# Novel pathologic aspects of glomerular crescents

*Mitra Mehrazma*

*Professor of Pathology*

*Hasheminejad Kidney Center*

*Iran University of Medical Sciences*

# Definition

- Cellular glomerular crescents are defined as two or more layers of proliferating cells in Bowman's space involving 10% or more of the circumference of Bowman‘s capsule.
- Crescents can be composed of a variable mixture of cells, fibrin, and fibrous matrix.
- A composition of more than 75% cells and fibrin and less than 25% fibrous matrix is referred to as ‘cellular crescent’, a composition of more 25–75% cells and fibrin and the remainder fibrous matrix is a ‘fibrocellular crescent’, and more than 75% fibrous matrix and less than 25% cells and fibrin is a ‘fibrous crescent

- the severity of the renal failure and other clinical manifestations of glomerulonephritis (eg, hypertension, edema) correlates with the percentage of glomeruli that exhibit crescents
- The duration and potential reversibility of the underlying disease correspond with the relative predominance of cellular or fibrous components in the crescents.

Lippincott Williams & Wilkins Open Access

CURRENT OPINION IN NEPHROLOGY AND HYPERTENSION

Curr Opin Nephrol Hypertens. 2020 May; 29(3): 302–309.
Published online 2020 Mar 5. doi: 10.1097/MNH.0000000000000596: 10.1097/MNH.0000000000000596

PMCID: PMC7170443
PMID: 32132388

# The glomerular crescent: triggers, evolution, resolution, and implications for therapy

Lidia Anguiano,[a] Renate Kain,[b] and Hans-Joachim Anders[a]

[a]Renal Division, Department of Medicine IV, University Hospital of the Ludwig Maximilian University, Munich, Germany
[b]Department of Pathology, Medical University of Vienna, Vienna, Austria
Correspondence to Hans-Joachim Anders, MD, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Ziemssenstr. 1, 80336 München, Germany. Tel: +49 89 440053583; fax: +49 89 440053379; e-mail: hjanders@med.uni-muenchen.de



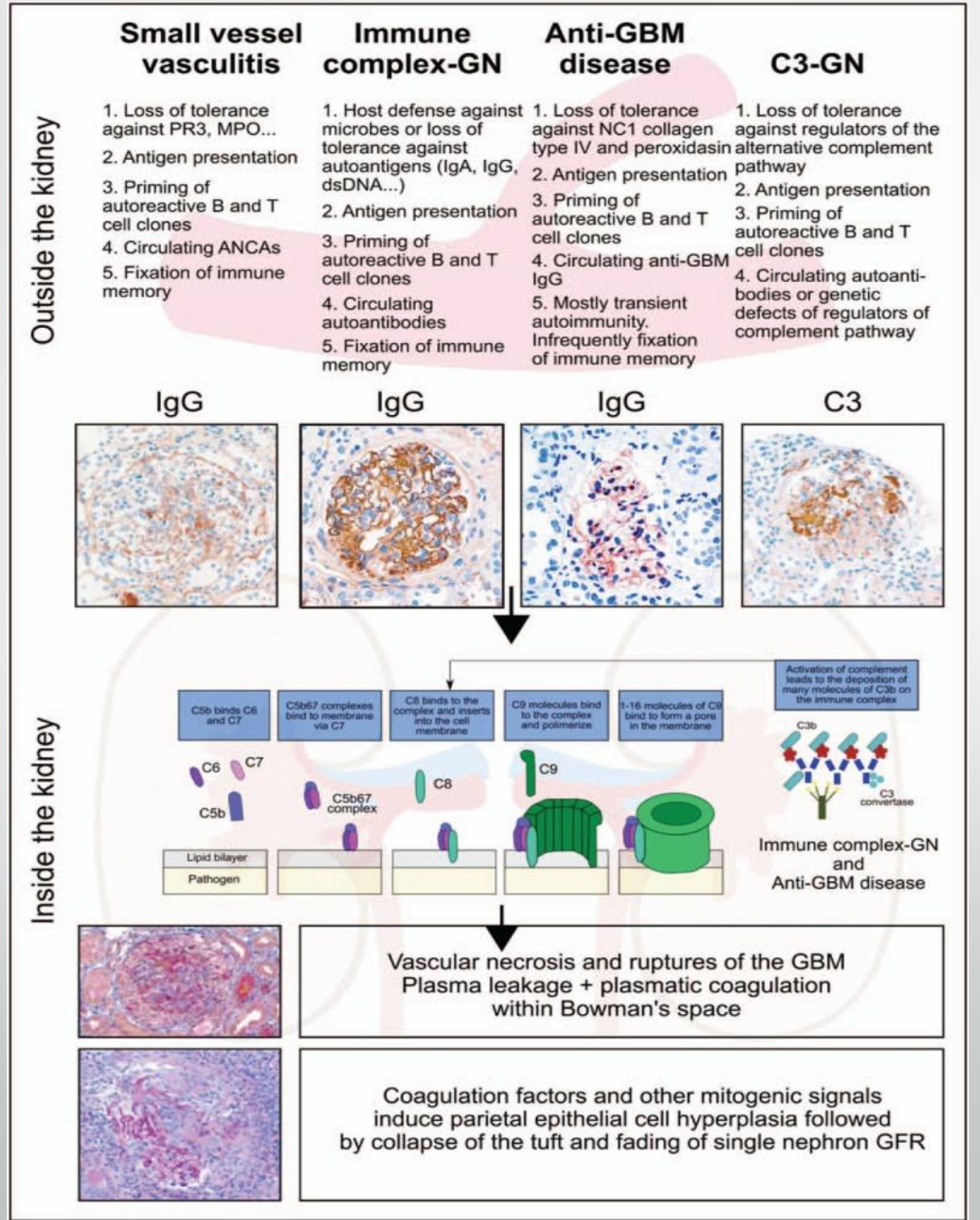
## Abstract

### Purpose of review

Crescents are classical histopathological lesions found in severe forms of rapidly progressive glomerulonephritis, also referred to as crescentic glomerulonephritis (CGN). Crescent formation is a consequence of diverse upstream pathomechanisms and unraveling these mechanisms is of great interest for improving the management of patients affected by CGN. Thus, in this review, we provide an update on the latest insight into the understanding on how crescents develop and how they resolve.

# Evolution of crescent formation

- injury to the glomerular microvasculature involve *local complement activation* as a shared molecular target for therapeutic interventions. Whenever, microvascular injury leads to *rupture of the glomerular basement membrane (GBM),* the leakage of plasma proteins drives parietal epithelial cell hyperplasia as the key cellular component of the crescent.
- Single nephron GFR decreases because of tuft collapse, rupture of the Bowman capsule, and influx of immune cells and fibroblasts are all secondary events that may or may not occur in individual glomeruli.
- Periglomerular immune cell infiltrates or fibrotic encasing of the activated parietal cells (fibrocellular crescents) are subsequent events that may affect the dynamics and prognosis of the disease.


Small vessel vasculitis
Immune complex-GN
Anti-GBM disease
C3-GN
Outside the kidney
1. Loss of tolerance against PR3, MPO...
2. Antigen presentation
3. Priming of autoreactive B and T cell clones
4. Circulating ANCAs
5. Fixation of immune memory
1. Host defense against microbes or loss of tolerance against autoantigens (IgA, IgG, dsDNA...)
2. Antigen presentation
3. Priming of autoreactive B and T cell clones
4. Circulating autoantibodies
5. Fixation of immune memory
1. Loss of tolerance against NC1 collagen type IV and peroxidasin
2. Antigen presentation
3. Priming of autoreactive B and T cell clones
4. Circulating anti-GBM IgG
5. Mostly transient autoimmunity. Infrequently fixation of immune memory
1. Loss of tolerance against regulators of the alternative complement pathway
2. Antigen presentation
3. Priming of autoreactive B and T cell clones
4. Circulating autoanti-bodies or genetic defects of regulators of complement pathway
IgG
IgG
IgG
C3
Inside the kidney
C5b binds C6 and C7
C5b67 complexes bind to membrane via C7
C8 binds to the complex and inserts into the cell membrane
C9 molecules bind to the complex and polimerize
1-16 molecules of C9 bind to form a pore in the membrane
Activation of complement leads to the deposition of many molecules of C3b on the immune complex
C6
C7
C5b
C5b67 complex
C8
C9
C3b
C3 convertase
Lipid bilayer
Pathogen
Immune complex-GN and Anti-GBM disease
Vascular necrosis and ruptures of the GBM
Plasma leakage + plasmatic coagulation within Bowman's space
Coagulation factors and other mitogenic signals induce parietal epithelial cell hyperplasia followed by collapse of the tuft and fading of single nephron GFR

# MOLECULAR PATHWAYS OF PARIETAL EPITHELIAL CELL HYPERPLASIA IN CRESCENTIC GLOMERULONEPHRITIS

# CD44

- CD44, a cell surface glycoprotein that plays a key role in various cellular processes, is expressed in activated PECs and that its deficiency was associated with reduced presence of PECs in Bowman‘s space
- CD44 deficiency reduced glomerular cell proliferation and reduced albuminuria, indicating a link among CD44-expresing activated PECs, the formation of crescents, and the development of albuminuria.

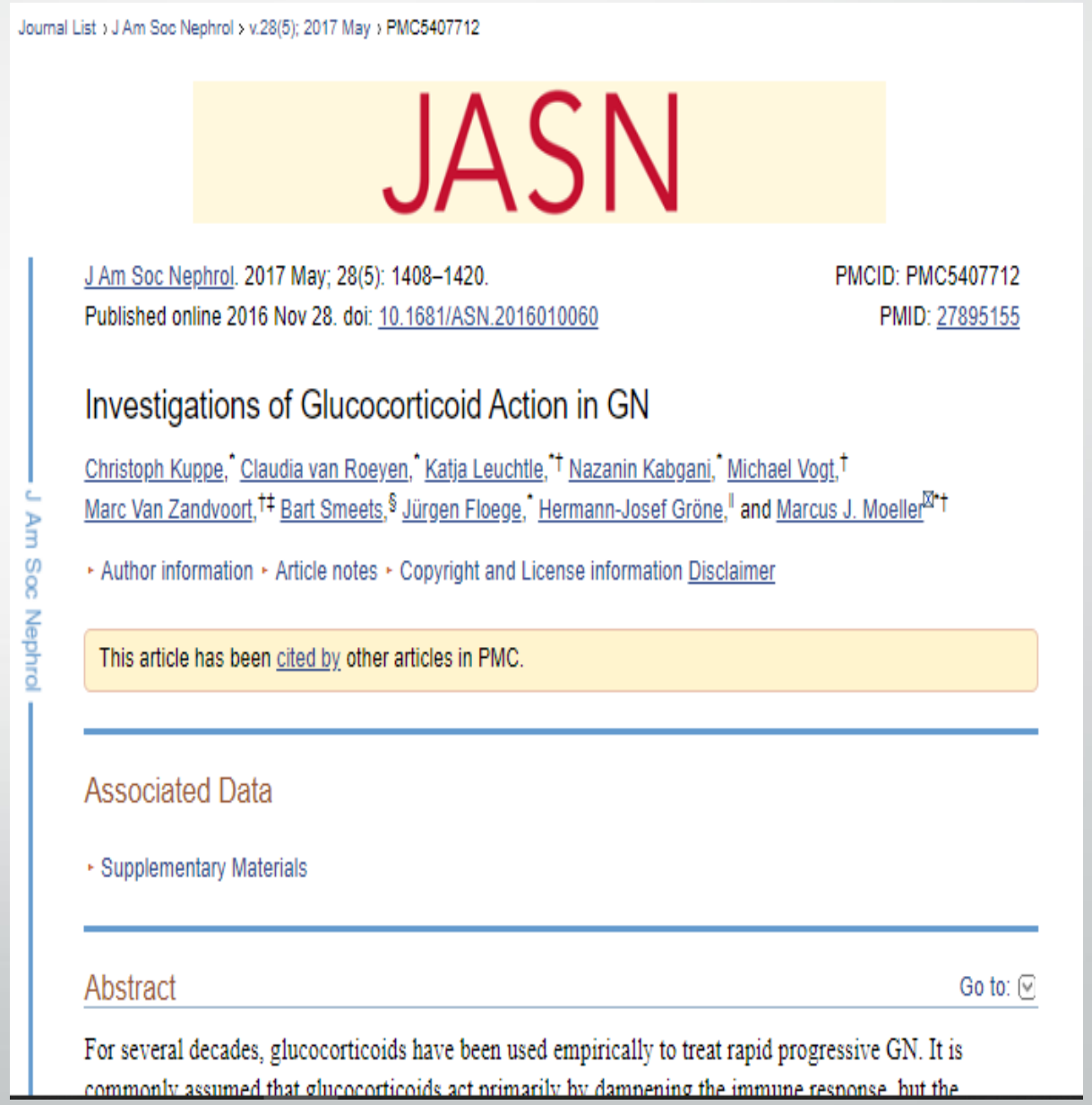
# CD9

- In association with CD44 expression, CD9, a tetraspanin involved in cell proliferation, migration, adhesion, and survival was found in PECs of a CGN-like rodent model. Silencing CD9 attenuated the ability of PECs to proliferate and migrate and attenuated glomerulosclerosis.
- One possible mechanism of PEC activation via CD9 relates to the activation of *epidermal growth factor receptor*, a key driver of kidney damage in early stages of glomerulonephritis . Thus, suppressing the local expression of CD9 can alleviate glomerular damage and could be a therapeutic option for crescentic glomerulonephritis.

# Glucocorticoids

- Glucocorticoids have remained in use for the treatment of glomerulonephritis since decades. A recent study investigated the effects of glucocorticoids in glomerulonephritis and found that ***glucocorticoid receptor*** inhibition was associated with decreased cellular crescent formation and inhibition of proliferation and migration of PECs . This therapeutic approach also reduced the inflammatory infiltrate within the kidney, suggesting intracellular steroid receptors may contribute to inflammation in CGN.

- Collectively, the data show that glucocorticoids act directly on activated glomerular parietal epithelial cells in crescentic nephritis. Furthermore, we identified a novel therapeutic approach in crescentic nephritis, that of glucocorticoid antagonism, which was at least as effective as high-dose prednisolone with potentially fewer adverse effects.



Journal List › J Am Soc Nephrol › v.28(5); 2017 May › PMC5407712

JASN

J Am Soc Nephrol. 2017 May; 28(5): 1408–1420.
Published online 2016 Nov 28. doi: 10.1681/ASN.2016010060
PMCID: PMC5407712
PMID: 27895155

## Investigations of Glucocorticoid Action in GN

Christoph Kuppe,[*] Claudia van Roeyen,[*] Katja Leuchtle,[*†] Nazanin Kabgani,[*] Michael Vogt,[†] Marc Van Zandvoort,[†‡] Bart Smeets,[§] Jürgen Floege,[*] Hermann-Josef Gröne,[‖] and Marcus J. Moeller[✉*†]



### Associated Data

Supplementary Materials

### Abstract

Go to:

For several decades, glucocorticoids have been used empirically to treat rapid progressive GN. It is commonly assumed that glucocorticoids act primarily by dampening the immune response, but the

# Heparin-binding epidermal growth factor-like growth factor (HB-EGF)

- a member of the EGF family, increases phosphorylation of the EGFR
- In an animal model of CGN, proHB-EGF was induced in PECs and podocytes even before the first appearance of crescents.
- HB-EGF deficiency attenuated CGN as did conditional deletion of EGFR only in podocytes, suggesting autocrine and paracrine feedback loops. Indeed, even delayed pharmacological inhibition of the EGFR mice could still attenuate CGN, which may be of translational relevance for human RPGN.

# The Epidermal Growth Factor Receptor Promotes Glomerular Injury and Renal Failure in Rapidly Progressive Crescentic Glomerulonephritis; the Identification of Possible Therapy

al List › HHS Author Manuscripts › PMC3198052

HHS Public Access
Author manuscript
Peer-reviewed and accepted for publication

About author manuscripts | Submit a manuscript

Nat Med. Author manuscript; available in PMC 2012 Apr 1.
Published in final edited form as:
Nat Med. 2011 Oct; 17(10): 1242–1250.
Published online 2011 Sep 25. doi: 10.1038/nm.2491

PMCID: PMC3198052
NIHMSID: NIHMS320013
PMID: 21946538

The Epidermal Growth Factor Receptor Promotes Glomerular Injury and Renal Failure in Rapidly Progressive Crescentic Glomerulonephritis; the Identification of Possible Therapy

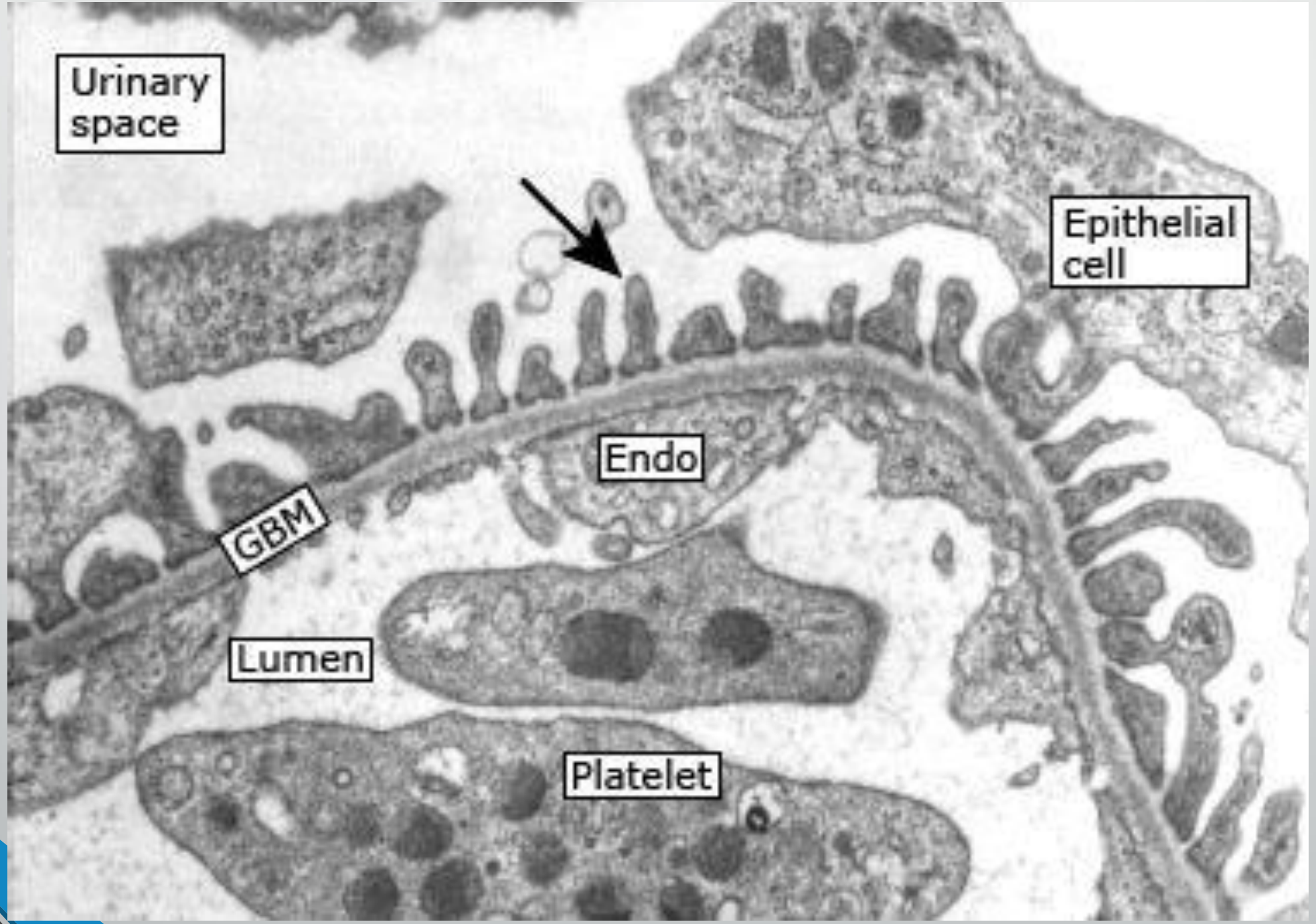
Guillaume Bollée,[1,2,21] Martin Flamant,[3,4,21] Sandra Schordan,[5] Cécile Fligny,[1,2] Elisabeth Rumpel,[5] Marine Milon,[1,2] Eric Schordan,[5] Nathalie Sabaa,[6,7] Sophie Vandermeersch,[6,7] Ariane Galaup,[8,9] Anita Rodenas,[10] Ibrahim Casal,[11,12] Susan W Sunnarborg,[13] David J Salant,[14] Jeffrey B. Kopp,[15] David W Threadgill,[16] Susan E Quaggin,[17] Jean-Claude Dussaule,[6,7,18] Stéphane Germain,[8,9] Laurent Mesnard,[6,7] Karlhans Endlich,[5] Claude Boucheix,[11,12] Xavier Belenfant,[19] Patrice Callard,[7,10] Nicole Endlich,[5] and Pierre-Louis Tharaux[1,2,20]

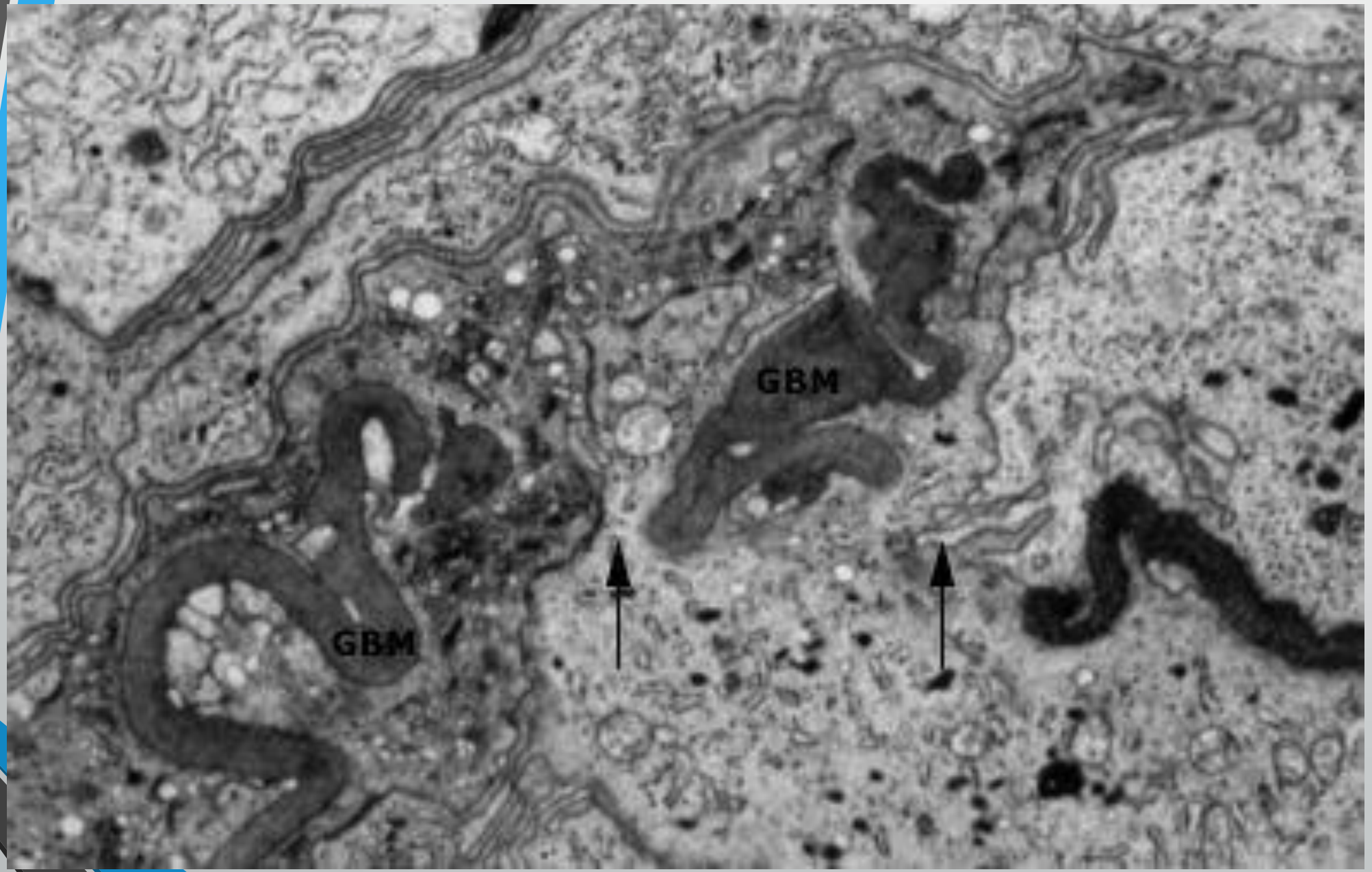
Author information · Copyright and License information Disclaimer

- Pharmacological blockade of EGFR also improves the course of RPGN, even when started 4 days after the induction of experimental RPGN. This suggests that targeting the HB-EGF/EGFR pathway could also be beneficial for treatment of human RPGN.

# Initiating events

- nonspecific response to severe injury to the glomerular capillary wall
- The initiating event is the development of physical gaps (also called rents or holes) in the glomerular capillary wall, glomerular basement membrane, and Bowman's capsule
- These gaps permit the entry into Bowman's space of coagulation factors, which lead to fibrin formation (due to conversion of fibrinogen to fibrin polymers and delayed fibrinolysis) and cellular elements (such as monocytes and lymphocytes), both of which promote crescent formation
- The plasmatic coagulation process within the crescent, which is a direct stimulus for parietal cell hyperplasia, as for re-epithelialization of other bleeding wounds


Urinary space
Epithelial cell
Endo
GBM
Lumen
Platelet

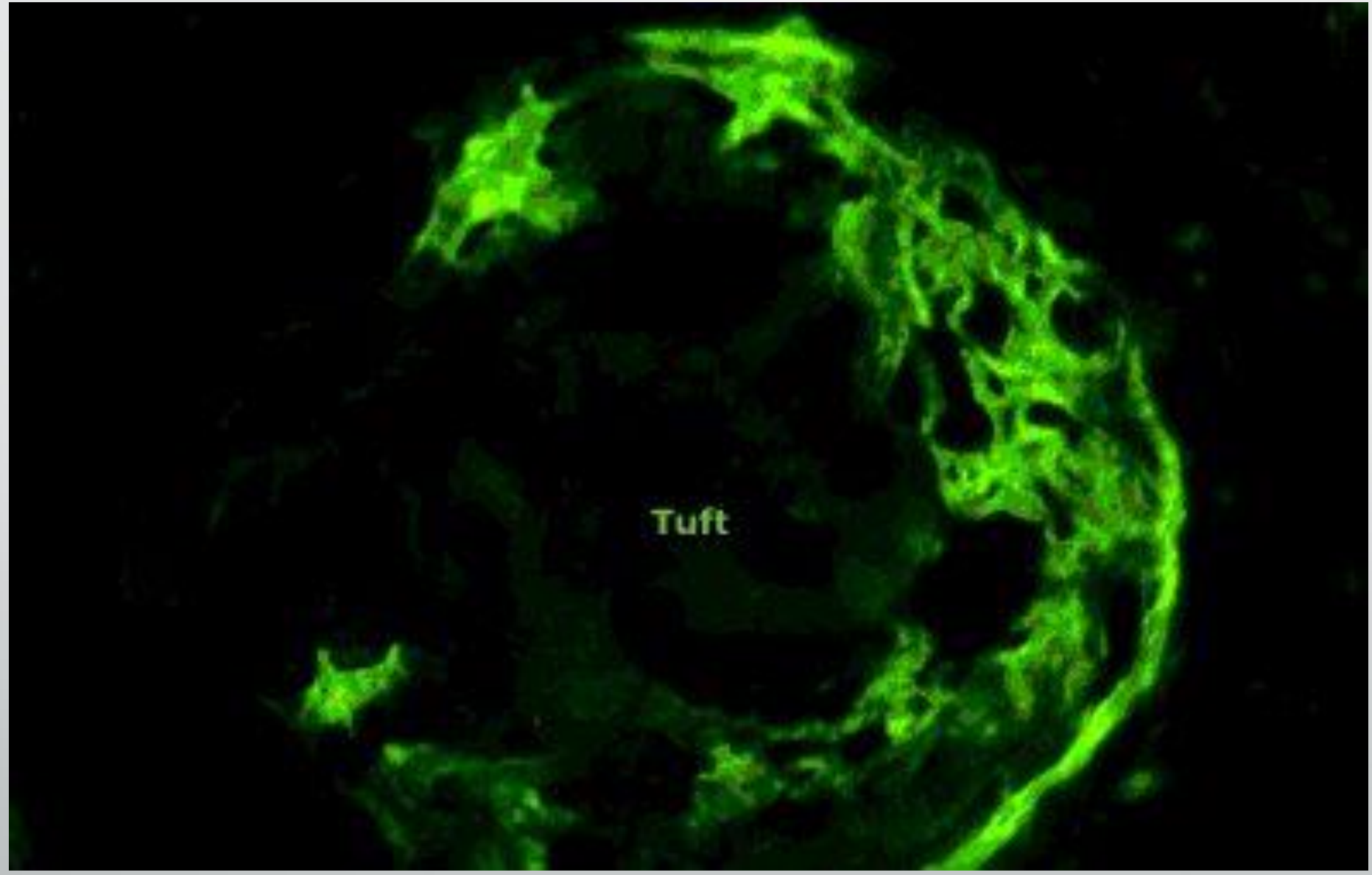

GBM
GBM

# FORMATION AND COMPOSITION

- Rents in the glomerular capillary wall and glomerular basement membrane allow circulating cells, mostly macrophages and T cells, inflammatory mediators, and plasma proteins, particularly coagulation proteins, to pass through the capillary wall and basement membrane and into Bowman's space.
- The contents in Bowman's space can enter the interstitium, contributing to periglomerular inflammation.

# Coagulation proteins

- A central feature of crescent formation is the presence in Bowman's space of coagulation factors that lead to the cross-linking of fibrin and a deficiency in fibrinolytic mechanisms, both of which can facilitate fibrin deposition. The importance of fibrin is illustrated by the findings in animal models that defibrination can prevent or reverse crescent formation .
- Tissue factor, tissue factor inhibitor, thrombin, and the plasminogen/plasmin system are procoagulant molecules that are central to this process.


Tuft

# Tissue factor

- The primary stimulus to fibrin deposition in crescent formation appears to be tissue factor, which binds to and activates factor VII.
- Tissue factor is derived from endothelial cells, glomerular visceral epithelial cells (podocytes), and macrophages . In addition, macrophage-derived interleukin-1 and tumor necrosis factor (TNF) stimulate tissue factor production by glomerular endothelial cells

# Tissue factor pathway inhibitor

- Accompanying the increase in tissue factor activity is an early reduction in tissue factor pathway inhibitor (TFPI), which also favours fibrin deposition.
- Administration of recombinant TFPI which, in experimental crescentic glomerulonephritis, reduces both fibrin deposition and crescent formation.

# Thrombin

- An important role for thrombin in crescent formation was suggested in a mouse model in which hirudin, a selective thrombin antagonist, or the absence of protease-activated receptor 1, a cellular thrombin receptor, significantly reduced both glomerular crescent formation and macrophage and T-cell infiltration

# Plasminogen/plasmin system

- The plasminogen/plasmin system plays a central role in fibrinolysis and the resolution of glomerular crescents. In experimental and human crescentic glomerulonephritis, there is decreased fibrinolytic activity due to both a reduction in tissue-type plasminogen activator and an increase in plasminogen activator inhibitor-1 (PAI-1)
- The end result is that extraglomerular fibrin cross-linking occurs in Bowman's space. Fibrin is a potent chemotactic factor that also helps recruit macrophages into the glomeruli

# Macrophages

- Macrophages play a central role in the formation of glomerular crescents since both tissue factor expression and fibrin deposition are macrophage-dependent phenomena. In an experimental model of anti-glomerular basement membrane (GBM) antibody-induced glomerulonephritis, macrophages accounted for 42 percent of cells in early crescents and 64 to 71 percent of cells in advanced cellular or fibrocellular crescents .
- Macrophages in the glomeruli presumably derive from the circulation and also probably enter from the periglomerular interstitium via gaps in Bowman's capsule. These gaps may be caused by inflammatory processes similar to those that result in rupture of the glomerular basement membrane and/or by cell-mediated mechanisms

- Localization of macrophages to the glomeruli in crescentic glomerulonephritis involves multiple chemoattractants. These include:
- The C-C chemokines, macrophage chemoattractant protein-1 (MCP-1), macrophage inhibitory factor (MIF), macrophage inflammatory protein-1-alpha (MIP-1-alpha), and osteopontin. Expression of chemokine receptor 2B (CCR2B), which is the receptor for MCP-1, may be particularly important.
- Adhesion molecules, such as vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, and CD44, which are all expressed on glomerular parietal epithelial cells.
- Renal cell-derived granulocyte-macrophage colony stimulating factor (GM-CSF) may increase expression of VCAM-1, MCP-1, and interleukin (IL)-1 beta, thereby promoting crescent formation [ 42 ].

- Once localized to Bowman's space, activated macrophages contribute to crescent formation by proliferating and by releasing the following molecules:
- Tissue factor.
- Interleukin (IL)-1 and TNF upregulate adhesion molecule expression, stimulate cell proliferation, and recruit more macrophages
- Selective blockade of IL-1 with IL-1 receptor antagonists or of TNF with anti-TNF antibodies or soluble TNF receptors markedly reduces crescent formation in experimental models
- the principal source of TNF may be intrinsic renal cells.

# TGF-β

- Transforming growth factor (TGF)-beta may play an important role in both disease activity and the transition from cellular to fibrocellular and fibrous crescents since it is a potent stimulus to the production of collagen I .
- TGF-beta signaling appears to play an important role in the development and progression of crescentic glomerulonephritis.

# Mannose receptor

- The mannose receptor, implicated in the uptake of endogenous and microbial ligands, is upregulated on activated macrophages.
- Mannose receptor-deficient mice were protected from crescentic glomerulonephritis in a mouse nephrotoxic nephritis model despite humoral and T-cell responses similar to those of wild-type mice.
- blocking the receptor might provide a more specific approach than broad-based immunosuppressive therapy.

# Matrix metalloproteinases

- Several studies in patients with crescentic glomerulonephritis found increased glomerular expression of matrix metalloproteinases (MMP)-2, 3, 9, and 11 and tissue inhibitor of metalloproteinases (TIMP)-1, which correlated with cellular crescents and disease activity
- In experimental studies, MMP-9 protects against experimental crescentic glomerulonephritis through its fibrinolytic activity.

# T cells

- T cells are found in Bowman's space and in crescents.
- traditional chemoattractants (such as monocyte chemoattractant protein [MCP] and macrophage inflammatory protein [MIP]-1-alpha), certain cytokines (such as interleukin [IL]-12p40 and IL-18), mast cells, and costimulatory ligands on macrophages and non-lymphoid cells (such as CD80 and CD86).
- Some of these cytokines may also stimulate production of proinflammatory cytokines such as interferon-gamma and TNF.

- The role of T cells in glomerular injury may be related to antigen recognition and macrophage recruitment via the release of factors such as MIF and interferon-gamma .

# Glomerular parietal epithelial cells

- Glomerular parietal epithelial cells are significant constituents of crescents. Unlike glomerular visceral epithelial cells (podocytes), which are normally terminally differentiated cells with little proliferative capacity, glomerular parietal epithelial cells can and do proliferate, presumably in response to growth factors, such as platelet-derived growth factor and fibroblast growth factor-2 (basic fibroblast growth factor).
- Since glomerular parietal epithelial cells are not major sources of procoagulant molecules or growth factors, it is unlikely that they are as important as macrophages and interstitial fibroblasts in determining the course and consequences of crescent formation. However, glomerular parietal epithelial cells can undergo dysregulation and become macrophage-like inflammatory effector cells and may be the primary cells producing type I collagen

# Glomerular visceral epithelial cells (podocytes)

- to be terminally differentiated cells and had not been regarded as participants in crescent formation.
- new podocytes could be recruited from glomerular parietal epithelial cells through differentiation and proliferation.
- in murine models of and humans with GBM antibody disease in which podocytes adhered to both the glomerular basement membrane and the parietal basement membrane, forming podocyte bridges between the glomerular tuft and Bowman's capsule.
- It has been suggested that *podocyte bridging* may be an important event that occurs early in the development of crescentic glomerulonephritis.

International Journal of Nephrology and Renovascular Disease

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

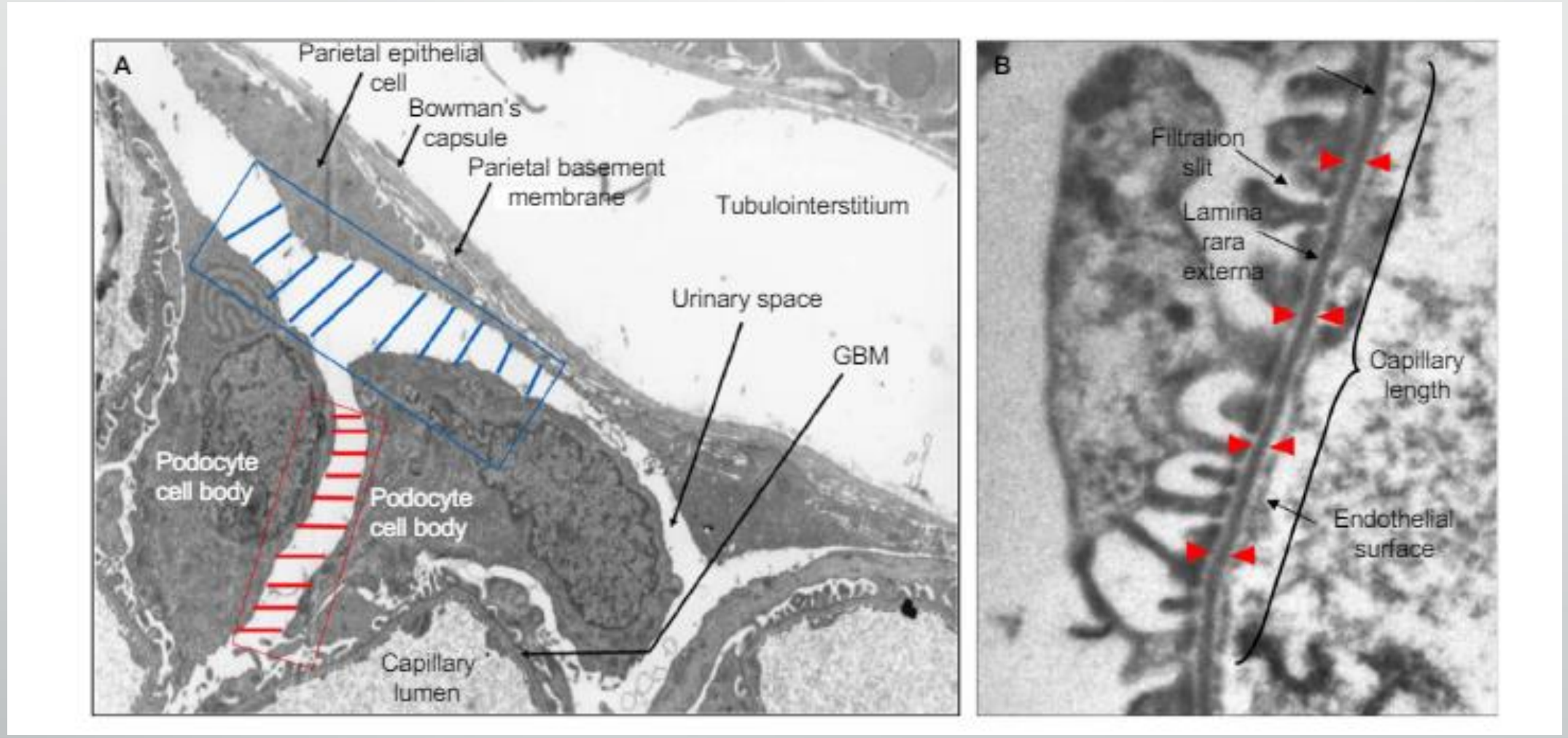
# Formation of tight junctions between neighboring podocytes is an early ultrastructural feature in experimental crescentic glomerulonephritis

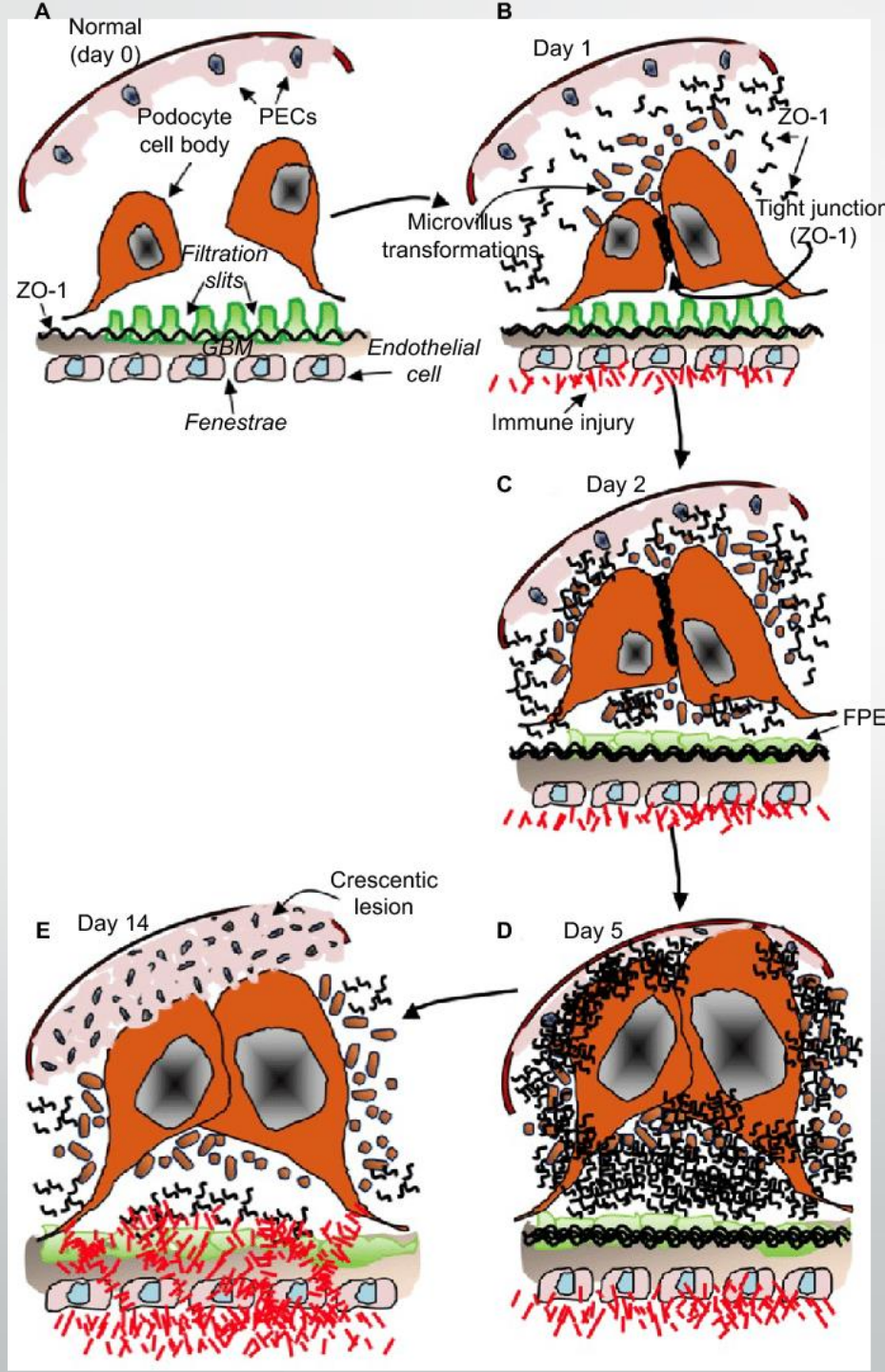
This article was published in the following Dove Press journal:
International Journal of Nephrology and Renovascular Disease
24 November 2016
Number of times this article has been viewed

Lena Succar[1]
Ross A Boadle[2]
David C Harris[1,3]
Gopala K Rangan[1,3]

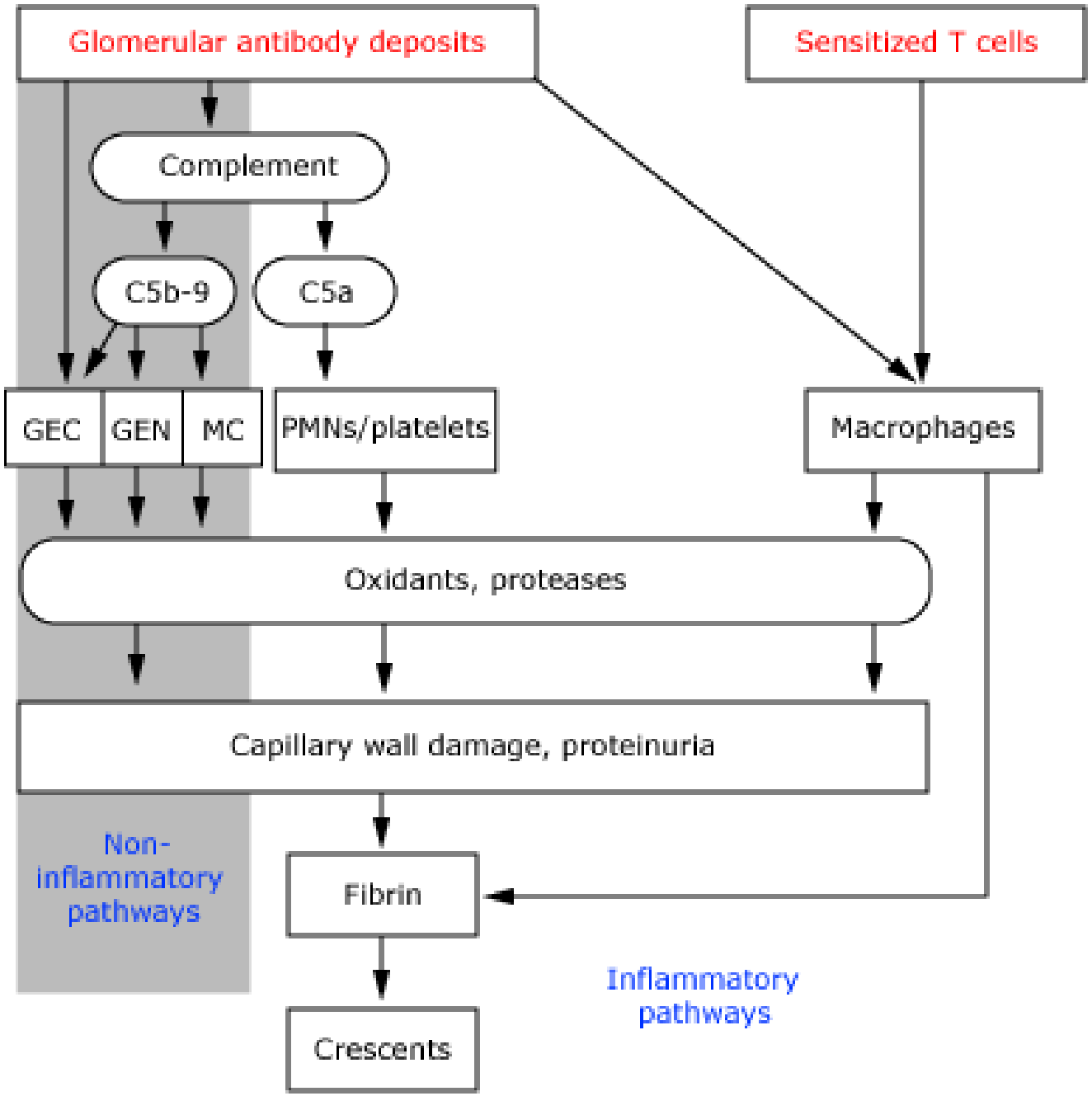
[1]Centre for Transplant and Renal Research, The Westmead Institute for Medical Research, The University of Sydney, [2]Electron Microscopy

**Purpose:** In crescentic glomerulonephritis (CGN), the development of cellular bridges between podocytes and parietal epithelial cells (PECs) triggers glomerular crescent formation. However, the sequential changes in glomerular ultrastructure in CGN are not well defined. This study investigated the time course of glomerular ultrastructure in experimental CGN.
**Methods:** Transmission electron microscopy (TEM) was performed using kidney samples from rats with nephrotoxic serum nephritis (NSN) from day 1 to day 14. Morphometric analysis was conducted on randomly selected glomeruli captured on TEM digital images.


A
Parietal epithelial cell
Bowman's capsule
Parietal basement membrane
Tubulointerstitium
Urinary space
GBM
Podocyte cell body
Podocyte cell body
Capillary lumen
B
Filtration slit
Lamina rara externa
Capillary length
Endothelial surface


A
Normal
(day 0)
Podocyte
cell body
PECs
Filtration
slits
ZO-1
GBM
Endothelial
cell
Fenestrae
B
Day 1
ZO-1
Tight junction
(ZO-1)
Microvillus
transformations
Immune injury
C
Day 2
FPE
D
Day 5
E
Day 14
Crescentic
lesion

- Podocytes also populate crescents  and may undergo epithelial mesenchymal transformation to contribute to crescent formation, particularly in early disease .


Glomerular antibody deposits
Sensitized T cells
Complement
C5b-9
C5a
GEC
GEN
MC
PMNs/platelets
Macrophages
Oxidants, proteases
Capillary wall damage, proteinuria
Non-inflammatory pathways
Fibrin
Inflammatory pathways
Crescents

# Renal progenitor cells

- Renal progenitor cells localized in *Bowman's capsule* are capable of regenerating podocytes. These cells are identified by stem cell markers CD133 and CD24 and are in various stages of differentiation.
- Data obtained in human crescentic glomerulonephritis suggest that crescent formation may primarily result from dysregulated proliferation of renal progenitor cells in response to the injured podocyte.

# Interstitial fibroblasts

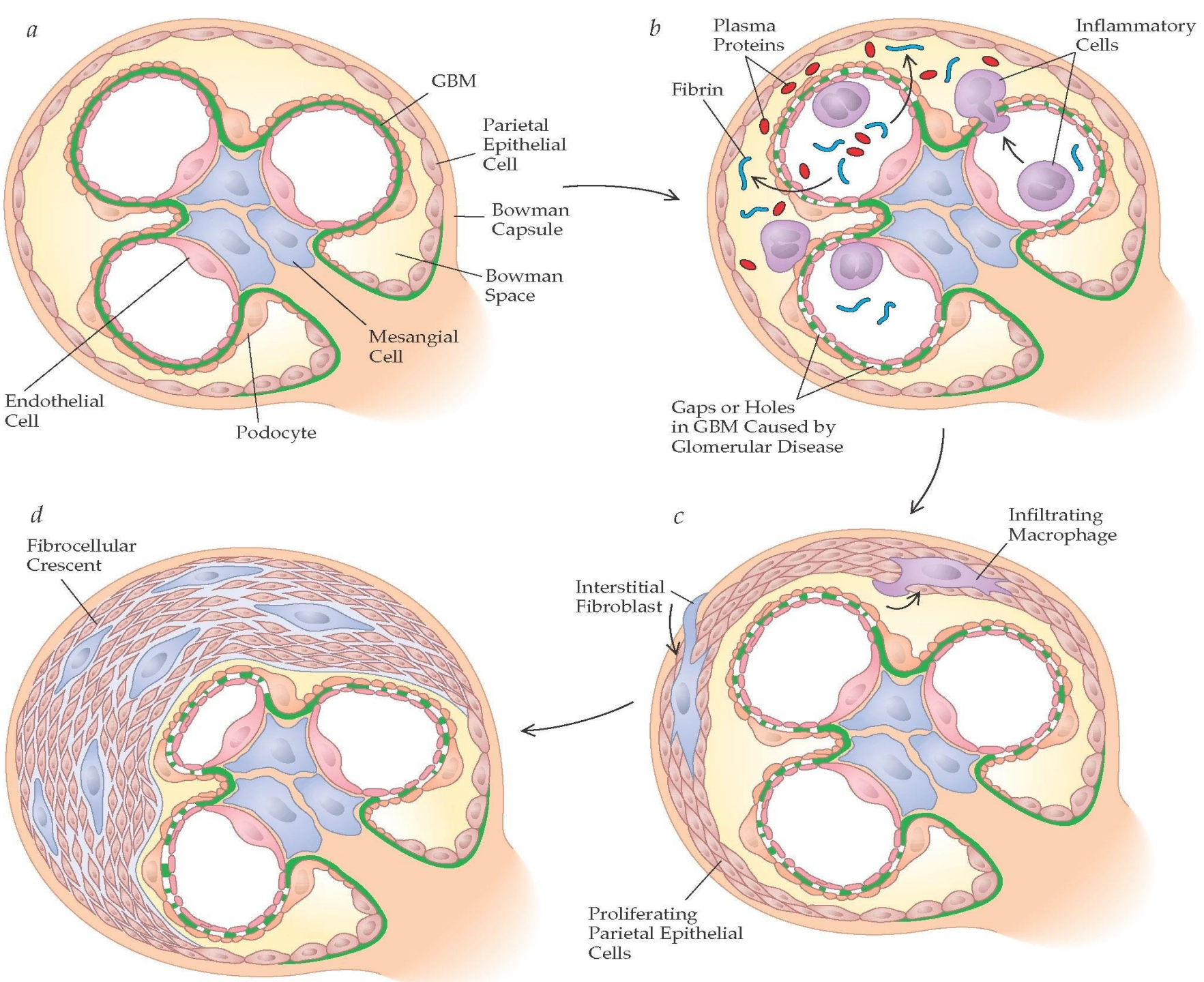
- In some models of experimental crescentic glomerulonephritis, interstitial fibroblasts are the second most prominent cell type after macrophages.
- from the periglomerular interstitium through gaps in Bowman's capsule.
- a major source of interstitial collagen, which characterizes the transition from cellular to fibrous crescents. Fibroblast proliferation is thought to be growth factor-dependent, probably involving basic fibroblast growth factor (also called fibroblast growth factor-2).

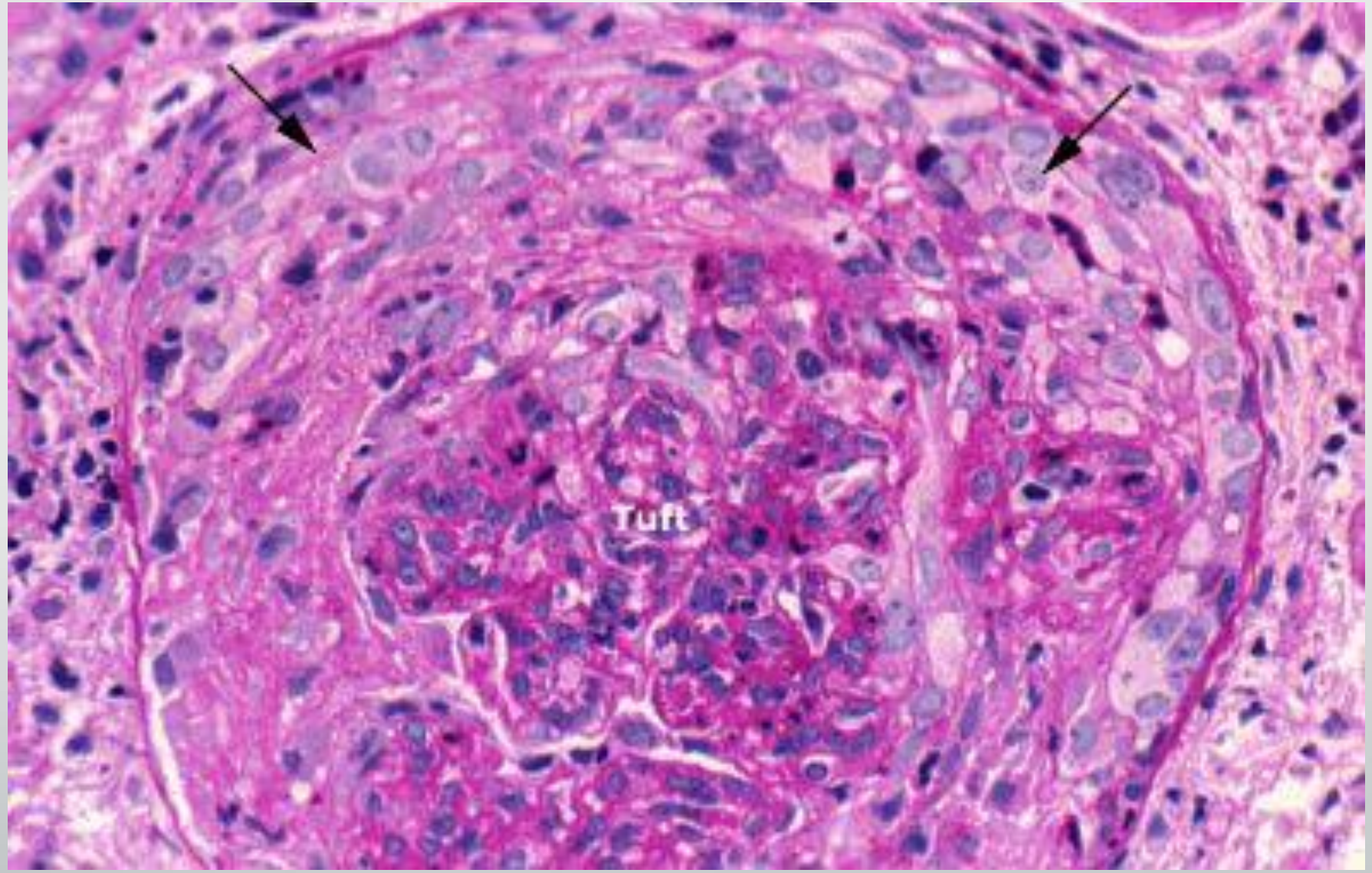
# COURSE OF CRESCENTS

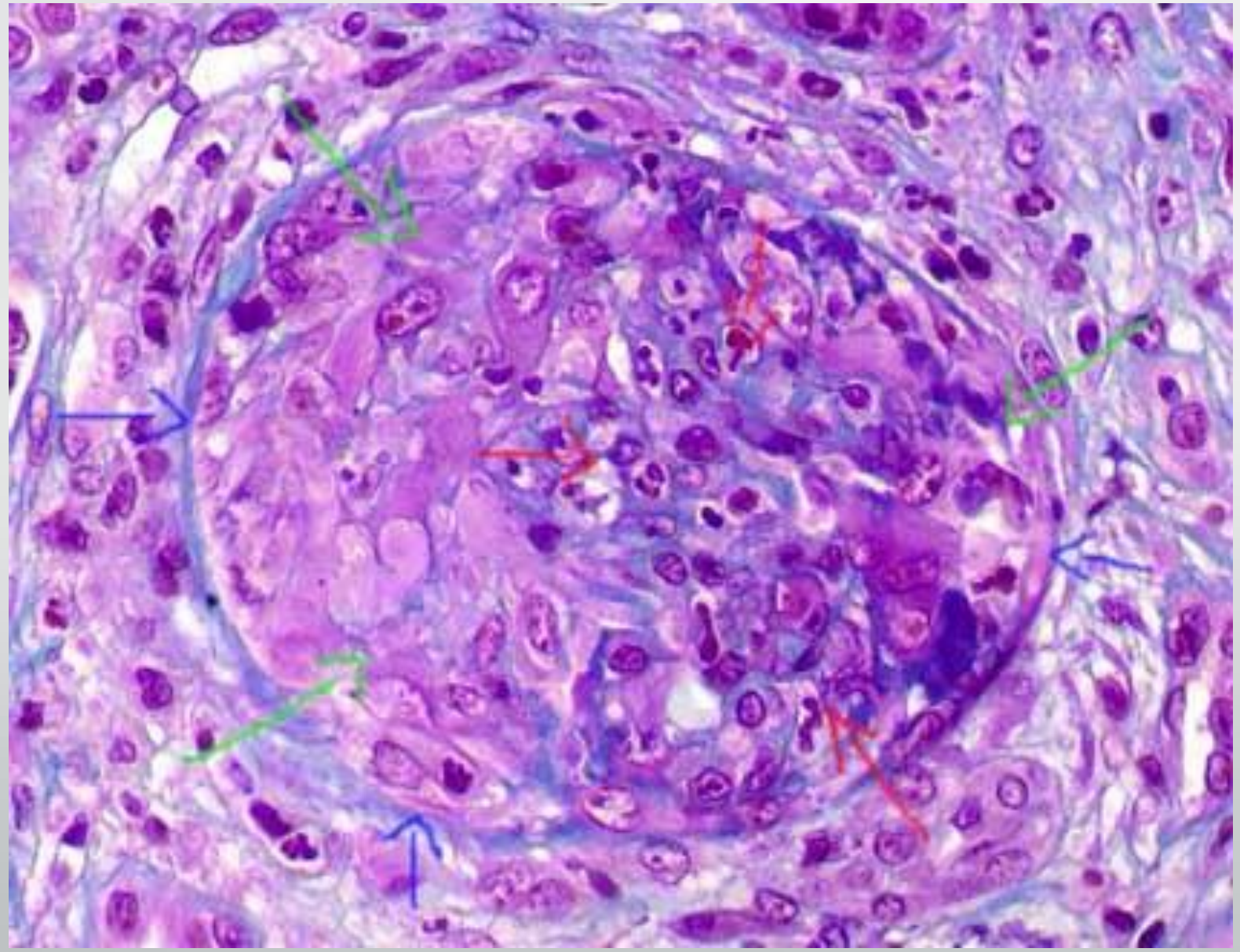
- The presence of crescents does not necessarily predict irreversible glomerular damage. This lack of progression occurs when the crescents are predominantly cellular, without a significant fibroblast or collagen component.

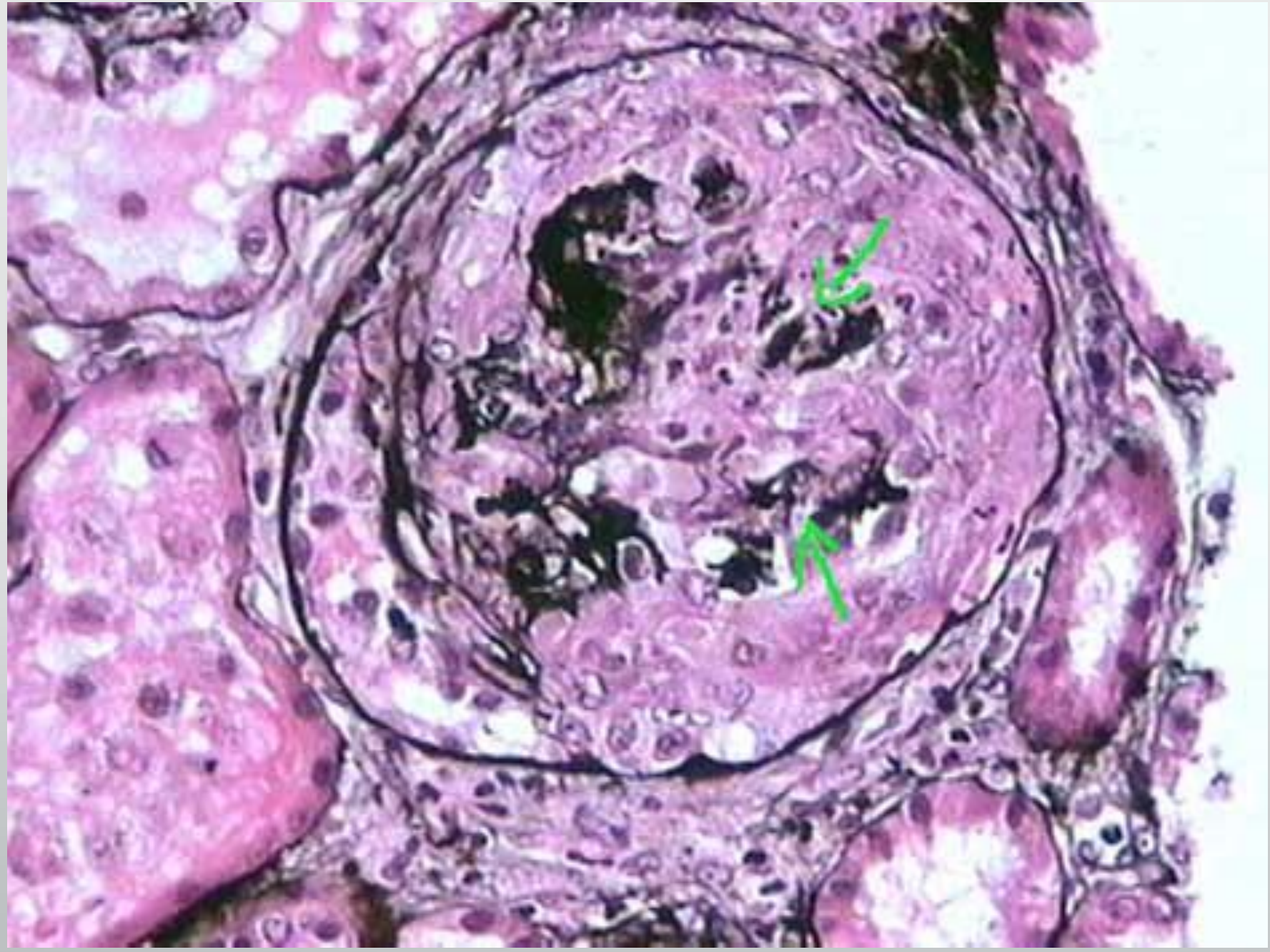
- ❑ The integrity of Bowman's capsule
- ❑ The cellular composition of the crescent.

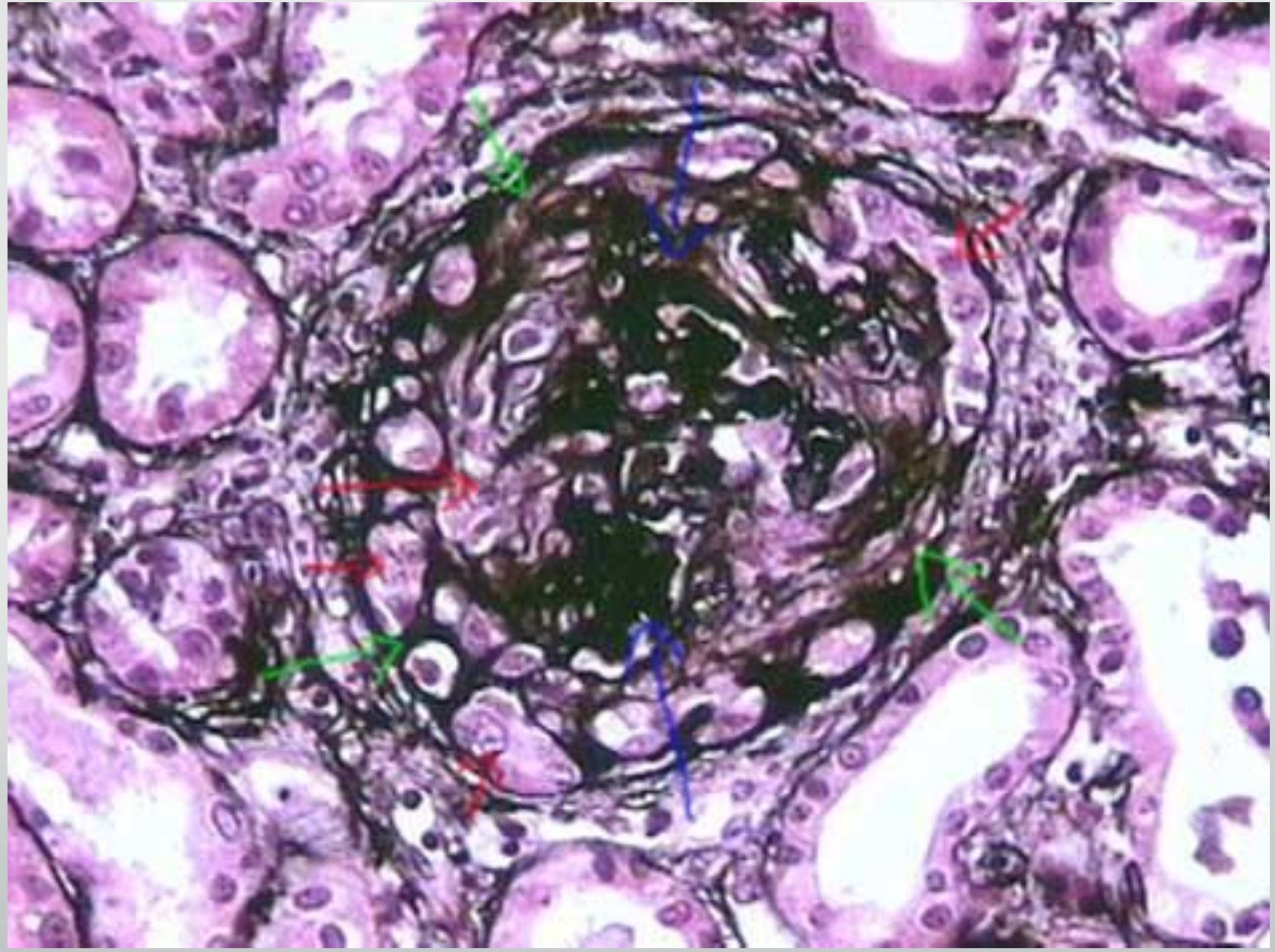
Production of interstitial collagen and progression to fibrous crescents are more common when capsular rupture occurs and fibroblasts and macrophages are prominent in Bowman's

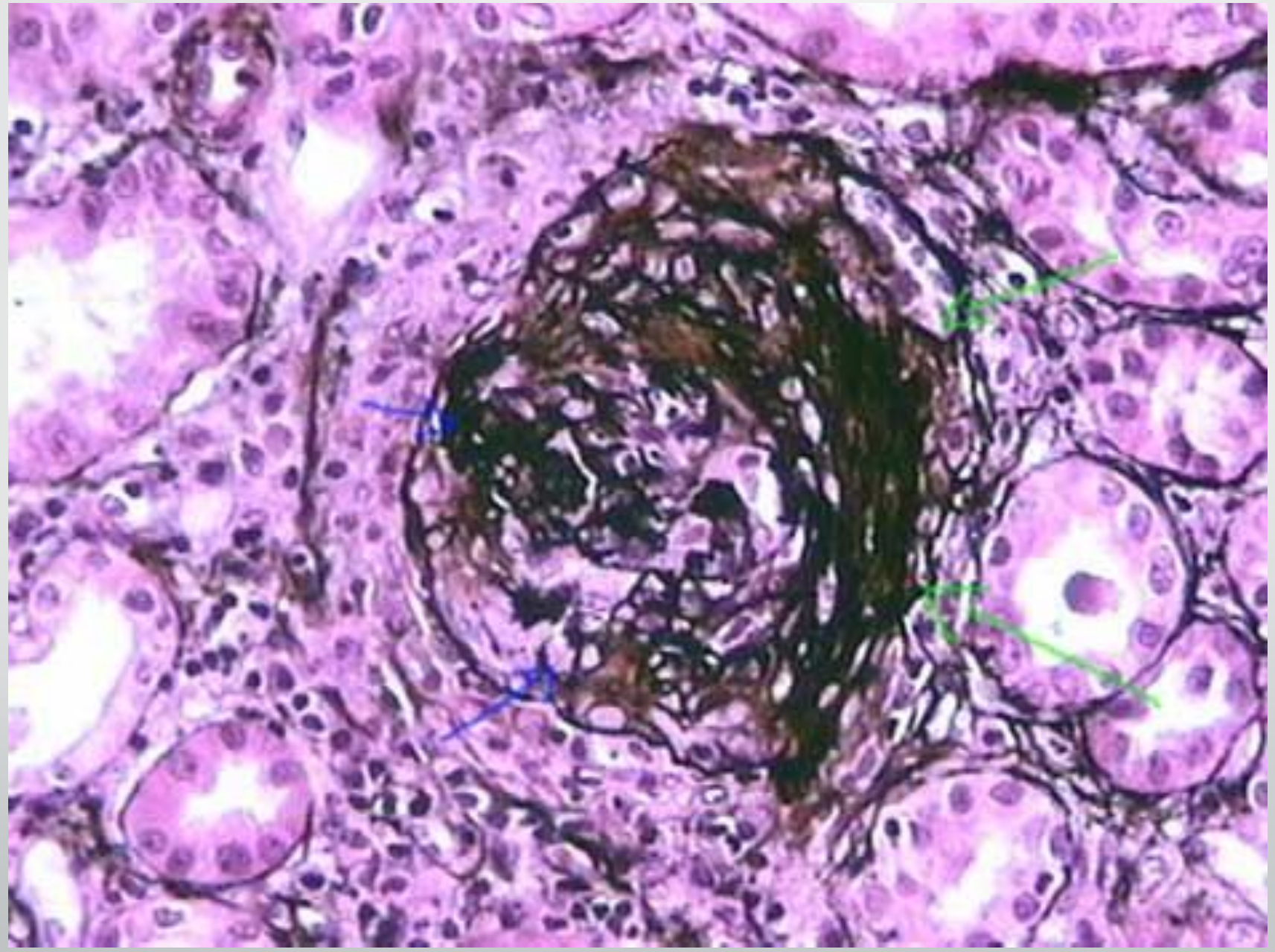

a
GBM
Parietal Epithelial Cell
Bowman Capsule
Bowman Space
Mesangial Cell
Endothelial Cell
Podocyte
b
Plasma Proteins
Fibrin
Inflammatory Cells
Gaps or Holes in GBM Caused by Glomerular Disease
c
Infiltrating Macrophage
Interstitial Fibroblast
Proliferating Parietal Epithelial Cells
d
Fibrocellular Crescent

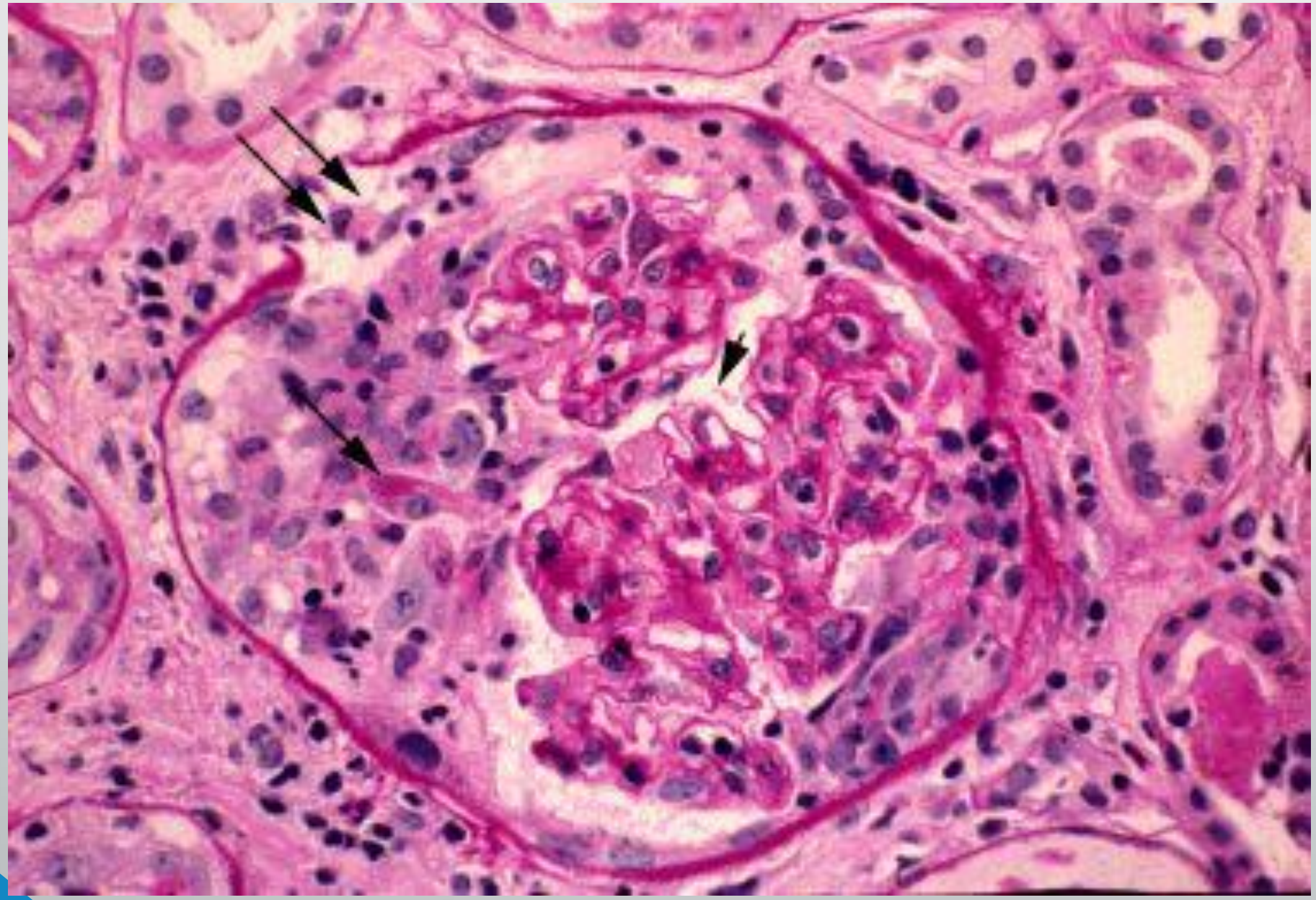

Tuft











- Although the presence of fibrous crescents generally correlates with glomerular sclerosis, there is no evidence that events in the crescents cause injury to the glomerular capillaries. As an example, defibrination abolishes crescent formation in animal models without improving renal function.
- Crescent formation appears to be a consequence, not a cause , of severe glomerular injury. However, there is increasing evidence that large crescents may occlude the outlet from Bowman's capsule to the proximal tubule to produce "atubular glomeruli" with subsequent degeneration of both glomeruli and tubules.
- The treatment and prognosis of the renal disease varies with disease severity and the cause of the glomerulonephritis.

# Key points

- Glomerular crescents indicate ruptures of glomerular capillaries with leakage of plasma driving hyperplasia of parietal epithelial cells, which impairs single nephron GFR via different mechanisms, hence crescentic glomerulonephritis usually presents together with renal failure.
- Fibrotic transformation, rupture of Bowman's capsule, and immune cell infiltrates are downstream events and less suitable as therapeutic targets.
- Targeting the pathomechanisms upstream of vascular necrosis has proven effective to improve outcomes of crescentic glomerulonephritis.
- Such validated targets include systemic autoimmunity, specific circulating autoantibodies, NET release or complement mediators activated within the glomerulus.
- Whether selectively targeting parietal cell hyperplasia and not vascular injury, as suggested by experimental studies, can improve also human CGN is still unclear.

- Therapeutic interventions should target the upstream mechanisms of vascular necrosis, such as extrarenal autoimmunity, pathogenic autoantibodies, and intrarenal complement activation and inflammation.

# Small vessel vasculitides

- ANCA renders neutrophils more susceptible to the release of neutrophil extracellular traps (NETs) along the endothelial interface of the renal microvasculature
- NETs are composed of nuclear DNA that by itself contributes few to vascular necrosis. Rather the nuclear, granular, and cytoplasmic proteins, such as elastase, myeloperoxidase, cathepsins, and histones decorating the NETs confer severe endothelial cell and vascular wall injury.
- NETs also deposit neutrophil autoantigens along the capillary wall that are picked up by antigen-presenting cells that can trigger local T-cell responses.

- Local complement dysregulation, promising therapeutic avenue for small vessel vasculitis.
- Recently B-cell-targeting therapies have been found to be as potent in abrogating vasculitis and CGN. This may not only relate to the role of B cells as precursors for ANCA-secreting plasma cells but also to their role as antigen-presenting cells.

# Immune complex glomerulonephritis

- In crescentic IC-GN, the proportion of glomeruli affected by crescents is lower and more frequently shows signs of chronicity, for example, in IgA nephropathy .
- However, as immune complexes trigger glomerular injury via complement activation, complement inhibitors are upcoming options to be tested in clinical trials on patients with IC-GN

# Antiglomerular basement membrane disease

- autoimmune response against antigens located in the *NC1 domain of collagen type IV* and the *peroxidase peroxidasin*
- undefined environmental factors
- The circulating 'anti-GBM' antibodies are considered pathogenic as the appearance and disappearance of these antibodies coincides with CGN disease activity, although occasionally antibodies reacting in GBM bioassays may not bind to patient's GBM or not all linear IgG deposits in CGN may relate to 'GBM antibodies' .
- These pathogenic autoantibodies are the central therapeutic target in anti-GBM disease and either depleting circulating IgG by plasma exchange or by a specific IgG-degrading enzyme improves disease activity.

- Peroxidasin, a heme peroxidase, has significant structural overlap with myeloperoxidase (MPO), and MPO-ANCA is present both before and at GP diagnosis in some patients. These autoantibodies directed against peroxidasin are also detected in GP.



JASN

J Am Soc Nephrol. 2018 Nov; 29(11): 2619–2625.
Published online 2018 Oct 2. doi: 10.1681/ASN.2018050519

PMCID: PMC6218858
PMID: 30279272

# Inhibitory Anti-Peroxidasin Antibodies in Pulmonary-Renal Syndromes

A. Scott McCall,[1,2] Gautam Bhave,[1,2,3] Vadim Pedchenko,[1,2] Jacob Hess,[4] Meghan Free,[4] Dustin J. Little,[5] Thomas P. Baker,[5] William F. Pendergraft, III,[4] Ronald J. Falk,[4] Stephen W. Olson,[5] and Billy G. Hudson[1,2,3,6,7,8,9]

‣ Author information ‣ Article notes ‣ Copyright and License information Disclaimer

See editorial "Peroxidasin—a Novel Autoantigen in Anti-GBM Disease?" in volume 29 on page 2605.

This article has been cited by other articles in PMC.

## Associated Data

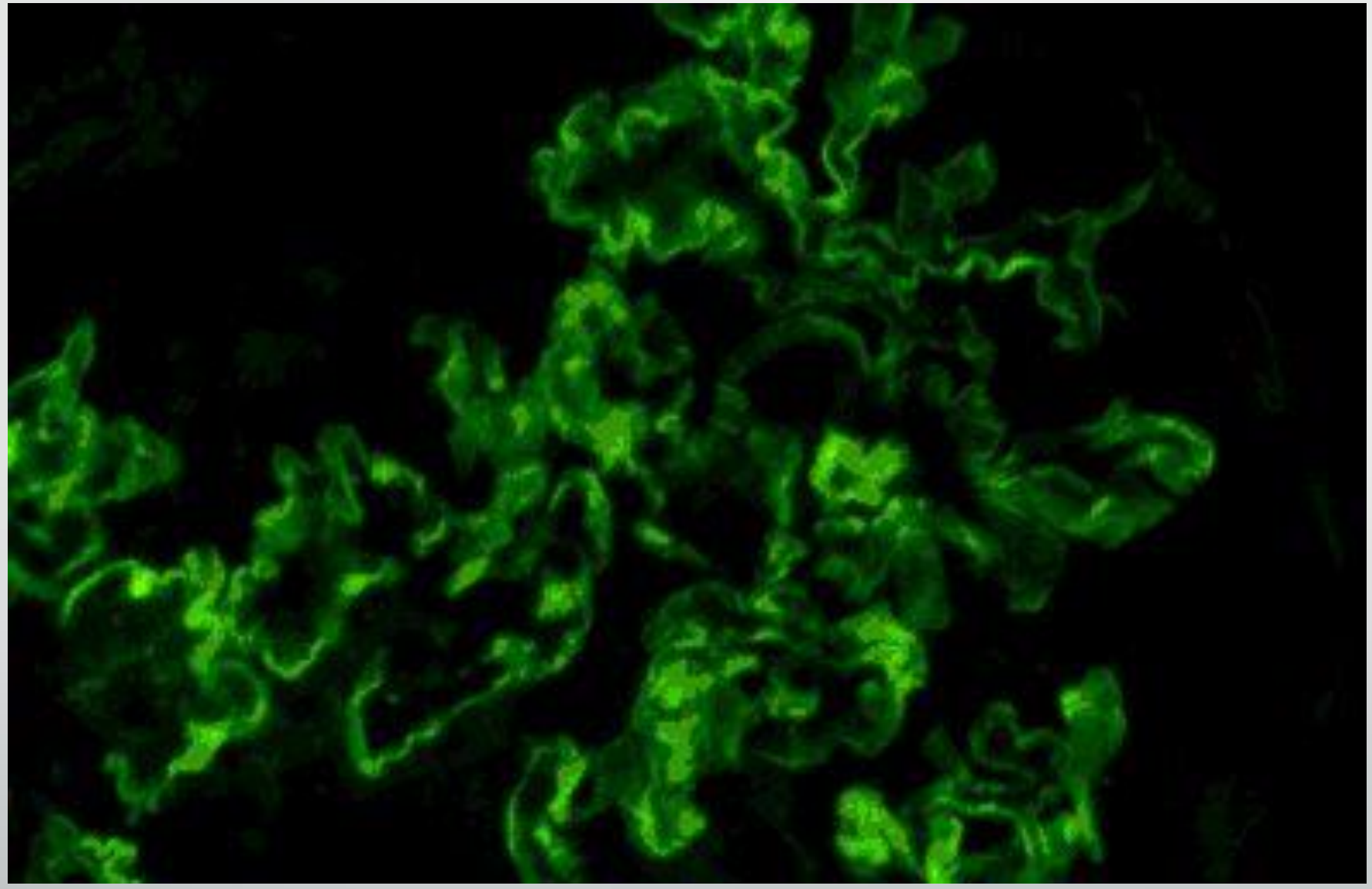
‣ Supplementary Materials

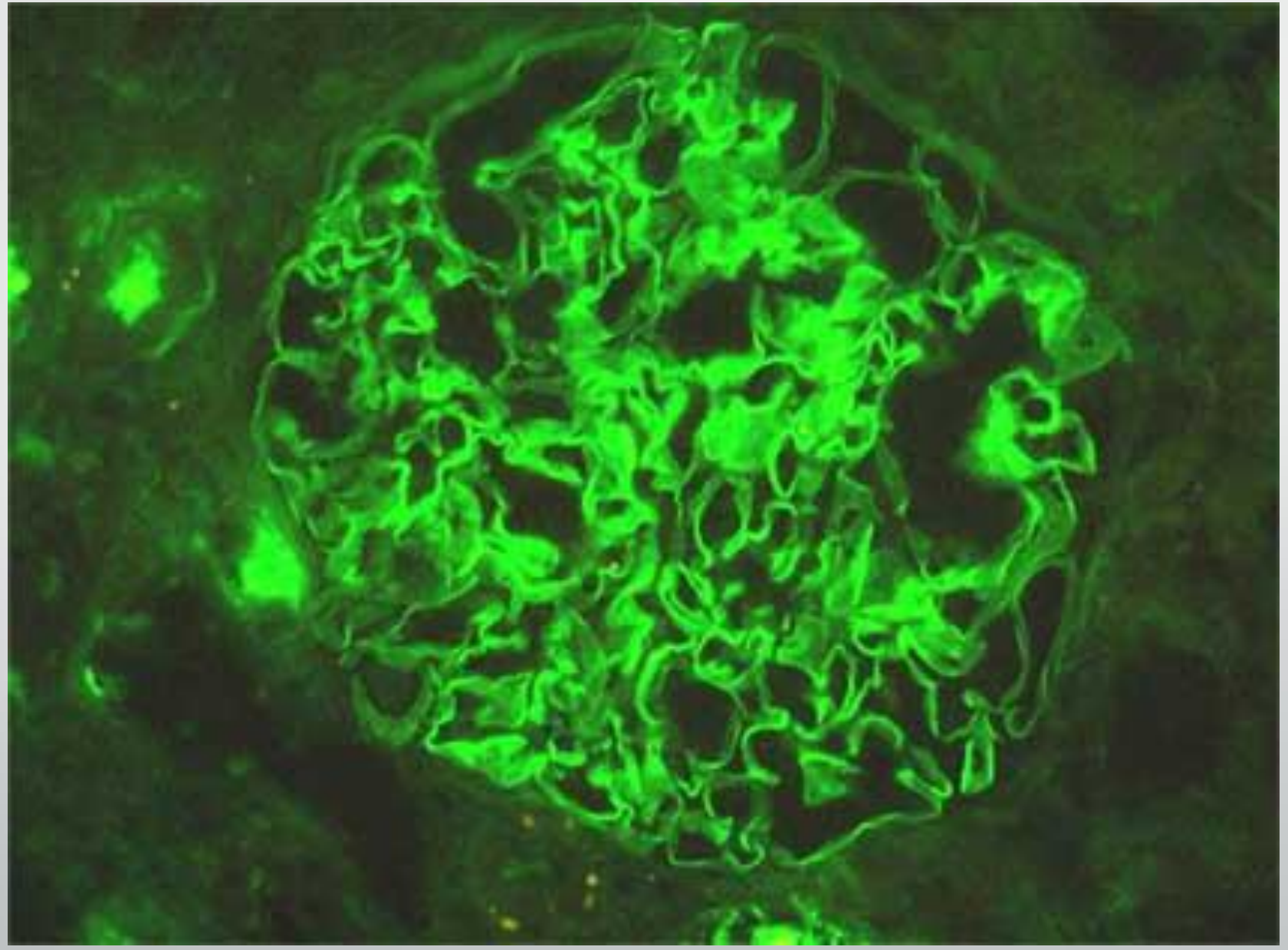
## Abstract

Go to:

### Background

Goodpasture syndrome (GP) is a pulmonary-renal syndrome characterized by autoantibodies directed





# C3 glomerulonephritis

- abnormal regulation of the *alternative complement pathway* leading to electron dense deposits in the mesangium or along the glomerular filtration barrier that contain complement but no immunoglobulins.
- Mostly membranoproliferative lesions, but severe necrotizing and crescentic glomerulonephritis in humans and mice
- When acquired antibodies against factor H, B or other complement regulators are the cause of a C3GN, drugs that suppress the adaptive immune system such as steroids, mycophenolate mofetil or rituximab may be effective.
- In contrast, patients with genetic defects in complement regulators may benefit from therapy with C3 convertase inhibitors or other downstream elements of the complement cascade