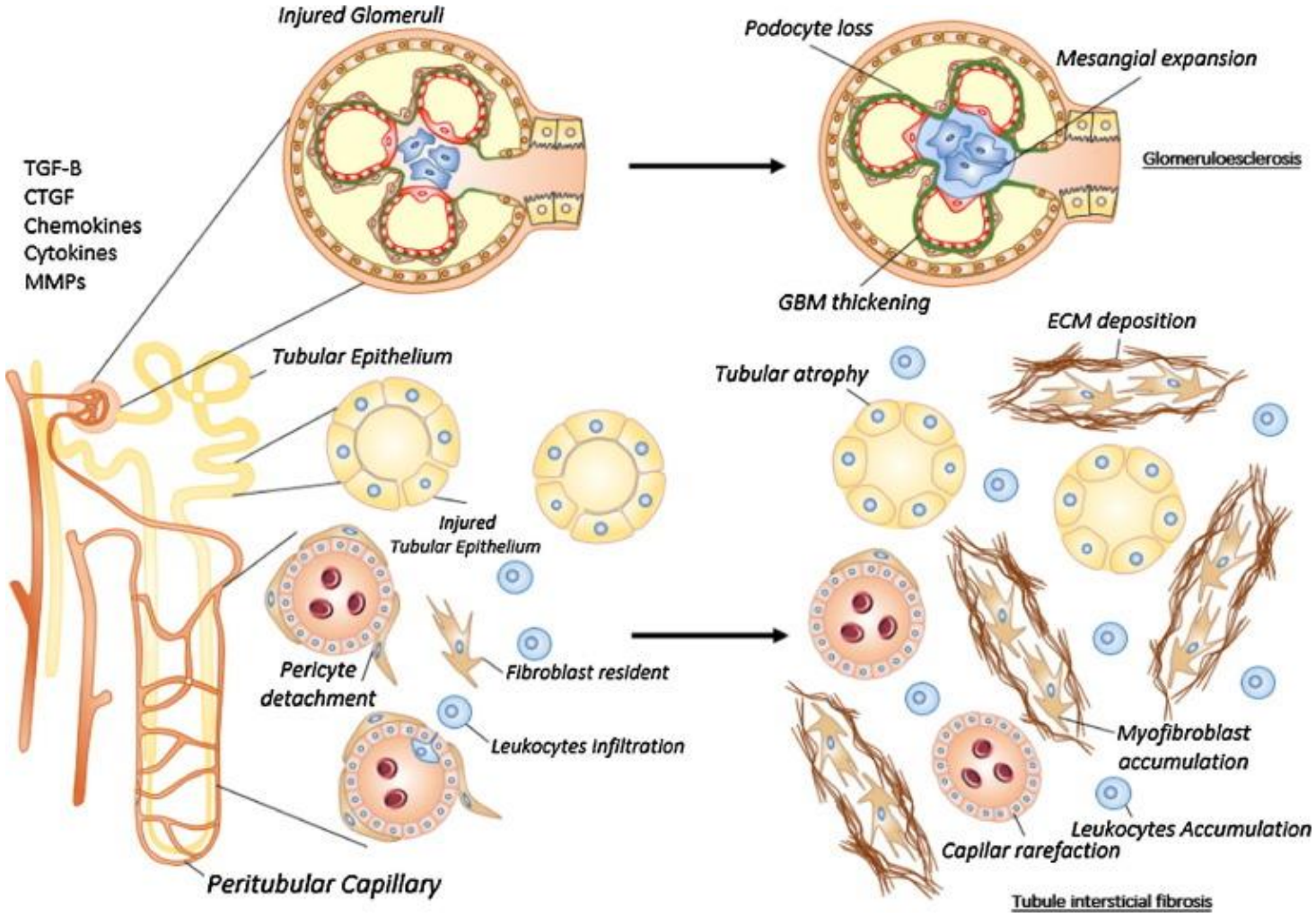
High glucose (HG) levels affect mesangial cells

Cellular Response	Pathway	Effect on mesangial cells
Oxidative Stress	ROS production	ECM accumulation and Fibrosis
Fibrotic Response	TGF-β/ Smad, Integrin β1	Fibrosis
Inflammatory Response	NF-κB, IL-6, TNF-α, IL-1β, Inflammatory cytokines	Inflammaton
Ferroptosis	HMGB1 ,Nrf2	Cell death

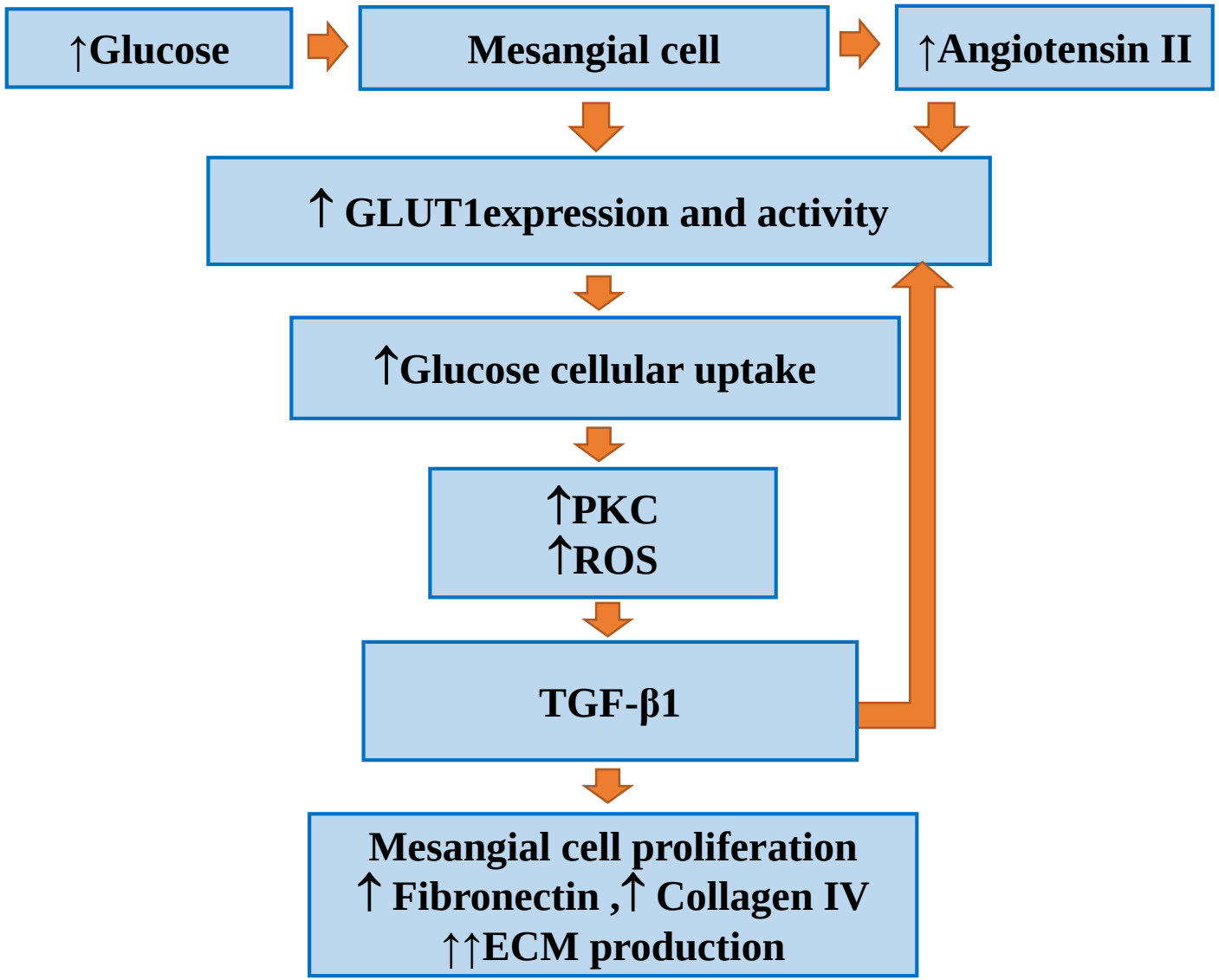
Mesangial Cells and Renal Fibrosis



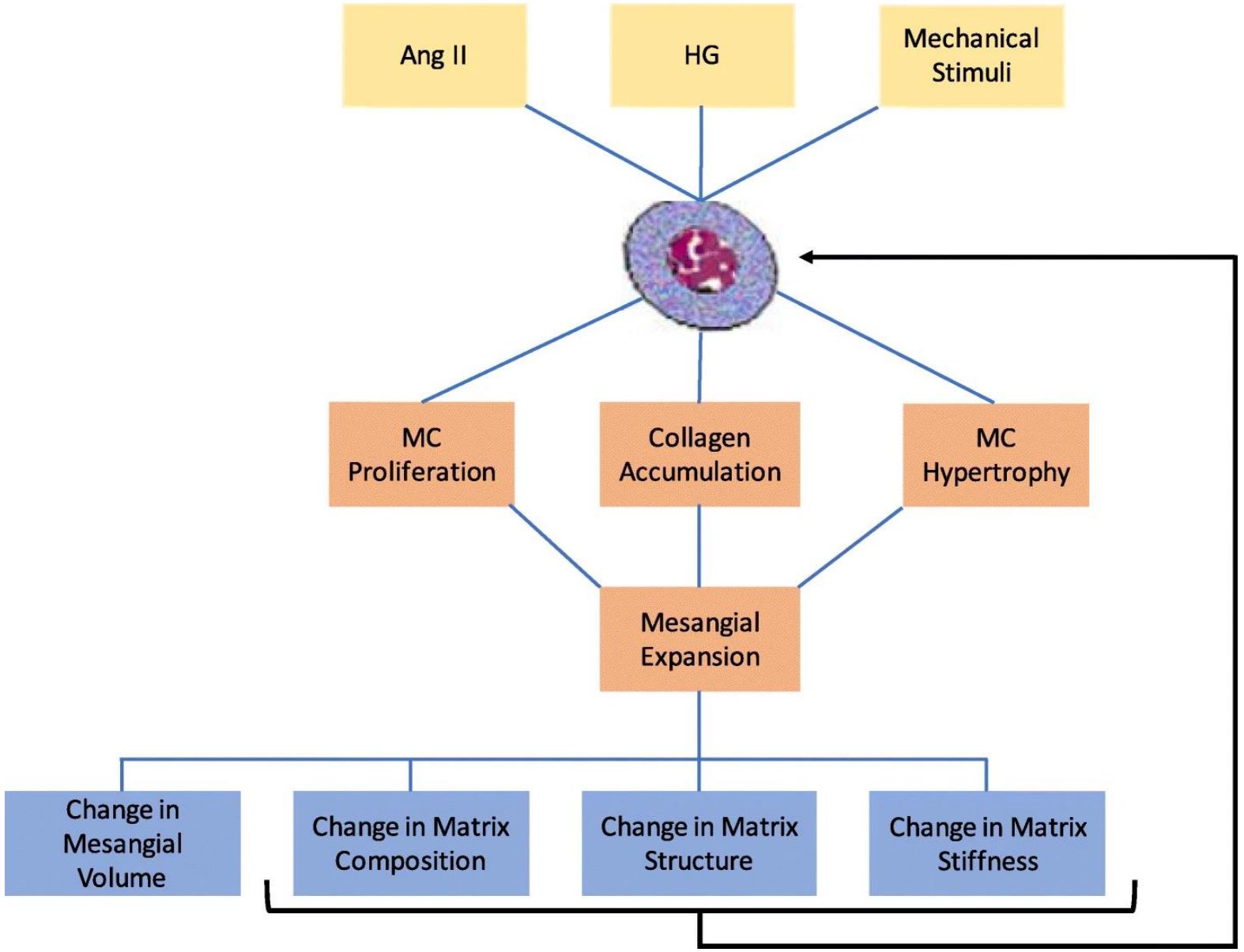
Mesangial Cells and Renal Fibrosis

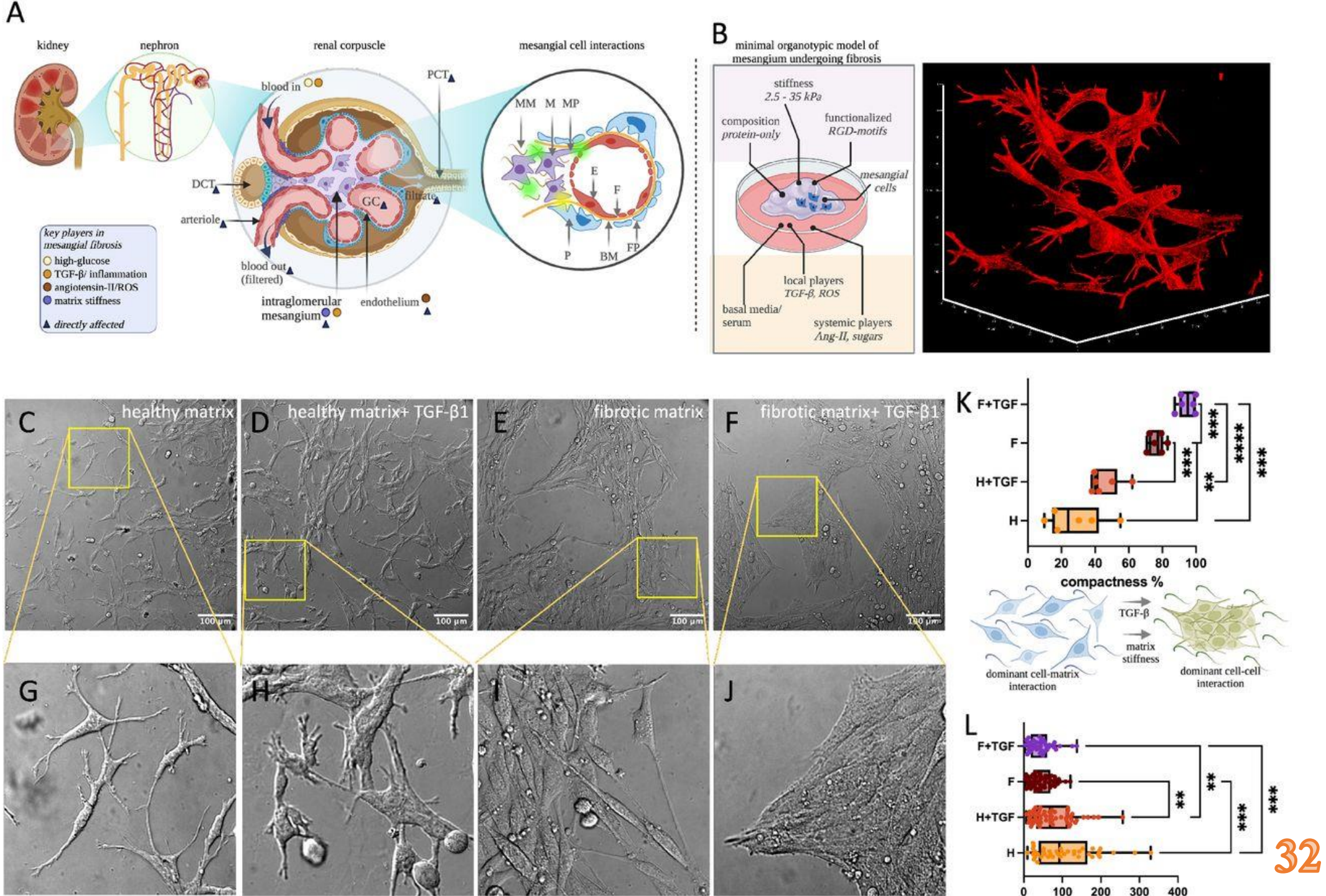


Mesangial Cell and Podocyte Interactions in Diabetic Nephropathy

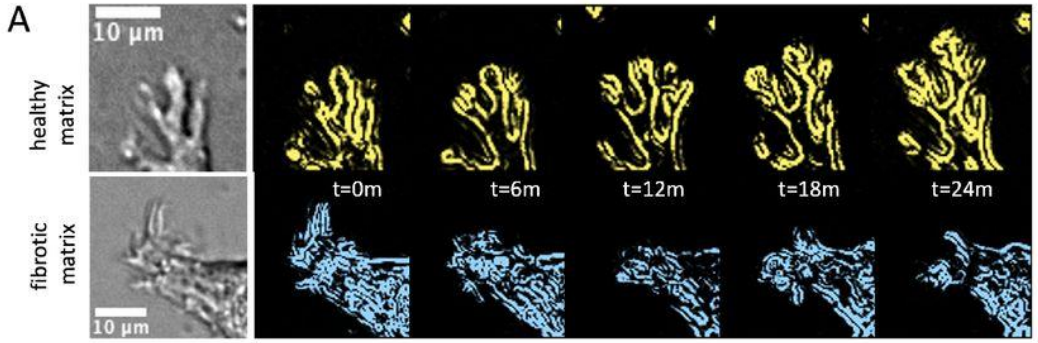


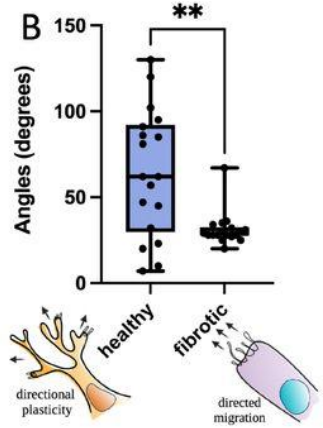
Multiscale Process That Governs Mesangial Expansion

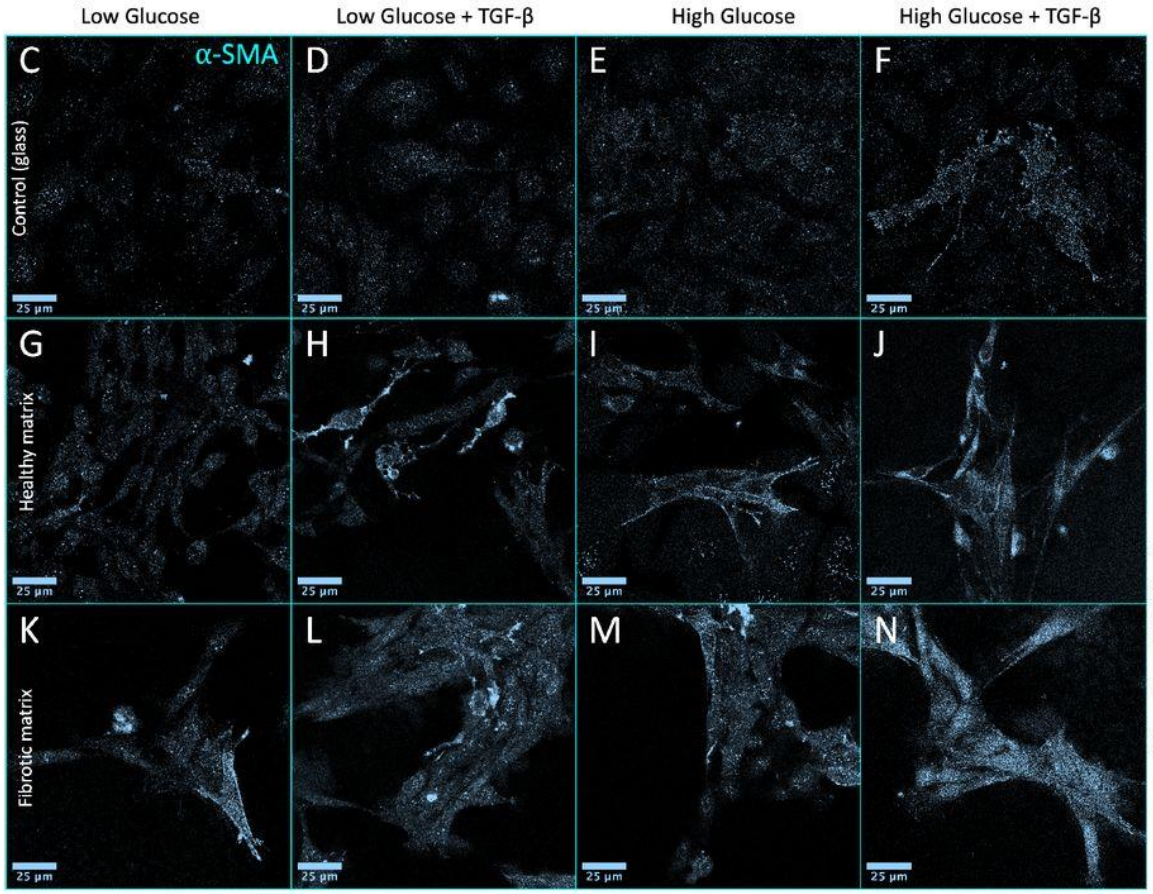


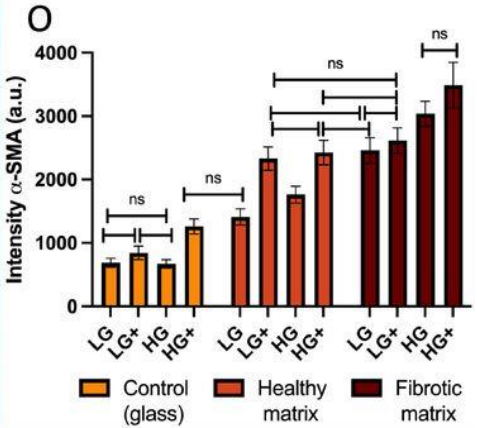

A
kidney
nephron
renal corpuscle
mesangial cell interactions
blood in
PCT
DCT
GC
filtrate
arteriole
blood out (filtered)
intraglomerular mesangium
endothelium
MM M MP
E
F
P
BM
FP
key players in mesangial fibrosis
high-glucose
TGF-β/ inflammation
angiotensin-II/ROS
matrix stiffness
directly affected
B
minimal organotypic model of mesangium undergoing fibrosis
stiffness
2.5 - 35 kPa
composition
protein-only
functionalized
RGD-motifs
mesangial cells
local players
TGF-β, ROS
basal media/ serum
systemic players
Ang-II, sugars
C
healthy matrix
D
healthy matrix+ TGF-β1
E
fibrotic matrix
F
fibrotic matrix+ TGF-β1
100 µm
G
H
I
J
K
F+TGF
F
H+TGF
H
0
20
40
60
80
100
compactness %
TGF-β
matrix stiffness
dominant cell-matrix interaction
dominant cell-cell interaction
L
F+TGF
F
H+TGF
H
0
100
200
300
400

Changes in Mesangial Cell Motility and Contractility

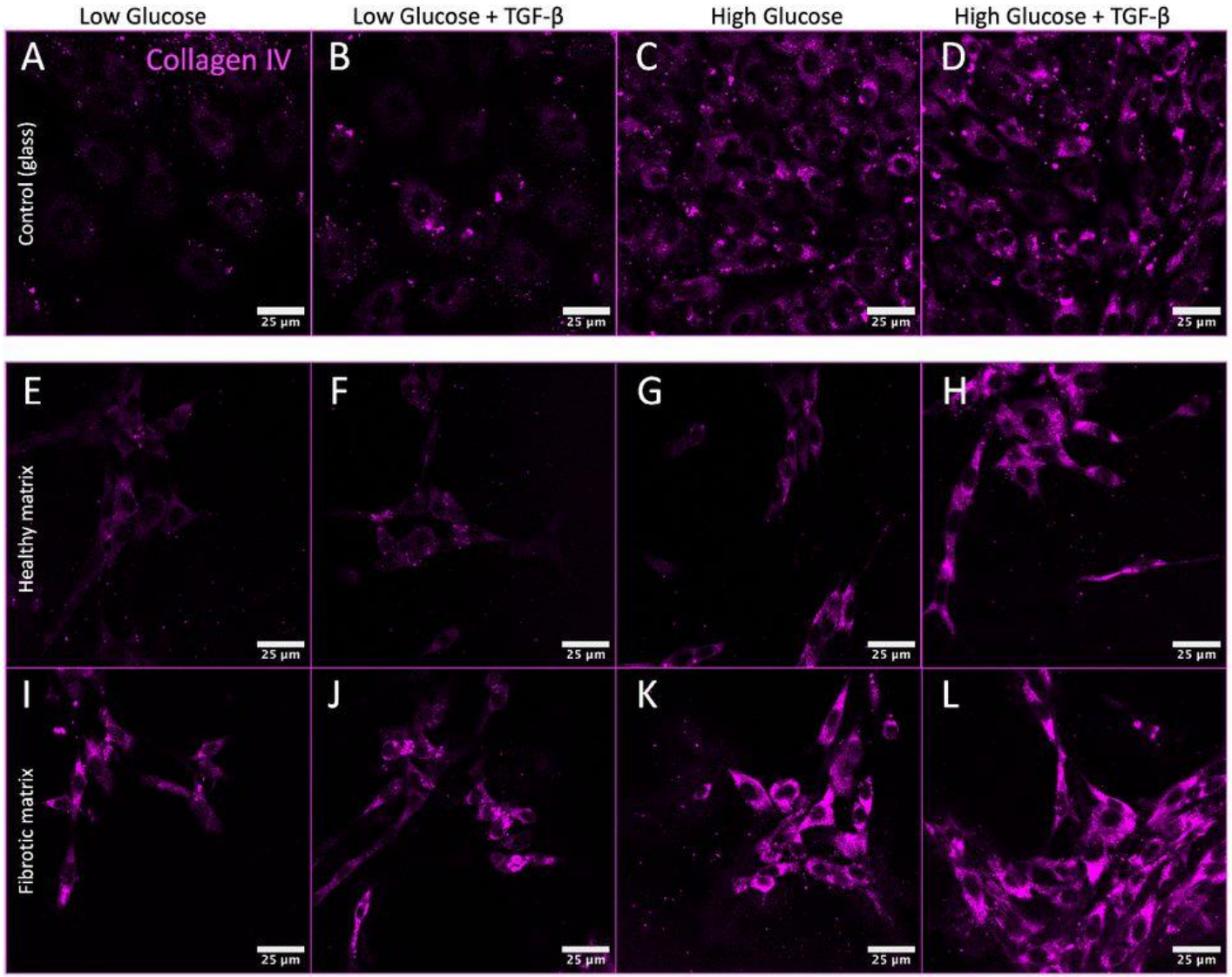


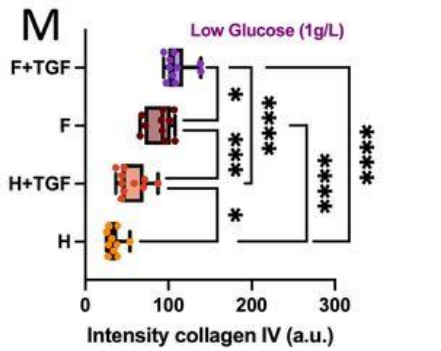


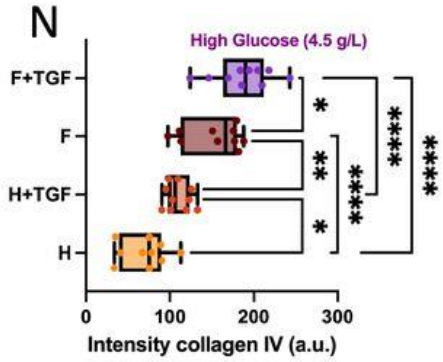




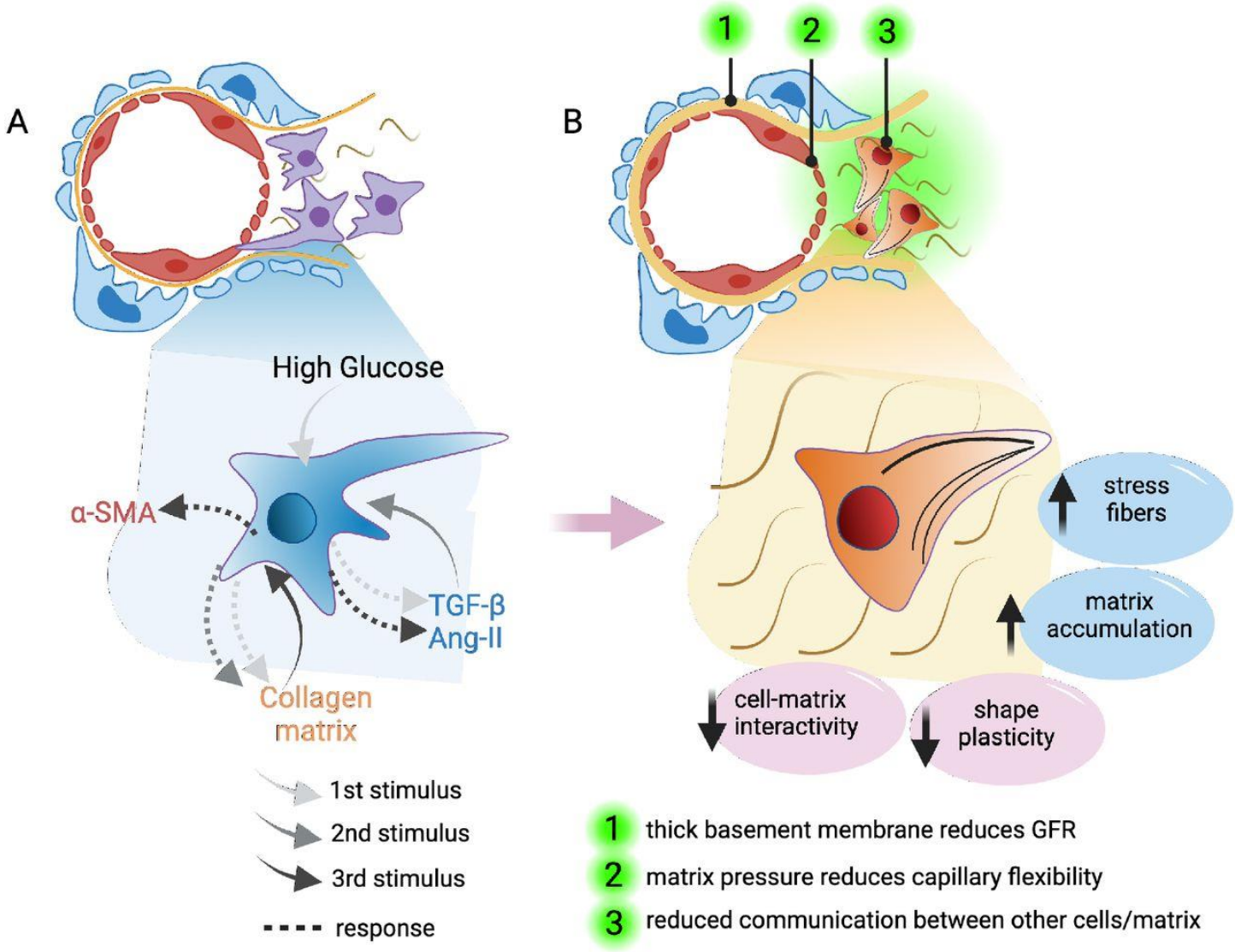
Effect of Mechano-chemical Conditions on MCs



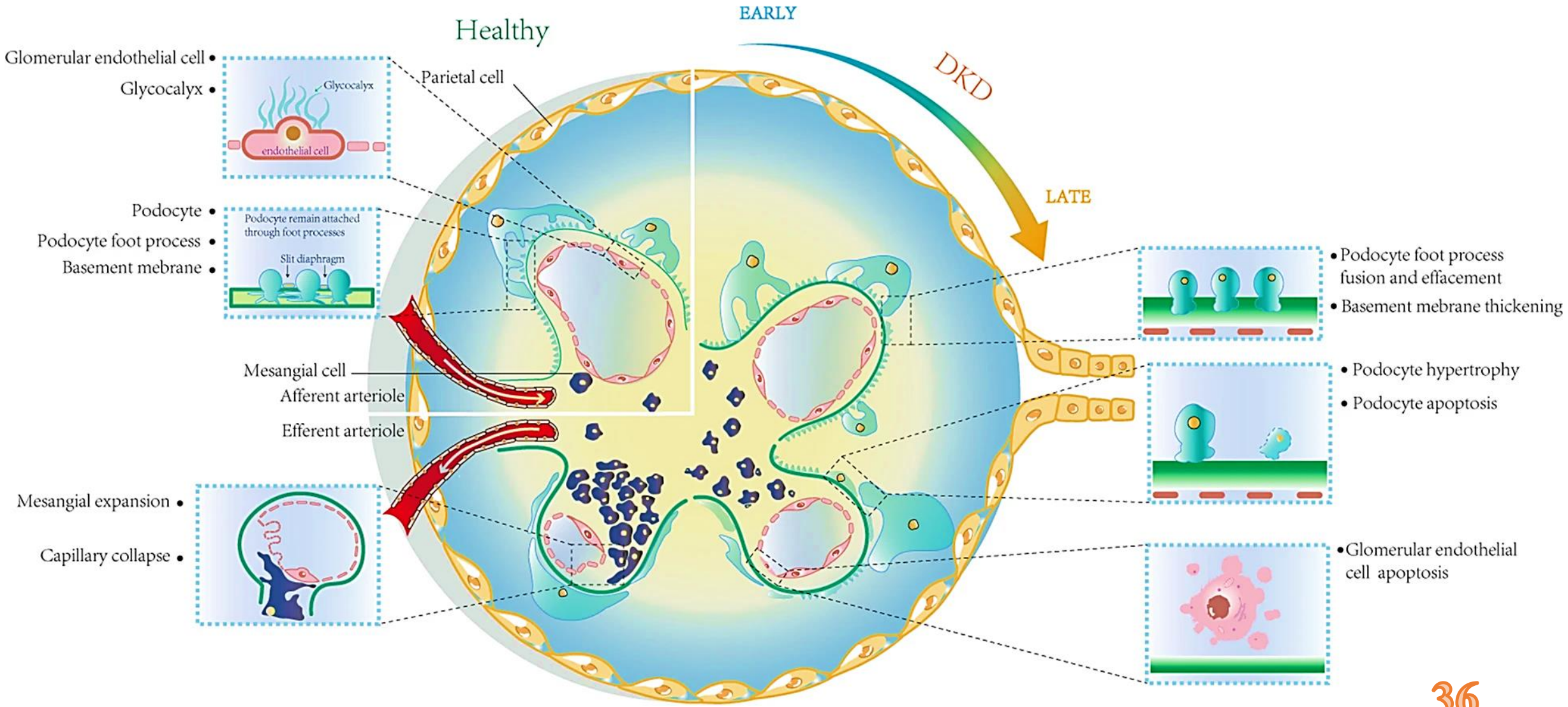




The Effect of Mechano-chemical Co-stimulation on MCs in DKD



Crosstalk Among Podocytes, Glomerular Endothelial Cells and Mesangial Cells in DKD



Mesangial Cell and Podocyte Interactions in Diabetic Nephropathy

High glucose

Oxidative stress, and Inflammatory factors

Podocyte injury Podocytopenia

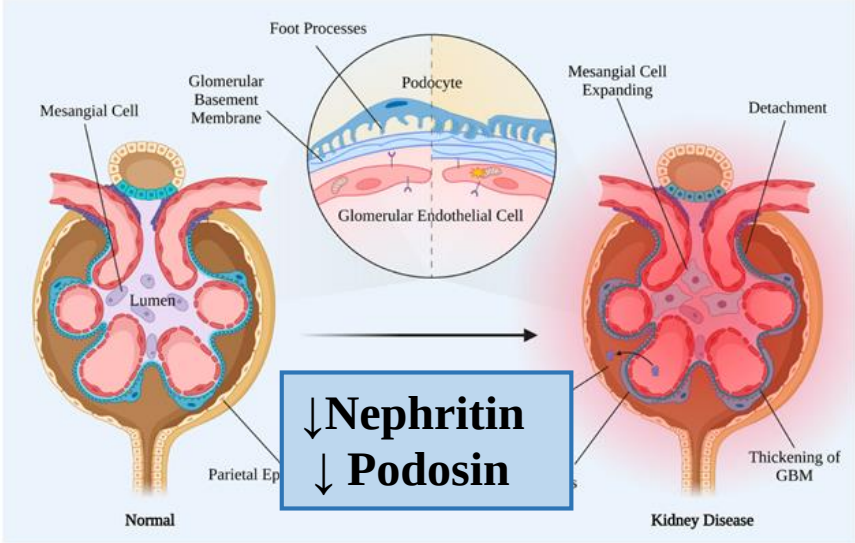
Disruption of the filtration barrier

Proteinuria

Cytokines production

Activating mesangial cells

Mesangial cells releasing TGF-β, IL-6



↓Nephritin
↓ Podosin

Therapeutic Targets:
Podocyte-protecting therapies (ACE inhibitors, ARBs)
Anti-inflammatory therapies (cytokine inhibitors)

Glomerular inflammation and fibrosis
Mesangial Cell Proliferation
Glomerulosclerosis
Expansion of the ECM


Thanks for your attention