Review Article

Pathogenesis of Immune-Mediated Glomerulonephritis

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ABSTRACT

Most forms of glomerulonephritis (GN) are characterized by a pathogenic immune response, which is mediated by the action of various immune system elements, both innate and adaptive. What is clear is that the immunopathogenesis of GN is very broad and complex. Deposits of immune complexes in the glomeruli activate complement and glomerular injury due to the involvement of circulating inflammatory cells and glomerular intrinsic cells, ultimately resulting in a wide variety of clinical manifestations, which depend in part on the location and immunopathology of the patient, including genetic and environmental factors, from asymptomatic to rapidly progressive GN. Most of the treatment strategies for GN are non-specific, consisting of corticosteroids and cytotoxic agents. Thus, an advanced understanding of GN immunopathogenesis may offer many opportunities for future therapeutic interventions on an individual basis. To further facilitate understanding of the pathogenesis of GN, the author also includes a graphical abstract.

Keywords: Antibody-Mediated Glomerular Injury, Humoral and Cellular Component, Circulating Inflammatory Cells, Intrinsic Glomerular Cells Injury, Permeability Factors.

Introduction

A substantial body of immunological, clinical, and experimental data supports the hypothesis that immunological mechanisms are the primary cause of most forms of human glomerulonephritis (GN).[1] The etiology of GN in humans remains largely unidentified and elusive.[2,3] The development of immune responses that can cause GN is influenced by genetic predisposition in certain individuals.[4–6] The unique glomerular physiology also facilitates trapping immune aggregates or exogenous antigens in the glomerular capillaries. Indeed, the immunopathogenesis of GN is broad and complex, involving a nephritogenic immune response, both cellular and humoral, resulting in diverse clinical and pathological manifestations, ranging from asymptomatic urinary abnormalities to acute kidney injury (AKI) or end-stage renal disease (ESRD).[1,7] The humoral immune response causes immunoglobulin (Ig) deposition to form, subsequently triggering an inflammatory response by activating the complement factor cascade.[1,8] Meanwhile, the cellular immune facilitates the infiltration of circulating mononuclear inflammatory cells in the glomerulus and crescent formation.[9] There is a close and integrated interaction between intrinsic glomerular cells under physiological and illness or injury conditions.[10] In inflammatory lesions, glomerular hypercellularity may be seen due to infiltration of hematopoietic cells (mainly macrophages and neutrophils), intrinsic

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glomerular cell proliferation, or a combination of both. These effector cells further instigate various pathological changes, including thrombosis, necrosis, and crescent formation, potentially culminating in renal insufficiency and rapidly progressive GN (RPGN). Meanwhile, non-inflammatory lesions caused by immune injury typically involve podocytes as the primary effector cells and are associated with increased protein permeability.[9]

A further understanding of GN's pathogenic mechanisms can lead to more appropriate diagnostic considerations and treatment options for the halting or interrupting pathophysiology underlying individual disease, which causes significant and progressive glomerular disease. The author has also included a graphical summary at the end of this article to facilitate better understanding.

The role of glomerular physiology in immune-mediated injury

The glomerulus can be thought of as a "capillary network" that produces ultrafiltrate. Glomerular filtration is determined by glomerular blood flow and ultrafiltration pressure, regulated by arterial tone, which generates a pressure gradient, and the filtration surface area, which is affected by mesangial contractility. With their fenestrations, glomerular endothelial cells (GECs) can prevent blood cell filtration but cannot prevent water movement. The glycocalyx covers the GEC, which contains negatively charged glycosaminoglycans, which block the diffusion of negatively charged molecules and have anti-thrombotic and anti-adhesive properties. The glycocalyx is also crucial in regulating capillary permeability, mediating interactions between leukocytes and GECs, and transducing shear stress.[11]

Overall, the glomerular endothelium (with the glycocalyx), glomerular basement membrane (GBM), and podocytes collectively constitute the glomerular filtration barrier (GFB). This specialized structure facilitates the substantial filtration of solutes and water while also acting on the physicochemical and electrostatic charge of a molecule. Although the structure of the glomerular capillaries is typically designed to serve as a barrier to the passage of solutes, especially proteins, on the other hand, they are vulnerable to inflammatory injury from various causes, resulting in multiple causes of GN.[12] Conditions that can increase the vulnerability of the glomerulus to injury include: (1) the kidneys receiving 25% of high cardiac output; (2) high hydrostatic pressures within the glomerular capillaries; (3) highly fenestrated endothelium; and (4) sieving effect of glomerular filter. These conditions can maximize contact between reactants and GBM and concentrate substances potentially injuring the glomerulus, including circulating antigen-antibody complexes. The filtering ability of the glomerular capillaries for solutes is inversely related to the size of the substance. Large negatively charged molecules will be more readily filtered than positively charged molecules of the same size.[13] The inherent characteristic physiological conditions of the glomerulus will make it easier for the filtered substances to be trapped in certain places in the glomerulus, which in turn can trigger pathological processes in the kidney.

Components of the nephritogenic immune response in glomerular injury

A. **Humoral component**. The leading cause of glomerular injury is the humoral immune response. This glomerular injury is mediated by immune complexes (ICs) containing Ig and components of complements. This immune-mediated injury can occur directly, i.e., antibodies with intrinsic antigens (endogenous antigens as fixed-antigens), or indirectly, i.e., antibodies with embedded exogenous antigens (implanted antigens) and entrapment of circulating antigen-antibody complexes.[14] Immune deposits form as a result of antibodies targeting these antigens:

   a. Normal glomerular constituents

   - In anti-glomerular basement membrane (anti-GBM) disease:

interactions between antibodies and glomerular intrinsic antigen (as Goodpasture antigen), i.e., type IV collagen alpha-3 chains.[15,16]

- In membranous nephropathy (MN): interaction of antibodies against podocyte-specific antigens, such as phospholipase A2 receptor type-M (PLA2R), thrombospondin type-1 containing domain 7A (THSD7A)[17,18], and the third antigen, consisting of exostosins 1 and 2 (EXT1 and EXT2), neural epidermal growth factor-like 1 (NELL-1), neutral endopeptidase (NEP), Semaphorin 3B (Sema3B), protocadherin-7 (PCDH7), high-temperature recombinant protein A1 (HTRA1) and neural cell adhesion molecule 1 (NCAM-1).[19]

- In congenital nephrotic syndrome Finnish type (CNF): anti-nephrin antibodies in the diaphragmatic cleft can induce proteinuria without immune deposits and inflammation.[20]

b. Non-glomerular endogenous antigens localized to glomeruli

- In lupus nephritis (LN): DNA nucleosome complexes.[21]
- In IgA nephropathy (IgAN): abnormally glycosylated IgA.[22]
- On antineutrophil cytoplasmic antibody (ANCA) - associated vasculitis (AVV): myeloperoxidase (MPO) or proteinase 3 (PR3).[23]

The localization of non-glomerular endogenous antigens within the glomeruli occurs due to passive trapping through their interaction with the glomerular capillary wall, i.e., at negatively charged sites or through spontaneous aggregation.[9]

c. Immune aggregates or exogenous antigens localized in the glomerular capillaries. This process occurs through various mechanisms, including passive trapping, local precipitation of macromolecular aggregates, or loading affinity for glomerular structures.

- In membranoproliferative GN (MPGN) associated with hepatitis C virus (HCV): Cryoglobulin containing HCV antigen.[24]

However, in asymptomatic individuals, autoantibodies to MPO, PR3, and GBM may also be found, and anti-PLA2R antibodies may develop months or years before the onset of MN.[25] This shows that humoral immunity to target antigens does not always show pathogenicity.

B. **Cellular components.** Pathogenic T-cell responses in immune-mediated GN are linked to the most severe forms of GN, i.e., crescentic GN (cGN), which pathologically consists of immune complex (IC), pauci-immune, and anti-GBM GN. T helper-1 (Th1) cells recruit monocytes to the kidney by promoting the expression of chemokines in glomerular intrinsic cells. Further, an increase in interferon ɣ (IFNɣ) by activated Th1 cells and glomerular intrinsic cells promotes macrophage recruitment and differentiation of monocytes into inflammatory M1 macrophages, which mediate tissue damage and crescent formation. T helper-2 (Th2) cells are involved in driving immune complex deposition, which subsequently induces glomerular infiltration of neutrophils. These neutrophils contribute to tissue damage through reactive oxygen species (ROS) production, neutrophil extracellular traps (NET) formation, and serine protease degranulation.[26]

Immune mechanism responses to glomerular injury

A. Inflammatory injury. The cellular inflammatory response occurs due to the deposit of immune complexes with the

activation of complement factor cascades in the glomerulus.[8,27] The inflammation it causes is influenced by the site where the IC deposits occur. For example, IC is deposited on the GBM in anti-GBM antibodies disease, subendothelial deposition in class III or IV LN and MPGN, and deposits in the mesangium in IgAN and LN.[9] Besides occurring due to the influence of IC deposits, severe inflammation can also happen without IC deposits, as seen in conditions like vasculitis (ANCA-positive necrotizing GN).[1] In the presence of inflammatory changes, glomerular hypercellularity results from the infiltration of macrophages and neutrophils, proliferation of intrinsic glomerular cells, or both. Furthermore, these effector cells can further contribute to necrosis, thrombosis, and crescent formation, leading to renal insufficiency and RPGN.[1]

B. **Non-inflammatory injury**. Non-inflammatory lesions caused by immune injury typically involve podocytes as primary effector cells, leading to increased glomerular permeability to albumin and other proteins without detectable light microscopic damage.[1] The main clinical features of this non-inflammatory glomerular lesion are proteinuria and nephrotic syndrome (NS).[9]

Effector cells and mediator in the inflammatory GN

The inflammatory response involves the coordinated activation of signaling pathways that control the production of inflammatory mediators in resident tissue cells and blood-derived recruited inflammatory cells.[28] This mechanism is commonly observed in inflammatory response processes, as with glomerular injury. The glomerular injury also typically driven by the activation of effector cells (i.e., neutrophils, macrophages, natural killer (NK) cells, T cells, and platelets as well as glomerular intrinsic cells) and release of inflammatory mediators (i.e., complement activation products, oxidants, and proteases; and various cytokines, chemokines, growth factors (GFs), and other vasoactive agents).[2,9,29]

A. Role of circulating inflammatory cells

Role of Neutrophils - Neutrophils are among the first leukocyte subsets recruited to deposit IC, consisting of autoantibodies or antibodies essential in promoting glomerular injury.[30] This is evidenced by the presence of neutrophils in kidney biopsies from patients with antibody-mediated GN such as PSGN, MPGN, IgA vasculitis (Henoch-Schoenlein purpura), LN, anti-GBM disease, and some forms of cGN.[31] Based on its cellularity, GN can be classified into two categories: proliferative forms due to the influx of immune cells and intrinsic cell proliferation and non-proliferative forms. Leukocytes play a central role in developing proliferative GN at multiple levels, including influencing the development of adaptive and humoral immune responses and modulating local effector mechanisms that directly contribute to glomerular damage.[30] Although the role of neutrophils in glomerular injury is recognized, the molecular mechanisms underlying immune complex-mediated recruitment of neutrophils in the glomerulus, where capillaries serve as the main site of leukocyte recruitment, remain indeterminate.[32] In general, some of the important roles of neutrophils in glomerular injury include:

- Neutrophils phagocytose immune complex aggregates, leading to their activation and the initiation of a respiratory burst that produces ROS. These ROS contribute to glomerular injury by interacting with MPO, a cationic enzyme derived from neutrophils that localizes in the glomerulus due to its positive charge.[9]

- Neutrophils are the storage site for cationic serine proteases, including cathepsin G and elastase, in azurophilic granules, released upon neutrophil activation, which can further degrade elements of the glomerular capillary wall.[9]

- Neutrophils generate NETs, as in AGN and LN. NETs are net-like histone structures decorated with peptides, proteases, and enzymes, which are also detrimental.[33]

- Role of neutrophils in ANCA-associated vasculitis (AAV)— Neutrophil involvement in AAV is linked to cationic proteases, PR3, and MPO, localized in neutrophil primary granules. Upon activation by certain cytokines, these proteases are translocated to the surface of neutrophils, making them accessible to circulating ANCA antibodies targeting PR3 or MPO, contributing to the pathogenesis of glomerular injury.[9,34]

Role of Macrophages — Macrophages are innate immune cells and major components of the mononuclear phagocytic system. They are involved in numerous cellular processes crucial in maintaining tissue homeostasis.[35] IC or cells of the adaptive immune system (T lymphocytes and their cytokines) can activate macrophages. In renal disease, macrophage activation is typically secondary to the activation of complementary or effector T cells, which are triggered by antigens that are not specific to the kidney. This suggests that macrophages may not be the primary initiators of renal disease.[36] However, in immune-mediated GN, there is an increased number of macrophages in the kidney.[37] In some glomerular lesions, especially those showing crescent formation, macrophages are the prominent constituents.[29,38] The following aspects should be addressed regarding the role and function of macrophages in human GN:

- In proliferative GN, the number of glomerula macrophages correlates with disease severity. Macrophages were observed in the glomerular tuft in nearly all types of GNs, whose staining varied from "positive" to "intense." The intensity of this stain correlates with the cellular intensity of the glomerulus, either intrinsic glomerular cells or circulating inflammatory cells. Macrophage staining was more intense on cGNs, i.e., LN and AAV, whereas staining was less intense on less proliferative GNs, i.e., IgAN and MN.[39]

- In most severe lesions, macrophages are localized in the glomeruli. AGN and cryoglobulinemia GN are 2 diseases characterized by comparable massive macrophage glomerular infiltration, though they differ in their localization. In AGN, macrophage accumulates mainly in areas of extra-capillary proliferation (crescent) and granulomatous glomerular lesions. Contrarily, in cryoglobulinemic GN, macrophages are more homogeneously distributed throughout the glomerular tufts but are absent from the periglomerular interstitium.[38]

- Macrophages are recruited to glomeruli and glomerular lesions by chemokines secreted by intrinsic glomerular cells. Monocyte chemoattractant protein-1 (MCP-1) has been identified in IgAN, LN and GPA. Additionally, MCP-1 and its chemokine receptor 2B (CCR2B) are expressed in human cGN, with CD68+ cells being the primary glomerular cell type that expresses CCR2B.[40] Macrophages are also easily recruited by molecules derived from lymphocytes, like macrophage migration inhibitory (MIF), produced during interactions between T cells, particularly those with specific sensitivities and intraglomerular antigens.[41]

- Macrophages that are attracted become activated in proliferative glomerular lesions. In addition to differences in number and localization, AGN and cryoglobulinemic GN macrophages exhibit significant differences in cytokine production, activation, adhesion, and proliferation. De novo production of glomerular vascular cell adhesion molecule 1 (VCAM-1) was observed exclusively in AGN and was restricted to necrotizing extra-capillary lesions.[38] Likewise, the production of TNF-α and IL-1β is prominent in AGN. AGN differs from cryoglobulinemic GN in macrophage properties, contributing to its more severe disease progression. Macrophages are also seen in Henoch-Schönlein syndrome, necrotizing IgA nephritis, and GN associated with endocarditis and have not been seen in other glomerular diseases.[42,43]

Overall, it has been shown that acute macrophage activation immediately affects the production of proinflammatory cytokines in the glomeruli and adhesion molecules in the endothelium, thereby exacerbating the severity of the disease.[39] In addition, macrophages release tissue factor, which triggers crescent formation and fibrin deposition, as well as transforming growth factor (TGF)-ß, leading to extracellular matrix (ECM) synthesis and development of glomerular sclerosis.[9]

Role of T Cells – T cells are detectable in conditions primarily characterized by macrophage-mediated mechanisms, such as cGN.[2,29,31] The functional role of T cells in cGN pathogenesis was first demonstrated in a study of athymic nude mice treated with human renal GBM. This study demonstrated that without T cells, neither autologous anti-GBM antibodies nor glomerular injury developed.[44] The significance of T cells in LN disease pathology was highlighted in MRL-lpr mice. T cell depletion led to less severe renal disease in this genetic autoimmune model mice strain.[45] The important role of CD4+ T cells in disease pathology was also demonstrated in anti-MPO GN. In this context, depletion of CD4+ T cells reduced renal immune cell infiltration and mitigated cGN.[46,47]

While experimental evidence suggests that systemic T cells can induce glomerular injury without antibody deposition, evidence supporting that glomerular T cells alone are nephritogenic is limited, except for T cell-derived permeability factors.[48,49] T-cell-mediated injury primarily presents through the release of chemokines and the subsequent recruitment of macrophages, which serve as effector cells.

Role of T helper 17 cells. All T cell subsets are involved in GN, but IL17-producing T helper 17 (Th17) cells are likely the primary contributors to T cell-induced inflammation. Th17 cells in kidney biopsies in several forms of human GN.[50] These cells also facilitate anti-MPO-mediated GN through the secretion of IL-17a. IL-17a-deficient mice are protected against anti-MPO-mediated GN and have reduced accumulation of renal macrophages.[51] Th17 cells are recruited via chemokine and receptor interactions, releasing cytokines including IL9, IL17, IL21, IL22, and TNFα. These cytokines stimulate other cells to produce additional proinflammatory chemokines, attracting neutrophils and monocytes while activating intrinsic glomerular cells.[50]

Role of Regulatory T Cells — In contrast to effector T cells like Th17 cells, which exacerbate glomerular injury, regulatory T cells (Tregs) have been shown to aid in injury repair and promote tolerance.[52–54] Tregs are known to suppress innate and adaptive immune responses in the kidney, and abnormalities in their number or function have been reported in certain forms of GN.[55]

Tregs were identified as T-cells that express high levels of the IL-2 receptor alpha (CD25) and the transcription factor forkhead box P3 (Foxp3), a hallmark of their control function of Treg cells. IL-2 is the master regulator of Treg, and a deficiency in IL-2 has an important influence on decreasing the number and function of Treg cells.[52,56] The functions of Tregs include controlling innate and adaptive immunity, regulating cell damage, and promoting repair.[52] In SLE, there is immune dysregulation, with deficiency of IL-2 production, excessive production of proinflammatory cytokines, and resistance to Treg-mediated suppression. Given the role of Tregs, many new therapeutic strategies are currently being developed that target Treg enhancement. It has been demonstrated that the cytokines IL-2, IL-2/mCD25, IL-6, and IL233 directly promote strong Treg expansion, preventing autoimmunity and LN.[52]

Role of Platelets - Some glomerular lesions have prominent platelets, especially in lesions involving intraglomerular thrombosis, such as thrombotic microangiopathy and anti-phospholipid antibody syndrome. While platelets are best known for their involvement in thrombotic processes associated with endothelial cell injury, they also secrete various bioactive substances that contribute to and exacerbate

glomerular injury. These include chemotactic, mitogenic, and vasoactive substances.[9]

A. Role of Glomerular Intrinsic Cells Injury

Endothelial, mesangial, parietal epithelial, and visceral epithelial cells (podocytes) in the glomerulus all have unique and specific roles, which are essential for the normal functioning of the glomerulus. However, these glomerular intrinsic cells are also the main target of various disease processes, including immune injury. Response to injury depends on the damage's duration, nature, and magnitude. An overview of the typical intrinsic cell responses to injury is provided in Table 1.[31]

Table 1. Key functions and responses to injury of intrinsic glomerular cells[31]

Cell Type	Normal Function and Features	Responses to Injury	Relevant Glomerular Diseases (Examples)
Mesangial cells	Maintain structural architecture of glomerulus Mesangial matrix homeostasis Regulate filtration surface area Phagocytose apoptotic cells	Lysis with healthy remodeling Apoptosis Hypertrophy Proliferation and matrix expansion leading to glomerulosclerosis	IgA nephropathy Diabetic nephropathy
Glomerular endothelial cells	Fenestrations and glycocalyx facilitate selective permeability and filtration	Apoptosis Loss of fenestrations Widening of cell-cell junctions, transcellular holes Glycocalyx damage, loss of GAG synthesis	ANCA-associated GN Lupus nephritis (Class III and IV) Hemolytic uremic syndrome Diabetic nephropathy
Podocytes	Foot processes wrap around capillaries Adherence to GBM Slit diaphragm regulates filtration	Apoptosis Foot process effacement Detachment from GBM, podocyte loss Loss of slit diaphragm	Minimal change disease FSGS Diabetic nephropathy
Parietal epithelial cells	Line Bowman's capsule Several subsets of cells likely with different functions Subset of cells may be able to differentiate into podocytes and play a reparative function	Apoptosis Migration to glomerular tuft, production of ECM proteins leading to glomerulosclerosis Proliferation leading to crescent and pseudocrescent formation	Crescentic GN FSGS

GAG, glycosaminoglycan; GBM, glomerular basement membrane; ECM, extracellular matrix

There are intimate and integrated interactions among cellular components of the glomerulus under physiological conditions and in disease or injury. Podocytes, mesangial cells, and endothelial cells engage in complex, multi-directional cross-talk both among themselves and with leukocytes.[10] Although a particular disease may primarily target a particular cell type, it typically indirectly affects other cells.[31] Podocyte injury can lead to mesangial cell proliferation, while mesangial cell injury can result in thinning and fusion of podocyte foot processes. Additionally, signals from mesangial and endothelial cells are essential for the normal function of podocytes.[57]

a. **Injury of glomerular endothelial cells (GEC).** GECs, with their unique properties and functions as previously described, are more prone to become major targets of injury in hemolytic uremic syndrome, certain forms of vasculitis, and preeclamptic toxemia in pregnancy.[58] GECs injury can lead to cell proliferation, detachment, apoptosis, adhesion of leukocytes, and thrombosis.[59,60] The above conditions underlying GEC injury are commonly associated with proliferative GN, which may mediate the progression of cGN. The proliferation of mesangial and endothelial cells, along with leukocyte infiltration, causes endocapillary proliferation, resulting in narrowing and occlusion of the glomerular capillary lumen.[61]

b. **Injury of glomerular mesangial cell.** Glomerular mesangial cell injury is observed in IgAN and LN, where immune deposits occur and involve the mesangium.[62,63] Mesangial cell activation generally results in proliferation and hypertrophy, production of ROS, and excessive matrix production.[62] Mesangial cell activation also produces cytokines and chemokines, which influence mesangial and glomerular cells and other leukocytes. In response, these leukocytes release mediators that affect the mesangial cells, forming a paracrine loop.[63] The expansion of the mesangial matrix and the release of vasoactive mediators lead to a decrease in glomerular surface area and changes in glomerular hemodynamics, ultimately decreasing GFR.[62,63] Several mediators have been identified that can activate mesangial cells, i.e., cytokines, GFs; C5b-9, the complement MAC; immune complexes, and ROS.[9]

c. **Injury of glomerular parietal epithelial cell (PEC).** Compared with the other 3 intrinsic glomerular cell types, the occurrence of well-defined glomerular disease primarily due to abnormalities arising in PECs is lacking.[64] However, evidence based on GN mouse models targeting early injury to glomerular endothelial cells and GBM suggests that the ensuing proliferation of glomerular PEC results in a significant increase in cell numbers within the crescent.[65] This is consistent with the main feature of cGN, i.e., PEC proliferation.[9] Besides proliferating, activated PEC (which is induced by fibrin) also migrates and produces ECM.[66,67] The proliferated or increased PECs can attenuate urine flow and release cytokines and chemokines, which can interfere with the function of the affected glomerulus. Conversely, PEC may migrate from Bowman's capsule to capillary bundles and differentiate into podocytes in response to injury.[68,69] It suggests a regenerative and reparative role when podocytes are lost. PECs presenting cellular crescents undergo epithelial-to-mesenchymal transition (EMT) with increased ECM synthesis, which ultimately leads to the formation of classical honeycomb-like lesions.[70]

d. **Injury of glomerular visceral epithelial cells (podocyte).** Podocytes are the most sensitive component of the glomerulus to injury and are frequently damaged or dysfunctional.[71] Besides their important role in preventing proteinuria, podocytes also contribute to crescent formation through the formation of cellular masses due to proliferation.[72,73] Podocyte injury may also be involved in PEC proliferation and crescent formation by reducing the expression of Krüppel-like factor 4, a zinc-finger transcription factor critical for maintaining

podocyte homeostasis and keeping PEC in a quiescent state.[74,75]

During development and in various forms of renal pathology, podocytes, and PEC are interdependent. Rapid loss of podocytes in diseases, including RPGN and collapsing and cellular subtypes of FSGS, is associated with the proliferation and migration of PEC toward capillary bundles, leading to the formation of crescents and pseudo-crescents.[76] The occurrence of severe proteinuria in IgAN is another illustration of the interaction between various glomerular cell types. Mesangial expansion can cause compression of individual podocytes leading to effacement of their foot processes, changes in the filtration slits, shedding of podocytes, and proteinuria.[77,78]

Role of the location of deposit immune complexes in glomerular injury

Different places or locations of injury in the glomerulus can give a different clinical picture according to the physiological function of each part of the glomerulus. Therefore, the primary factor in determining whether a patient develops nephritic or nephrotic syndrome is the site of glomerular injury.[9] Table 2 lists examples of GN caused by IC deposition.[14]

Table 2. Immune complex-mediated glomerulonephritis[14]

Location of glomerular immune complex deposits	Associated glomerulonephritides, with examples	Associated diseases involving loss of immune homeostasis, examples
Subendothelial	Membranoproliferative GN IgA nephropathy Lupus nephritis (classes III & IV)	Autoimmune disease (e.g., Sjogren's syndrome, scleroderma, SLE)
Mesangial	Membranoproliferative GN IgA nephropathy Lupus nephritis (classes I & II)	Autoimmune disease (e.g., Coeliac disease, SLE) Inflammatory disease (Crohn's disease)
Subepithelial	Membranoproliferative GN Infection-related GN MN Lupus nephritis (class V)	Autoimmune disease (e.g. SLE, anti-PLA2R disease)

- **Endothelial cells and glomerular mesangium**: Formation or deposition of IC in the subendothelial space or mesangial matrix often results in glomerular inflammation and nephritic syndrome (the subendothelial deposition of IC is more severe than the mesangium because the mesangium is relatively localized). Injury to the endothelium and subendothelial causes recruitment of leukocytes with consequent inflammatory GN, impaired hemostasis causing thrombotic microangiopathy, and vasoconstriction and contraction of mesangial cells, eventually leading to AKI. This deposition in the sub-endothelial causes the formation of chemotactic factors, which will attract infiltrating leukocytes and mononuclear cells. These cells will phagocytize ICs and release mediators such as chemo-kines and cytokines, which then cause inflammation of the glomerulus, which clinically displays active sediment in the urine, such as hematuria, pyuria, and proteinuria.[9]

- **Visceral epithelial cells or podocytes**: Injured podocytes will give the dominant picture through massive proteinuria and nephrotic range or NS (MCD; FSGS) and do not cause active inflammation.[9]

- **Subepithelial and basement membranes**. As with podocyte injury, injury or IC that deposits in the capillary wall adjacent to the podocytes (sub-epithelial deposits) does not produce an inflammatory response due to GBM, a separator of immune deposits from the systemic circulation.[9] Deposits of antigen-antibody complexes on the basolateral surface of podocytes activate the C5b-9 membrane attack complex (MAC), leading to oxidative damage and DNA injury to podocytes. This, in turn, results in damage to the actin cytoskeleton. Collapse of the actin cytoskeleton, loss of GBM adhesion, and loss of diaphragmatic cleft integrity lead to proteinuria.[79]

- **Parietal epithelial cell**. Injury to the parietal epithelial cells results in the formation of crescents, which are clinically indicated by a rapid decrease in glomerular filtration. This glomerular crescent formation is considered a non-specific response to severe injury to the glomerular capillary wall. This condition involves multiple upstream immune mechanisms, such as the deposition of autoantibodies and IC, complement activation, and recruitment of inflammatory cells.[80]

Role of other factors in glomerular injury

Apart from the location of glomerular injury as described above, other factors can cause glomerular injury, namely:

1. Biological properties of the Ig that forms the deposit. Inflammation is more severe when caused by IgG subtypes, such as IgG1 and IgG3, compared to IgA and IgG4, which activate complement poorly.[81]

2. Mechanism of deposit formation. Compared with passive trapping of circulating IC, local complement activation resulting from the formation of IC in situ is much more nephritogenic.[82,83]

3. The magnitude of the formation of immune deposits. A positive relationship exists between the amount of immune deposits and the degree of tissue injury.[9]

4. Recognized nature of the epitopes. There is a relationship between kidney injury and pathogenic antibodies to the linear epitope on the Goodpasture antigen.[84] Similarly, certain disease-specific MPO epitopes for active ANCA have been found[85,86], whereas other epitopes persist during remission or in healthy individuals.[85,86]

Despite immune deposits, significant tissue injury can occur due to immunoglobulin alone, as in patients with CNF, which is linked to

mutations in the nephrin gene, in which anti-nephrin antibodies can induce proteinuria without inflammation.[20]

Antibody-mediated injury without immune complex

Antineutrophil Cytoplasmic Antibodies - Associated Vasculitis (AAV)

AAV is a group of autoimmune disorders that includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and their localized forms.[87] The most common manifestation of AAV is ANCA-associated GN (AGN).[88] The clinical presentation of renal involvement in AAV includes proteinuria, hematuria, or RPGN, depending on the degree of vasculitic kidney damage. The extent of renal involvement in AAV varies based on the different ANCA serologies. Patients with PR3-ANCA showed minor kidney involvement compared to those with MPO-ANCA patients.[89,90] Conversely, patients with PR3-ANCA are more likely to experience extra-renal organ manifestations compared to those patients with MPO-ANCA.[91] The characteristic lesion in AGN patients is necrotizing crescent-immune GN, often presenting as crescentic or necrotizing GN without Ig deposition.[88]

The disease diagnosis is based on findings on ANCA staining, which can be either a cytoplasmic pattern (c-ANCA) or a perinuclear pattern (p-ANCA). c-ANCA is a neutrophil antigen, usually PR3, a constituent of primary neutrophil granules, whereas p-ANCA is usually an MPO antigen, another granule constituent that migrates to the perinuclear region.

C3 nephritic factor

C3 nephritic factor (C3NF) is a group of autoantibodies that allow continuous activation of alternative complement pathways.[92] This IgG autoantibody, C3NF, stabilizes C3 conversion, causing uncontrolled C3 activation leading to very low C3 levels but normal C4. Consequently, deleterious C3 deposits can form in the glomerulus, triggering downstream inflammatory cascades and increasing leukocyte infiltration.[14] In dense deposition disease (DDD), small bands of electron-dense deposits form along the GBM, causing it to thicken and become dysfunctional.[93] In addition to GBM deposits, C3 glomerulopathy exhibits varying degrees of mesangial C3 deposits, contributing to mesangial cell proliferation and matrix expansion. C3NF is most common in MPGN (C3 glomerulonephritis). Currently, DDD with isolated intramembrane C3 deposition and MPGN is classified as C3 glomerulopathy.[94,95]

The clinical features of DDD and C3 glomerulonephritis (C3GN), classified as C3 glomerulopathy, vary widely.[96] The diagnosis of C3GN or DDD is made through an immuno-fluorescence examination of a kidney biopsy specimen, along with studies of the complement system. An electron microscope is required to distinguish DDD from C3GN. DDD is characterized by highly electron-dense deposits in the GBM ('sausage-like deposits), whereas subendothelial and mesangial electron-dense deposits of lower intensity characterize C3GN.[96,97]

Non-inflammatory mechanisms of immune glomerular injury

In contrast to inflammatory injury, non-inflammatory immune glomerular injury usually results in proteinuria with little or no hematuria. Among non-inflammatory immune glomerular injuries, MCD, FSGS, and MN are the most prevalent causes. This disorder is characterized by increased glomerular permeability, corresponding to the main target of injury, i.e., podocytes.[9]

Evidence for the role of circulating factors

Evidence supporting the patho-physiological role of circulating factors influencing podocyte function and structure are: (1) resolved nephrotic proteinuria in children of mothers with FSGS and NS.[98] (2) transplant success in diabetic patients with grafts derived from transplanted FSGS recipients due to intractable recurrent massive proteinuria and renal insufficiency[99]; (3) perfused rat glomeruli

isolated with plasma from patients with FSGS-induced increased glomerular capillary permeability to albumin[100]; (4) The occurrence of massive proteinuria and FSGS histological lesions after kidney organ transplantation from healthy donors in approximately 30% of patients with FSGS[101]; (5) with prior plasma exchange, some patients were successfully treated[101]; (6) The risk of FSGS recurrence (rFSGS) following transplantation can be reduced by preemptive plasmapheresis[102]; (7) one year after transplantation, kidneys from a donor with FSGS transplanted into two uremic recipients showed no signs of proteinuria and had normal renal function.[103]

Glomerular permeability factors

- **Cardiotrophin-like cytokine factor 1 (CLC-1).** CLC-1, a member of the IL-6 family, is detected in the plasma fraction of patients with FSGS. CLC-1 increases glomerular albumin permeability, and its injection induces proteinuria in rats.[100]

- **Radical oxygen species (ROS).** Oxidative stress in isolated rat glomeruli induces proteinuria.[104] Resting PMNs from idiopathic NS (INS) patients demonstrated a tenfold higher ROS production than normal PMNs. This oxidative burst by PMNs is highly regulated by T lymphocytes, especially Tregs, through soluble factors. However, this regulatory circuitry is altered in INS.[105]

- **Hemopexin**. Hemopexin is a heme scavenger protein that increases during acute phase reactions to inflammation. Upon activation, hemopexin alters the function of both glomerular endothelium and podocytes.[106] It has been shown that activated hemopexin induces reversible proteinuria in rats, accompanied by podocyte foot process effacement. Similarly, hemopexin levels are elevated in children during relapsing MCD.[107] However, the cause of hemopexin activation is still unclear, possibly involving the inhibition of hemopexin inhibitors or their leakage into urine. In the second scenario, hemopexin activation should only be a secondary event, dependent on the increased permeability of the GFB to proteins.[108]

- **Soluble urokinase-type plasminogen activator receptor (su-PAR).** Urokinase plasminogen activator receptor (uPAR), a cell membrane glycosylphosphatidylinositol (GPI)-anchored membrane glycoprotein, contributes to the migration of activated T-lymphocytes, monocytes, and neutrophils to sites of inflammation.[106] The role of uPAR in its soluble form (suPAR) in the pathogenesis of human FSGS remains a topic of ongoing debate.[108] Therefore, further research is needed using tests to differentiate the various forms of circulating suPAR across different glomerular pathologies.

- **Angiopoietin-like 4 protein (Angptl4).** Podocyte Angtpl4 has been suggested to contribute to the development of proteinuria in MCD.[109,110] Angptl4 podocyte overexpression has been observed in MCD in relapse[110–112] and other human glomerular diseases.[113,114] However, studies have proven that Angptl4 is not a good biomarker in MCD.[115] Increased urinary agptl4 in glomerular disease appears to reflect more with the degree of proteinuria than with the specific disease.

- **Calcium/calmodulin-dependent serine/threonine kinase (CASK).** CASK was produced mostly by monocytes and M2 macrophages rather than by T or B lymphocytes via exosomes to alter the GFB in patients with USGS.[116] A soluble form of CASK acts as a permeability factor in patients with rFSGS.[117]

- **Anti-nephrin antibodies**. Anti-nephrin antibodies are the newest candidates for permeability factors in MCD. In the Nephrotic Syndrome Study Network (NEPTUNE) cohort, 11 out of 18 patients with positive anti-nephrin antibodies during active disease showed a reduction or complete absence of these antibodies during remission.[118] Based on the NEPTUNE cohort, a new molecular classification of

MCD nephrin autoantibodies has been proposed. This classification provides a framework for initiating precise therapy for these patients.

Although clinical and experimental data indicate that circulating permeability factors induce glomerular proteinuria and NS, one suspected responsible factor remains un-identified. The identity of permeability factors and mechanisms for increasing glomerular permeability in humans with NS are uncertain. Likewise, the correlation with clinical activity is inconsistent.

Conclusion

Available evidence has shown that most forms of human GN result from immunological mechanisms, although the etiology of the majority remains unknown. The precipitating factor is thought to be infection, cancer, drug or toxin exposure, which in turn triggers a nephritogenic immune response, which includes cellular and humoral components, as well as intrinsic glomerular cell involvement and their cross-talk, resulting in various manifestations of GN. Genetic and environmental factors also influence the nature of the immune response that causes GN and the individuals who develop it.

The humoral immune response causes the deposition of IC in the glomeruli, triggering an inflammatory response and activation of the complement factor cascade. Meanwhile, the cellular immune response leads to circulating mononuclear inflammatory cell infiltration in the glomerulus, promoting crescent formation. In inflammatory lesions, hematopoietic cells infiltrate (mainly macrophages and neutrophils) and proliferation of intrinsic glomerular cells, leading to glomerular hypercellularity. These effector cells can also induce thrombosis, necrosis, and crescent formation, leading to RPGN. Immune injury that produces non-inflammatory lesions usually involves podocytes as the primary effector cells and is associated with increased protein permeability.

The site of glomerular injury is the key factor determining whether a patient presents with an inflammatory injury characterized by active urinary sediment (nephritic syndrome) or a non-inflammatory injury marked by proteinuria and minimal or absent hematuria (nephrotic syndrome). Injury to GEC and mesangial cells usually results in inflammatory injury. In contrast, a glomerular injury that primarily involves podocytes generally results in non-inflammatory injury. Additional factors modulating glomerular injury include the biological nature of the Ig involved in forming immune deposits, i.e., IC formed in situ or trapped of circulating IC; the quantity of formation of immune deposits; epitope properties; and diffusion of the immune response (spread of epitopes).

Perspective

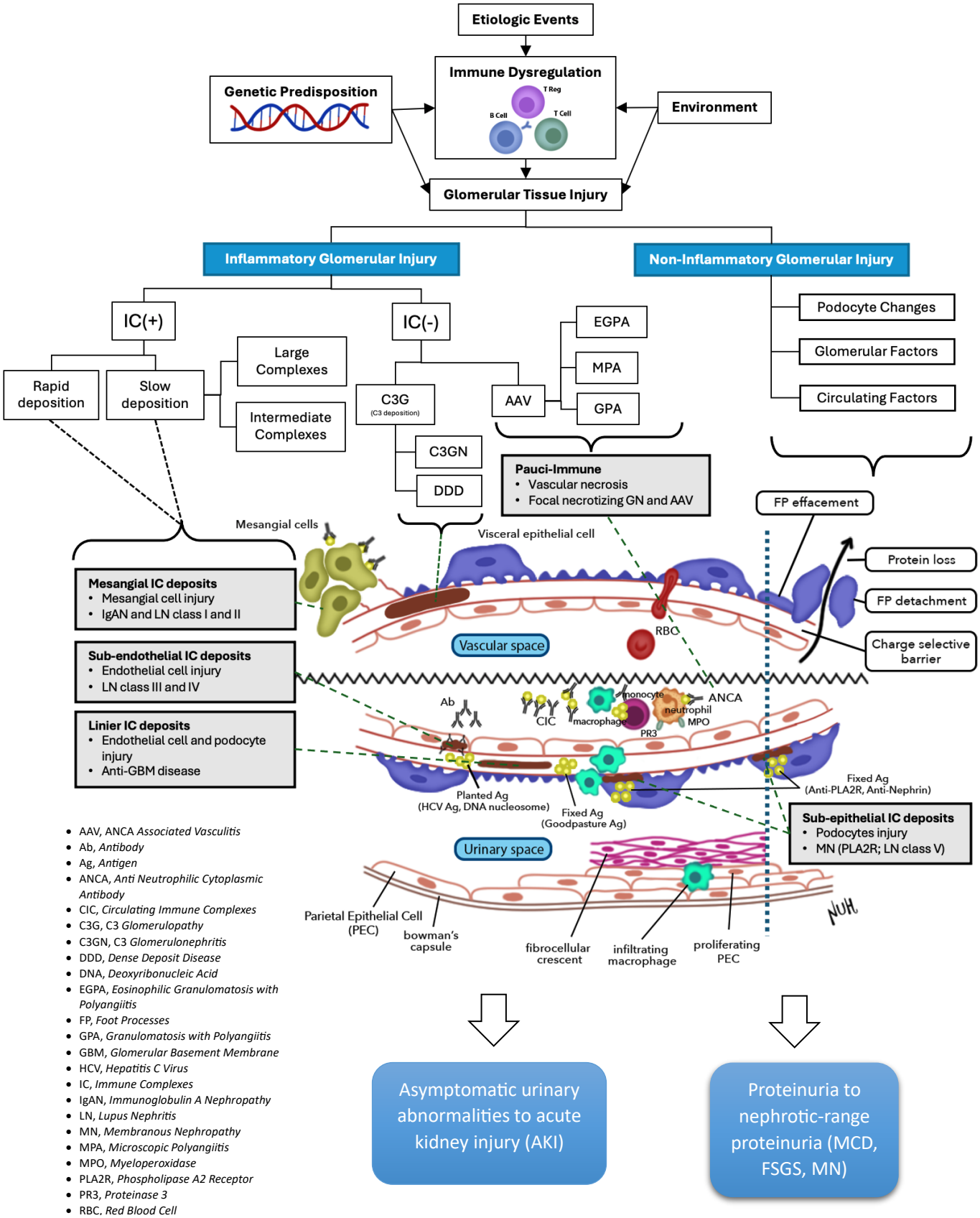
Indeed, a comprehensive understanding of the pathogenesis of immune-mediated GN may lead to a more precise diagnosis. However, because of the breadth and complexity of the pathogenesis of GN, it undoubtedly poses many challenges in the work-up of patients with the clinical presentation of glomerular disease. GN is indeed a highly variable and unpredictable condition, ranging from benign and spontaneous remission to rapidly progressive. These conditions can contribute to a delay in the diagnosis of GN, coupled with uncertainty in prognosis and therapy, all of which can lead to poor patient outcomes.

Renal biopsy remains the gold standard of diagnosis for almost all adult GN. However, it has been shown that biopsies often fail to predict clinical course or response to therapy. The existence of heterogeneous pathogenetic mechanisms causes a histological picture that cannot be distinguished from the clinical picture, the progression rate, and the therapy response. In cases of MN, the disease's diagnosis, treatment, and prognosis may be assessed without biopsy, based solely on the patient's serum anti-PLAR2 Ab titer. However, anti-PLA2R antibodies can appear months or years before the development of MN.[25] Similarly, antibodies to MPO, PR3, and

GBM can be found in asymptomatic individuals, complicating interpretation.

Based on the conditions above, the management of GN seems to require a paradigm shift. For diagnosing GN, biomarkers, diagnostic panels, or scoring/classification systems may be needed to make the diagnosis more specific. There is a need for biomarkers that reflect the molecular mechanisms underlying clinical pathology diagnosis. By identifying new biomarkers, it is hoped that it can improve diagnosis, predict prognosis, and make appropriate therapeutic decisions. The presence of biomarkers of glomerular disease across the genotype-phenotype continuum, in turn, provides an opportunity to shift to precision medicine, i.e., therapies that maximize efficacy and minimize toxicity

Graphical Summary: Pathogenesis of Immune-mediated Glomerulonephritis



- AAV, ANCA *Associated Vasculitis*
- Ab, *Antibody*
- Ag, *Antigen*
- ANCA, *Anti Neutrophilic Cytoplasmic Antibody*
- CIC, *Circulating Immune Complexes*
- C3G, C3 *Glomerulopathy*
- C3GN, C3 *Glomerulonephritis*
- DDD, *Dense Deposit Disease*
- DNA, *Deoxyribonucleic Acid*
- EGPA, *Eosinophilic Granulomatosis with Polyangiitis*
- FP, *Foot Processes*
- GPA, *Granulomatosis with Polyangiitis*
- GBM, *Glomerular Basement Membrane*
- HCV, *Hepatitis C Virus*
- IC, *Immune Complexes*
- IgAN, *Immunoglobulin A Nephropathy*
- LN, *Lupus Nephritis*
- MN, *Membranous Nephropathy*
- MPA, *Microscopic Polyangiitis*
- MPO, *Myeloperoxidase*
- PLA2R, *Phospholipase A2 Receptor*
- PR3, *Proteinase 3*
- RBC, *Red Blood Cell*

Declarations

Competing interests

The author declares no conflict of interest.

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Author's Contribution

Idea/concept, design, control/ supervision, data collection/processing, analysis/ interpretation, literature review, writing the article, critical review: NS. Author has critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

References

1. Russo GE, Musto TG, Glomerulonephritis MT. Pathogenetic Mechanisms and Therapeutic Options: An Overview. J Nephrol Ther. 2014;4(4):1–9. doi:10.4172/2161-0959.1000175
2. Couser WG. Basic and translational concepts of immune-mediated glomerular diseases. J Am Hear Assoc [Internet]. 2012;23(3):381–99. Available from: http://dx.doi.org/10.1681/asn.2011030304doi:10.1681/asn.2011030304
3. Anders HJ, Fogo AB. Immunopathology of lupus nephritis. Semin Immunopathol [Internet]. 2014;36(4):443–59. Available from: http://dx.doi.org/10.1007/s00281-013-0413-5doi:10.1007/s00281-013-0413-5
4. Kashtan C. Autotopes and allotopes. J Am Soc Nephrol [Internet]. 2005;16(12):3455–7. Available from: http://dx.doi.org/10.1681/asn.2005090943doi:10.1681/asn.2005090943
5. Stanescu HC, Arcos-Burgos M, Medlar A, Bockenhauer D, Kottgen A, Dragomirescu L, et al. Risk HLA-DQA1 and PLA2R1 alleles in idiopathic membranous nephropathy. New Engl J Med [Internet]. 2011;364(7):616–26. Available from: http://dx.doi.org/10.1056/nejmoa1009742doi:10.1056/nejmoa1009742
6. Beerman I, Novak J, Wyatt RJ, Julian BA, Gharavi AG. The genetics of IgA nephropathy. Nat Clin Pr Nephrol [Internet]. 2007;3(6):325–38. Available from: http://dx.doi.org/10.1038/ncpneph0492doi:10.1038/ncpneph0492
7. Berg JG van den, Weening JJ. Role of the immune system in the pathogenesis of idiopathic nephrotic syndrome. Clin Sci. 2004;107(2):125–136. doi:10.1042/cs20040095
8. Couser WG, Baker PJ, Adler S. Complement and the direct mediation of immune glomerular injury: a new perspective. Kidney Int [Internet]. 1985;28(6):879–90. Available from: http://dx.doi.org/10.1038/ki.1985.214doi:10.1038/ki.1985.214
9. Bonegio RGB, Salant DJ. Mechanisms of immune injury of the glomerulus [Internet]. 2023 [cited 2023 Jun 14]. Available from: https://medilib.ir/uptodate/show/3068
10. Sol M, Kamps JAAM, van den Born J, van den Heuvel MC, van der Vlag J, Krenning G, et al. Glomerular endothelial cells as instigators of glomerular sclerotic diseases. Front Pharmacol [Internet]. 2020 Oct 6;11:573557. Available from: https://pubmed.ncbi.nlm.nih.gov/33123011doi:10.3389/fphar.2020.573557
11. Salmon AHJ, Satchell SC. Endothelial glycocalyx dysfunction in disease: albuminuria and increased microvascular permeability. J Pathol [Internet]. 2012;226(4):562–74. Available from: http://dx.doi.org/10.1002/path.3964doi:10.1002/path.3964
12. Cirillo L, De Chiara L, Innocenti S, Errichiello C, Romagnani P, Becherucci F. Chronic kidney disease in children: an update. Clin Kidney J [Internet]. 2023 Apr 24;16(10):1600–11. Available from:

https://pubmed.ncbi.nlm.nih.gov/37779846doi:10.1093/ckj/sfad097

13. Hall JE. Guyton and Hall Textbook of Medical Physiology Elsevier eBook on VitalSource, 13th Edition. elsivier Health Sciences; 2020.

14. Tecklenborg J, Clayton D, Siebert S. The role of the immune system in kidney disease. Clin Exp Immunol. 2018;192(2):142–150. doi:10.1111/cei.13119

15. Hudson BG. The molecular basis of Goodpasture and Alport syndromes: beacons for the discovery of the collagen IV family. J Am Soc Nephrol. 2004;15(10):2514–2527. doi:10.1097/01.asn.0000141462.00630.76

16. Hudson BG, Tryggvason K, Sundaramoorthy M, Neilson EG. Alport's syndrome, goodpasture's syndrome, and type IV collagen. N [Internet]. 2003;348(25):2543–56. Available from: http://dx.doi.org/10.1056/nejmra022296doi:10.1056/nejmra022296

17. Beck Jr LH, Bonegio RGB, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med [Internet]. 2009 Jul 2;361(1):11–21. Available from: https://pubmed.ncbi.nlm.nih.gov/19571279doi:10.1056/nejmoa0810457

18. Tomas NM, Jr LHB, Meyer-Schwesinger C, Seitz-Polski B, Ma H, Zahner G, et al. Thrombospondin type-1 domain-containing 7A in idiopathic membranous nephropathy. N Engl J Med. 2014;371(24):2277–2287. doi:10.1056/nejmoa1409354

19. Ronco P, Plaisier E, Debiec H. Advances in membranous nephropathy. J Clin Med [Internet]. 2021 Feb 5;10(4):607. Available from: https://pubmed.ncbi.nlm.nih.gov/33562791doi:10.3390/jcm10040607

20. Kestilä M, Lenkkeri U, Männikkö M, Lamerdin J, McCready P, Putaala H, et al. Positionally cloned gene for a novel glomerular protein—nephrin—is mutated in congenital nephrotic syndrome. Mol Cell [Internet]. 1998;1(4):575–82. Available from: http://dx.doi.org/10.1016/s1097-2765(00)80057-xdoi:10.1016/s1097-2765(00)80057-x

21. Kalaaji M, Fenton KA, Mortensen ES, Olsen R, Sturfelt G, Alm P, et al. Glomerular apoptotic nucleosomes are central target structures for nephritogenic antibodies in human SLE nephritis. Kidney Int [Internet]. 2007;71(7):664–72. Available from: http://dx.doi.org/10.1038/sj.ki.5002133 doi:10.1038/sj.ki.5002133

22. Tomana M, Novak J, Julian BA, Matousovic K, Konecny K, Mestecky J. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. J Clin Invest [Internet]. 1999 Jul;104(1):73–81. Available from: https://pubmed.ncbi.nlm.nih.gov/10393701doi:10.1172/jci5535

23. Jennette JC, Falk RJ, Gasim AH. Pathogenesis of antineutrophil cytoplasmic autoantibody vasculitis. Curr Opin Nephrol Hypertens [Internet]. 2011 May;20(3):263–70. Available from: https://pubmed.ncbi.nlm.nih.gov/21422922doi:10.1097/mnh.0b013e3283456731

24. Gupta A, Quigg RJ. Glomerular diseases associated with hepatitis B and C. Adv Chronic Kidney Dis [Internet]. 2015;22(5):343–51. Available from: http://dx.doi.org/10.1053/j.ackd.2015.06.003doi:10.1053/j.ackd.2015.06.003

25. Cui Z, Zhao M hui, Segelmark M, Hellmark T. Natural autoantibodies to myeloperoxidase, proteinase 3, and the glomerular basement membrane are present in normal individuals. Kidney Int [Internet]. 2010;78(6):590–7. Available from: http://dx.doi.org/10.1038/ki.2010.198doi:10.1038/ki.2010.198

26. Linke A, Tiegs G, Neumann K. Pathogenic T-cell responses in immune-mediated glomerulonephritis. Cells

[Internet]. 2022 May 12;11(10):1625. Available from: https://pubmed.ncbi.nlm.nih.gov/35626662doi:10.3390/cells11101625

27. Polci R, Feriozzi S. [Immunotherapy mechanisms in glomerulonephritis]. G Ital Nefrol. 2011;28(6):612–21.

28. Lawrence T. The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harb Perspect Biol [Internet]. 2009/10/07. 2009 Dec;1(6):a001651–a001651. Available from: https://pubmed.ncbi.nlm.nih.gov/20457564doi:10.1101/cshperspect.a001651

29. Hénique C, Papista C, Guyonnet L, Lenoir O, Tharaux PL. Update on crescentic glomerulonephritis. Semin Immunopathol [Internet]. 2014;36(4):479–90. Available from: http://dx.doi.org/10.1007/s00281-014-0435-7doi:10.1007/s00281-014-0435-7

30. Mayadas TN, Rosetti F, Ernandez T, Sethi S. Neutrophils: game changers in glomerulonephritis? Trends Mol Med [Internet]. 2010/07/29. 2010 Aug;16(8):368–78. Available from: https://pubmed.ncbi.nlm.nih.gov/20667782doi:10.1016/j.molmed.2010.06.002

31. Kitching AR, Hutton HL. The players: cells involved in glomerular disease. Clin J Am Soc Nephrol. 2016;11(9):1664–1674. doi:10.2215/cjn.13791215

32. Nishi H, Furuhashi K, Cullere X, Saggu G, Miller MJ, Chen Y, et al. Neutrophil FcγRIIA promotes IgG-mediated glomerular neutrophil capture via Abl/Src kinases. J Clin Invest [Internet]. 2017/09/11. 2017 Oct 2;127(10):3810–26. Available from: https://pubmed.ncbi.nlm.nih.gov/28891817doi:10.1172/jci94039

33. Kessenbrock K, Krumbholz M, Schönermarck U, Back W, Gross WL, Werb Z, et al. Netting neutrophils in autoimmune small-vessel vasculitis. Nat Med [Internet]. 2009 Jun;15(6):623–5. Available from: https://pubmed.ncbi.nlm.nih.gov/19448636doi:10.1038/nm.1959

34. Kurts C, Panzer U, Anders HJ, Rees AJ. The immune system and kidney disease: basic concepts and clinical implications. Nat Rev Immunol [Internet]. 2013;13(10):738–53. Available from: http://dx.doi.org/10.1038/nri3523doi:10.1038/nri3523

35. Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. Nature [Internet]. 2013 Apr 25;496:445–55. Available from: https://pubmed.ncbi.nlm.nih.gov/23619691doi:10.1038/nature12034

36. Duffield JS. Macrophages and immunologic inflammation of the kidney. Semin Nephrol [Internet]. 2010 May;30(3):234–54. Available from: https://pubmed.ncbi.nlm.nih.gov/20620669doi:10.1016/j.semnephrol.2010.03.003

37. Eardley KS, Cockwell P. Macrophages and progressive tubulointerstitial disease. Kidney Int. 2005;68(2):437–455. doi:10.1111/j.1523-1755.2005.00422.x.

38. Rastaldi MP, Ferrario F, Crippa A, Dell'antonio G, Casartelli D, Grillo C, et al. Glomerular monocyte-macrophage features in ANCA-positive renal vasculitis and cryoglobulinemic nephritis. J Am Soc Nephrol [Internet]. 2000;11(11):2036–43. Available from: http://dx.doi.org/10.1681/asn.v11112036doi:10.1681/asn.v11112036

39. Moll S, Angeletti A, Scapozza L, Cavalli A, Ghiggeri GM, Prunotto M. Glomerular macrophages in human auto- and allo-immune nephritis. Cells. 2021;10(3):603. doi:10.3390/cells10030603

40. Segerer S, Cui Y, Hudkins KL, Goodpaster T, Eitner F, Mack M, et al. Expression of the chemokine monocyte chemoattractant protein-1 and its receptor chemokine receptor 2 in human crescentic glomerulonephritis. J Am Soc Nephrol [Internet]. 2000;11(12):2231–42. Available from: http://dx.doi.org/10.1681/asn.v11122231doi:10.1681/asn.v11122231

41. Djudjaj S, Lue H, Rong S, Papasotiriou M, Klinkhammer BM, Zok S, et al. Macrophage migration inhibitory factor

mediates proliferative GN via CD74. J Am Soc Nephrol [Internet]. 2015/10/09. 2016 Jun;27(6):1650–64. Available from: https://pubmed.ncbi.nlm.nih.gov/26453615doi:10.1681/asn.2015020149

42. Ferrario F, Napodano P, Rastaldi MP, D'Amico G. Capillaritis in IgA nephropathy. Contrib Nephrol [Internet]. 1995;111:8–12. Available from: http://dx.doi.org/10.1159/000423869doi:10.1159/000423869

43. D'Amico G, Napodano P, Ferrario F, Rastaldi MP, Arrigo G. Idiopathic iga nephropathy with segmental necrotizing lesions of the capillary wall. Kidney Int. 2001;59(2):682–692. doi:10.1046/j.1523-1755.2001.059002682.x

44. Bolton WK, Benton FR, Lobo PI. Requirement of functional T-cells in the production of autoimmune glomerulotubular nephropathy in mice. Clin Exp Immunol. 1978;33(3):474–477.

45. Wofsy D, Ledbetter JA, Hendler PL, Seaman WE. Treatment of murine lupus with monoclonal anti-T cell antibody. J Immunol [Internet]. 1985;134(2):852–7. Available from: http://dx.doi.org/10.4049/jimmunol.134.2.852doi:10.4049/jimmunol.134.2.852

46. Ruth AJ, Kitching AR, Kwan RYQ, Odobasic D, Ooi JDK, Timoshanko JR, et al. Anti-neutrophil cytoplasmic antibodies and effector CD4+ cells play nonredundant roles in anti-myeloperoxidase crescentic glomerulonephritis. J Am Hear Assoc [Internet]. 2006;17(7):1940–9. Available from: http://dx.doi.org/10.1681/asn.2006020108doi:10.1681/asn.2006020108

47. Gan PY, Holdsworth SR, Kitching AR, Ooi JD. Myeloperoxidase (MPO)-specific CD4+ T cells contribute to MPO-anti-neutrophil cytoplasmic antibody (ANCA) associated glomerulonephritis. Cell Immunol [Internet]. 2013;282(1):21–7. Available from: http://dx.doi.org/10.1016/j.cellimm.2013.04.007doi:10.1016/j.cellimm.2013.04.007

48. Kurts C, Heymann F, Lukacs-Kornek V, Boor P, Floege J. Role of T cells and dendritic cells in glomerular immunopathology. Semin Immunol [Internet]. 2007;29(4):317–35. Available from: http://dx.doi.org/10.1007/s00281-007-0096-xdoi:10.1007/s00281-007-0096-x

49. Koyama A, Fujisaki M, Kobayashi M, Igarashi M, Narita M. A glomerular permeability factor produced by human T cell hybridomas. Kidney In [Internet]. 1991;40(3):453–60. Available from: http://dx.doi.org/10.1038/ki.1991.232doi:10.1038/ki.1991.232

50. Azadegan-Dehkordi F, Bagheri N, Shirzad H, Rafieian-Kopaei M. The role of Th1 and Th17 cells in glomerulonephritis. J Nephropathol. 2015 Apr;4(2):32–7. doi:10.12860/jnp.2015.07

51. Gan PY, Steinmetz OM, Tan DSY, O'Sullivan KM, Ooi JD, Iwakura Y, et al. Th17 cells promote autoimmune anti-myeloperoxidase glomerulonephritis. J Am Soc Nephrol [Internet]. 2010/03/18. 2010 Jun;21(6):925–31. Available from: https://pubmed.ncbi.nlm.nih.gov/20299361doi:10.1681/asn.2009070763

52. Venkatadri R, Sabapathy V, Dogan M, Sharma R. Targeting regulatory T cells for therapy of lupus nephritis. Front Pharmacol [Internet]. 2022 Jan 6;12:806612. Available from: https://pubmed.ncbi.nlm.nih.gov/35069220doi:10.3389/fphar.2021.806612

53. Sakai R, Ito M, Komai K, Iizuka-Koga M, Matsuo K, Nakayama T, et al. Kidney GATA3(+) regulatory T cells play roles in the convalescence stage after antibody-mediated renal injury. Cell Mol Immunol [Internet]. 2020/09/11. 2021 May;18(5):1249–61. Available from: https://pubmed.ncbi.nlm.nih.gov/32917984doi:10.1038/s41423-020-00547-x

54. Herrnstadt GR, Steinmetz OM. The role of Treg subtypes in glomerulonephritis. Cell Tissue Res [Internet]. 2020/12/14. 2021 Aug;385(2):293–304. Available from: https://pubmed.ncbi.nlm.nih.gov/33315

130doi:10.1007/s00441-020-03359-55.
Alikhan MA, Huynh M, Kitching AR, Ooi JD. Regulatory T cells in renal disease. Clin Transl Immunol [Internet]. 2018 Jan 30;7(1):e1004–e1004. Available from: https://pubmed.ncbi.nlm.nih.gov/29484182doi:10.1002/cti2.1004

56. Doglio M, Alexander T, Del Papa N, Snowden JA, Greco R. New insights in systemic lupus erythematosus: From regulatory T cells to CAR-T-cell strategies. J Allergy Clin Immunol [Internet]. 2022;150(6):1289–301. Available from: http://dx.doi.org/10.1016/j.jaci.2022.08.003doi:10.1016/j.jaci.2022.08.003

57. Saleem MA. One hundred ways to kill a podocyte. Nephrol Dial TransplantDialysis Transplant [Internet]. 2015;30(8):1266–71. Available from: http://dx.doi.org/10.1093/ndt/gfu363doi:10.1093/ndt/gfu363

58. Rabelink TJ, de Boer HC, van Zonneveld AJ. Endothelial activation and circulating markers of endothelial activation in kidney disease. Nat Rev Nephrol Rev Nephrol [Internet]. 2010;6(7):404–14. Available from: http://dx.doi.org/10.1038/nrneph.2010.65doi:10.1038/nrneph.2010.65

59. Kang DH, Kanellis J, Hugo C, Truong L, Anderson S, Kerjaschki D, et al. Role of the microvascular endothelium in progressive renal disease. J Am Soc Nephrol [Internet]. 2002;13(3):806–16. Available from: http://dx.doi.org/10.1681/asn.v133806doi:10.1681/asn.v133806

60. Segal MS, Baylis C, Johnson RJ. Endothelial health and diversity in the kidney. J Am Soc Nephrol [Internet]. 2006 Feb;17(2):323–4. Available from: https://pubmed.ncbi.nlm.nih.gov/16434502doi:10.1681/asn.2005121296

61. Eymael J, Sharma S, Loeven MA, Wetzels JF, Mooren F, Florquin S, et al. CD44 is required for the pathogenesis of experimental crescentic glomerulonephritis and collapsing focal segmental glomerulosclerosis. Kidney Int [Internet]. 2018;93(3):626–42. Available from: http://dx.doi.org/10.1016/j.kint.2017.09.020doi:10.1016/j.kint.2017.09.020

62. Abboud HE. Mesangial cell biology. Exp Cell Res [Internet]. 2012;318(9):979–85. Available from: http://dx.doi.org/10.1016/j.yexcr.2012.02.025doi:10.1016/j.yexcr.2012.02.025

63. Schlöndorff D, Banas B. The mesangial cell revisited: no cell is an island. J Am Soc Nephrol. 2009 Jun;20(6):1179–87. doi:10.1681/asn.2008050549

64. Jefferson JA, Nelson PJ, Najafian B, Shankland SJ. Podocyte disorders: core curriculum 2011. Am J Kidney Dis [Internet]. 2011/08/24. 2011 Oct;58(4):666–77. Available from: https://pubmed.ncbi.nlm.nih.gov/21868143doi:10.1053/j.ajkd.2011.05.032

65. Smeets B, Angelotti ML, Rizzo P, Dijkman H, Lazzeri E, Mooren F, et al. Renal progenitor cells contribute to hyperplastic lesions of podocytopathies and crescentic glomerulonephritis. J Am Soc Nephrol [Internet]. 2009/10/29. 2009 Dec;20(12):2593–603. Available from: https://pubmed.ncbi.nlm.nih.gov/19875807doi:10.1681/asn.2009020132

66. Ryu M, Migliorini A, Miosge N, Gross O, Shankland S, Brinkkoetter PT, et al. Plasma leakage through glomerular basement membrane ruptures triggers the proliferation of parietal epithelial cells and crescent formation in non-inflammatory glomerular injury. J Pathol [Internet]. 2012;228(4):482–94. Available from: http://dx.doi.org/10.1002/path.4046doi:10.1002/path.4046

67. Ohse T, Pippin JW, Chang AM, Krofft RD, Miner JH, Vaughan MR, et al. The enigmatic parietal epithelial cell is finally getting noticed: a review. Kidney Int [Internet]. 2009/10/21. 2009 Dec;76(12):1225–38. Available from: https://pubmed.ncbi.nlm.nih.gov/19847153doi:10.1038/ki.2009.386

68. Zhou W, Hildebrandt F. Inducible podocyte injury and proteinuria in transgenic zebrafish. J Am Soc Nephrol [Internet]. 2012/03/22. 2012

Jun;23(6):1039–47. Available from: https://pubmed.ncbi.nlm.nih.gov/22440901doi:10.1681/asn.2011080776

69. Zhang J, Hansen KM, Pippin JW, Chang AM, Taniguchi Y, Krofft RD, et al. De novo expression of podocyte proteins in parietal epithelial cells in experimental aging nephropathy. Am J Physiol Ren Physiol [Internet]. 2011/11/30. 2012 Mar 1;302(5):F571–80. Available from: https://pubmed.ncbi.nlm.nih.gov/22129965doi:10.1152/ajprenal.00516.2011

70. Shimizu M, Kondo S, Urushihara M, Takamatsu M, Kanemoto K, Nagata M, et al. Role of integrin-linked kinase in epithelial–mesenchymal transition in crescent formation of experimental glomerulonephritis. Nephrol Dial Transpl [Internet]. 2006;21(9):2380–90. Available from: http://dx.doi.org/10.1093/ndt/gfl243doi:10.1093/ndt/gfl243

71. Arif E, Kumari B, Wagner MC, Zhou W, Holzman LB, Nihalani D. Myo1c is an unconventional myosin required for zebrafish glomerular developement. Kidney Int. 2013;84(6):1154–1165. doi:10.1038/ki.2013.201

72. Moeller MJ, Soofi A, Hartmann I, Le Hir M, Wiggins R, Kriz W, et al. Podocytes populate cellular crescents in a murine model of inflammatory glomerulonephritis. J Am Soc Nephrol [Internet]. 2004;15(1):61–7. Available from: http://dx.doi.org/10.1097/01.asn.0000102468.37809.c6doi:10.1097/01.asn.0000102468.37809.c6

73. Thorner PS, Ho M, Eremina V, Sado Y, Quaggin S. Podocytes contribute to the formation of glomerular crescents. J Am Soc Nephrol [Internet]. 2008/01/16. 2008 Mar;19(3):495–502. Available from: https://pubmed.ncbi.nlm.nih.gov/18199804doi:10.1681/asn.2006101115

74. Pace JA, Bronstein R, Guo Y, Yang Y, Estrada CC, Gujarati N, et al. Podocyte-specific KLF4 is required to maintain parietal epithelial cell quiescence in the kidney. SciAdv [Internet]. 2021/09/03. 2021 Sep 3;7(36):eabg6600–eabg6600. Available from: https://pubmed.ncbi.nlm.nih.gov/34516901doi:10.1126/sciadv.abg6600

75. Estrada CC, Paladugu P, Guo Y, Pace J, Revelo MP, Salant DJ, et al. Krüppel-like factor 4 is a negative regulator of STAT3-induced glomerular epithelial cell proliferation. JCI Insight [Internet]. 2018 Jun 21;3(12):e98214. Available from: https://pubmed.ncbi.nlm.nih.gov/29925693doi:10.1172/jci.insight.98214

76. Bronstein R, Pace J, Gowthaman Y, Salant DJ, Mallipattu SK. Podocyte-parietal epithelial cell interdependence in glomerular development and disease. J Am Soc Nephrol [Internet]. 2023/02/16. 2023 May 1;34(5):737–50. Available from: https://pubmed.ncbi.nlm.nih.gov/36800545doi:10.1681/asn.0000000000000104

77. Kriz W, Hähnel B, Hosser H, Rösener S, Waldherr R. Structural analysis of how podocytes detach from the glomerular basement membrane under hypertrophic stress. Front Endocrinol [Internet]. 2014 Dec 12;5:207. Available from: https://pubmed.ncbi.nlm.nih.gov/25566184doi:10.3389/fendo.2014.00207

78. Kriz W, Shirato I, Nagata M, LeHir M, Lemley K V. The podocyte's response to stress: the enigma of foot process effacement. Am J Physiol Ren Physiol [Internet]. 2013;304(4):F333–47. Available from: http://dx.doi.org/10.1152/ajprenal.00478.2012doi:10.1152/ajprenal.00478.2012

79. Raza A, Aggarwal S. Membranous Glomerulonephritis (Archived). In Treasure Island (FL); 2024.

80. Shankland SJ, Smeets B, Pippin JW, Moeller MJ. The emergence of the glomerular parietal epithelial cell. Nat Rev Nephrol [Internet]. 2014;10(3):158–73. Available from: http://dx.doi.org/10.1038/nrneph.2014.1doi:10.1038/nrneph.2014.1

81. Vivarelli M, Emma F, Pellé T, Gerken C, Pedicelli S, Diomedi-Camassei F, et al. Genetic homogeneity but IgG subclass–dependent clinical variability of alloimmune membranous nephropathy

with anti-neutral endopeptidase antibodies. Kidney Int [Internet]. 2015;87(3):602–9. Available from: http://dx.doi.org/10.1038/ki.2014.381doi:10.1038/ki.2014.381

82. Nangaku M, Couser WG. Mechanisms of immune-deposit formation and the mediation of immune renal injury. Clin Exp Nephrol [Internet]. 2005;9(3):183–91. Available from: http://dx.doi.org/10.1007/s10157-005-0357-8doi:10.1007/s10157-005-0357-8

83. Couser WG, Salant DJ. In situ immune complex formation and glomerular injury. Kidney Int [Internet]. 1980;17(1):1–13. Available from: http://dx.doi.org/10.1038/ki.1980.1doi:10.1038/ki.1980.1

84. Jia X yu, Cui Z, Yang R, Hu S yi, Zhao M hui. Antibodies against linear epitopes on the Goodpasture autoantigen and kidney injury. Clin J Am Soc Nephrol [Internet]. 2012/03/29. 2012 Jun;7(6):926–33. Available from: https://pubmed.ncbi.nlm.nih.gov/22461538doi:10.2215/cjn.09930911

85. Roth AJ, Ooi JD, Hess JJ, van Timmeren MM, Berg EA, Poulton CE, et al. Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis. J Clin Invest [Internet]. 2013/03/15. 2013 Apr;123(4):1773–83. Available from: https://pubmed.ncbi.nlm.nih.gov/23549081doi:10.1172/jci65292

86. Land J, Rutgers A, Kallenberg CGM. Anti-neutrophil cytoplasmic autoantibody pathogenicity revisited: pathogenic versus non-pathogenic anti-neutrophil cytoplasmic autoantibody. Nephrol Dial Transpl [Internet]. 2014;29(4):739–45. Available from: http://dx.doi.org/10.1093/ndt/gft416doi:10.1093/ndt/gft416

87. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(1):1–11. doi:10.1002/art.37715

88. Chen YX, Chen XN. Antineutrophil cytoplasmic antibodies-associated glomerulonephritis: From bench to bedside. Chronic Dis Transl Med [Internet]. 2018 Aug 16;4(3):187–91. Available from: https://pubmed.ncbi.nlm.nih.gov/30276365doi:10.1016/j.cdtm.2018.05.004

89. Cornec D, Cornec-Le GE, Fervenza FC. ANCA-associated vasculitis - clinical utility of using ANCA specificity to classify patients. Nat Rev Rheumatol. 2016;12(10):879–890. doi:10.1038/nrrheum.2016.123

90. Chen YX, Xu J, Pan XX, Shen PY, Li X, Ren H, et al. Histopathological classification and renal outcome in patients with antineutrophil cytoplasmic antibodies-associated renal vasculitis: a study of 186 patients and metaanalysis. J Rheumatol [Internet]. 2016;44(3):304–13. Available from: http://dx.doi.org/10.3899/jrheum.160866doi:10.3899/jrheum.160866

91. Franssen CFM, Stegeman CA, Kallenberg CGM, Gans ROB, De Jong PE, Hoorntje SJ, et al. Antiproteinase 3- and antimyeloperoxidase-associated vasculitis. Kidney Int [Internet]. 2000;57(6):2195–206. Available from: http://dx.doi.org/10.1046/j.1523-1755.2000.00080.xdoi:10.1046/j.1523-1755.2000.00080.x

92. Erez DL, Meyers KE, Sullivan KE. C3 nephritic factors: a changing landscape. J Allergy Clin Immunol. 2017;140(1):57–9. doi:10.1016/j.jaci.2017.02.018

93. Lionaki S, Gakiopoulou H, Boletis JN. Understanding the complement-mediated glomerular diseases: focus on membranoproliferative glomerulonephritis and C3 glomerulopathies. APMIS [Internet]. 2016;124(9):725–35. Available from: http://dx.doi.org/10.1111/apm.12566doi:10.1111/apm.12566

94. Riedl M, Thorner P, Licht C. C3 glomerulopathy. Pediatr Nephrol. 2017;32(1):43–57. doi:10.1007/s00467-015-3310-4

95. Bomback AS, Appel GB. Pathogenesis of the C3 glomerulopathies and

reclassification of MPGN. Nat Rev Nephrol. 2012;8(11):634–42. doi:10.1038/nrneph.2012.213

96. Kopel T, Salant DJ. C3 glomerulopathies: Dense deposit disease and C3 glomerulonephritis [Internet]. 2023 [cited 2023 Jun 14]. Available from: https://medilib.ir/uptodate/show/3090

97. Niepolski L, Czekała A, Seget-Dubaniewicz M, Frydrychowicz M, Talarska-Markiewicz P, Kowalska A, et al. Diagnostic problems in C3 glomerulopathy. Biomedicines. 2023 Apr 5;11(4):1101. doi:10.3390/biomedicines11041101

98. Kemper MJ, Wolf G, Müller-Wiefel DE. Transmission of glomerular permeability factor from a mother to her child. N Engl J Med [Internet]. 2001;344(5):386–7. Available from: http://dx.doi.org/10.1056/nejm200102013440517doi:10.1056/nejm200102013440517

99. Gallon L, Leventhal J, Skaro A, Kanwar Y, Alvarado A. Resolution of recurrent focal segmental glomerulosclerosis after retransplantation. N Engl J Med [Internet]. 2012;366(17):1648–9. Available from: http://dx.doi.org/10.1056/nejmc1202500doi:10.1056/nejmc1202500

100. McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. Clin J Am Soc Nephrol [Internet]. 2010;5(11):2115–21. Available from: http://dx.doi.org/10.2215/cjn.03800609 doi:10.2215/cjn.03800609

101. Kitchlu A, McArthur E, Amir E, Booth CM, Sutradhar R, Majeed H, et al. Acute kidney injury in patients receiving systemic treatment for cancer: A population-based cohort study. J Natl Cancer Inst. 2019 Jul;111(7):727–36. doi:10.1093/jnci/djy167

102. Gohh RY, Yango AF, Morrissey PE, Monaco AP, Gautam A, Sharma M, et al. Preemptive plasmapheresis and recurrence of FSGS in high-risk renal transplant recipients. Am J Transpl. 2005;5(12):2907–2912. doi:10.1111/j.1600-6143.2005.01112.x

103. Rea R, Smith C, Sandhu K, Kwan J, Tomson C. Successful transplant of a kidney with focal segmental glomerulosclerosis. Nephrol Dial Transpl [Internet]. 2001;16(2):416–7. Available from: http://dx.doi.org/10.1093/ndt/16.2.416 doi:10.1093/ndt/16.2.416

104. Sharma M, Mccarthy ET, Savin VJ, Lianos EA. Nitric oxide preserves the glomerular protein permeability barrier by antagonizing superoxide. Kidney Int [Internet]. 2005;68(6):2735–44. Available from: http://dx.doi.org/10.1111/j.1523-1755.2005.00744.xdoi:10.1111/j.1523-1755.2005.00744.x

105. Bertelli R, Trivelli A, Magnasco A, Cioni M, Bodria M, Carrea A, et al. Failure of regulation results in an amplified oxidation burst by neutrophils in children with primary nephrotic syndrome. Clin Exp Immunol [Internet]. 2010/05/19. 2010 Jul 1;161(1):151–8. Available from: https://pubmed.ncbi.nlm.nih.gov/20491793doi:10.1111/j.1365-2249.2010.04160.x

106. Ha TS. Circulating permeability factors in idiopathic nephrotic syndrome. Child Kid Dis [Internet]. 2019;23(1):7–21. Available from: http://dx.doi.org/10.3339/jkspn.2019.23.1.7doi:10.3339/jkspn.2019.23.1.7

107. Bakker WW, van Dael CML, Pierik LJWM, van Wijk JAE, Nauta J, Borghuis T, et al. Altered activity of plasma hemopexin in patients with minimal change disease in relapse. Pediatr Nephrol Nephrol [Internet]. 2005;20(10):1410–5. Available from: http://dx.doi.org/10.1007/s00467-005-1936-3doi:10.1007/s00467-005-1936-3

108. Davin JC. The glomerular permeability factors in idiopathic nephrotic syndrome. Pediatr Nephrol [Internet]. 2015/04/30. 2016 Feb;31(2):207–15. Available from: https://pubmed.ncbi.nlm.nih.gov/25925039doi:10.1007/s00467-015-3082-x

109. Clement LC, Avila-Casado C, Macé C, Soria E, Bakker WW, Kersten S, et al. Podocyte-secreted angiopoietin-like-4 mediates proteinuria in glucocorticoid-sensitive nephrotic syndrome. Nat Med [Internet]. 2010/12/12. 2011 Jan;17(1):117–22. Available from: https://pubmed.ncbi.nlm.nih.gov/21151138doi:10.1038/nm.2261

110. Chugh SS, Clement LC, Macé C. New insights into human minimal change disease: lessons from animal models. Am J Kidney Dis [Internet]. 2011/10/05. 2012 Feb;59(2):284–92. Available from: https://pubmed.ncbi.nlm.nih.gov/21974967doi:10.1053/j.ajkd.2011.07.024

111. Moon C, Soria JC, Jang SJ, Lee J, Obaidul Hoque M, Sibony M, et al. Involvement of aquaporins in colorectal carcinogenesis. Oncogene. 2003 Oct;22(43):6699–703. doi:10.1038/sj.onc.1206762

112. Gill S, Maus M V, Porter DL. Chimeric antigen receptor T cell therapy: 25years in the making. Blood Rev. 2016 May;30(3):157–67. doi:10.1016/j.blre.2015.10.003

113. Li JS, Chen X, Peng L, Wei SY, Zhao SL, Diao TT, et al. Angiopoietin-Like-4, a potential target of tacrolimus, predicts earlier podocyte injury in minimal change disease. PLoS One [Internet]. 2015 Sep 9;10(9):e0137049–e0137049. Available from: https://pubmed.ncbi.nlm.nih.gov/26352670doi:10.1371/journal.pone.0137049

114. Peng L, Ma J, Cui R, Chen X, Wei SY, Wei QJ, et al. The calcineurin inhibitor tacrolimus reduces proteinuria in membranous nephropathy accompanied by a decrease in angiopoietin-like-4. PLoS One [Internet]. 2014 Aug 28;9(8):e106164–e106164. Available from: https://pubmed.ncbi.nlm.nih.gov/25165975doi:10.1371/journal.pone.0106164

115. Cara-Fuentes G, Segarra A, Silva-Sanchez C, Wang H, Lanaspa MA, Johnson RJ, et al. Angiopoietin-like-4 and minimal change disease. PLoS One [Internet]. 2017 Apr 25;12(4):e0176198–e0176198. Available from: https://pubmed.ncbi.nlm.nih.gov/28441404doi:10.1371/journal.pone.0176198

116. Zhang X, Herr F, Vernochet A, Lorenzo HK, Beaudreuil S, Dürrbach A. CASK, the soluble glomerular permeability factor, is secreted by macrophages in patients with recurrent focal and segmental glomerulo-sclerosis. Front Immunol. 2020;11:875. doi:10.3389/fimmu.2020.00875

117. Beaudreuil S, Zhang X, Herr F, Harper F, Candelier JJ, Fan Y, et al. Circulating CASK is associated with recurrent focal segmental glomerulosclerosis after transplantation. PLoS One [Internet]. 2019 Jul 29;14(7):e0219353–e0219353. Available from: https://pubmed.ncbi.nlm.nih.gov/31356645doi:10.1371/journal.pone.0219353

118. Watts AJB, Keller KH, Lerner G, Rosales I, Collins AB, Sekulic M, et al. Discovery of autoantibodies targeting nephrin in minimal change disease supports a novel autoimmune etiology. J Am Soc Nephrol. 2022 Jan;33(1):238–52. doi:10.1681/asn.2021060794