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Review Article

Unraveling the immunopathogenesis of glomerular disease

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ABSTRACT

Immune-mediated damage to glomerular structures is largely responsible for the pathology associated with the majority of glomerular diseases. Therefore, a detailed understanding of the basic immune mechanisms responsible for glomerular damage is needed to inform the design of novel intervention strategies. Glomerular injury of immune origin is complex and involves both inflammatory and non-inflammatory processes driven by elements of the innate and adaptive immune system. This review summarizes the basic immune mechanisms that cause glomerular injury leading to the nephritic and nephrotic syndromes. A major focus of the review is to highlight the mechanisms by which antibodies cause glomerular injury through their interactions with glomerular cells, complement proteins, phagocytes bearing complement and Fcγ receptors, and dendritic cells expressing the neonatal receptor for IgG, FcRn.

Contents

1. Glomerular structure and function

The target of injury in glomerular disease is the filtration barrier, a structure composed of three core constituents: a fenestrated endothelium, the glomerular basement membrane (GBM), and an epithelium

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comprised of unique epithelial cells termed podocytes (Fig. 1). The filtration barrier functions as a formidable size- and charge-selective barrier with each layer performing a specific role in the formation of a plasma ultrafiltrate [1–3].

1.1. Glomerular endothelium

The first barrier, the endothelium, is highly fenestrated and thus permeable to cytokines, chemokines, antibodies, complement proteins, and other molecules ≤50–100 nm in diameter [4]. In the steady-state, the endothelium prevents the passive movement of red and white cells into the mesangium, and repels large negatively-charged proteins due to the presence of a 200-nm thick anionic glycocalyx consisting of membrane-associated heparan sulfate proteoglycans and soluble plasma- and endothelium-derived molecules such as hyaluronate [5,6]. The glomerular endothelium is supported by mesangial cells, which together with the matrix proteins they secrete comprise the mesangium. Mesangial cells are in close contact with the fenestrated endothelium and thus perform a significant structural role in addition to providing the contractility required to maintain the integrity of the microcirculation [7]. Functionally, there is significant tridirectional cytokine crosstalk between mesangial cells, endothelial cells, and podocytes [7]. As discussed later in Section 3.1, the close proximity of mesangial cells to the circulation facilitates their response to infectious agents, immune complexes, cytokines, and chemokines, but also makes them highly susceptible to immune injury [8].

1.2. Glomerular basement membrane

The GBM is a substantial barrier consisting of an amorphous, dense, mesh-like network containing membrane-associated heparan sulfate proteoglycans (perlcan and agrin), triple-helical alpha 3 type IV collagen fibrils, laminin, fibronectin, nidogen (entactin), and other glycoproteins that give this barrier an overall net negative charge and a thickness of 250–350 nm [9,10]. The density and anionic nature of the GBM effectively prevents the passage of molecules, large anionic proteins, and cells into the subepithelial space.

1.3. Podocytes

The final layer consists of a single layer of podocytes, specialized polarized epithelial cells with slit diaphragms positioned between interdigitating foot processes. The slit diaphragm is a specialized intercellular junction that forms a circumferential barrier connecting neighboring podocyte foot processes and restricts the movement of large proteins (>60–70 kDa) and cells [11]. It contains a number of membrane-associated signaling proteins such as nephrin, podocin, and Neph 1 that connect to the actin cytoskeleton and regulate the plasticity of foot processes [1,12]. The importance of the slit diaphragm as a barrier is illustrated by monogenic inherited proteinuric diseases caused by mutations in the genes encoding slit diaphragm proteins [13–17]. The filtration slits have a constant width of 30–40 nm and prevent the passage of proteins into Bowman's capsule (urinary space) [18–21]. However, as discussed later in this review, albumin and IgG are directly transported by podocytes into Bowman's capsule through the process of transcytosis. To appreciate the mechanisms by which the immune system causes damage to glomerular structures, a brief overview of innate and adaptive immunity is summarized next.

2. The innate and adaptive immune system

Elements of both the innate and adaptive immune system contribute to cellular injury in glomerular disease. Below, the cellular and soluble factors that comprise these two arms of the immune system are briefly reviewed.

2.1. Innate immunity

The innate immune system is the first line of defense against pathogens and encompasses a host of cells and soluble, fast-acting mediators including cytokines, chemokines, and complement. Macrophages and neutrophils, the major effector cells of the innate immune system, express pattern-recognition receptors and receptors for IgG and complement that detect pathogens and stimulate the release of proteases and reactive oxygen species. This response is necessary to clear an infection, but also causes collateral damage to tissues such as the glomerulus. While macrophages are constitutively present in most tissues and function as sentinels at sites throughout the body that are vulnerable to infection such as the skin and the mucosal tissues of the respiratory, gastrointestinal, and urogenital tracts, they are excluded from the glomerulus in the steady-state. Neutrophils are not normally found in healthy tissues but are rapidly recruited to sites of inflammation where they capture, engulf, and kill pathogens and then die by apoptosis.

Several soluble components of the innate immune system function as barriers to infection and complement in particular plays a major

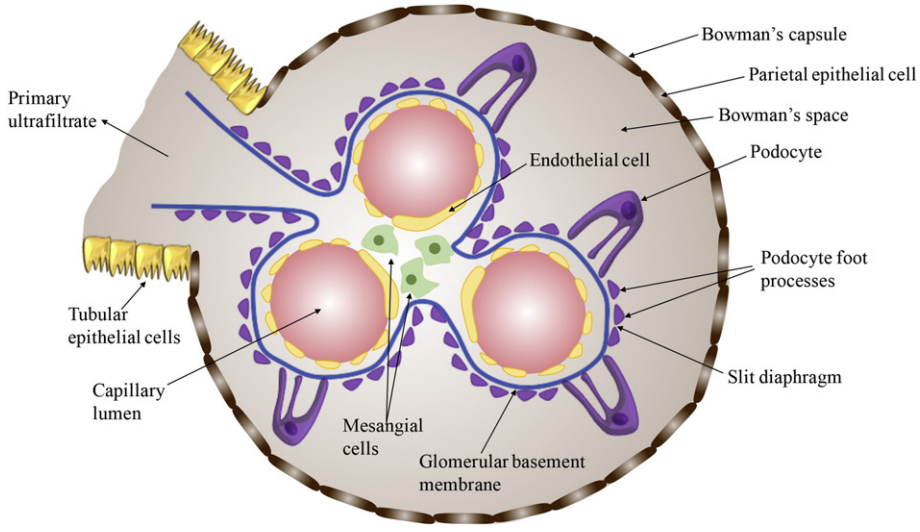

Fig. 1. The glomerular lobe. The glomerulus is the major filtration unit of the kidney and is composed of a fenestrated endothelium, mesangium containing mesangial cells, the glomerular basement membrane, and an epithelium comprised of podocytes. The glomerulus generates a plasma ultrafiltrate that then passes through the tubules of the nephron.