Lecture (5)

Disorders of the kidney

Disorders of the kidney arise from a wide range of pathological causes, many of which are common in other organ systems (e.g. infections, tumors, drug reactions, vascular disorders). However, the kidney is unusual in that it is much more prone to immunological disorders than most other organs and is of the greatest importance in the progress of the common metabolic disease, diabetes mellitus. Vascular diseases such as hypertension and vasculitis may also have profound effects on renal function. Disorders of the kidney can be conveniently divided into categories according to which structural component of the kidney is primarily affected:

- **Glomerulus Disorders**
- **Tubules and interstitium Disorders**
- **Blood vessels Disorders**

GLOMERULAR DISEASES

Disorders affecting the glomerulus encompass a clinically important category of renal disease. The glomerulus consists of an anastomosing network of capillaries invested by two layers of epithelium. The visceral epithelium (com posed of podocytes) is an intrinsic part of the capillary

wall, whereas the parietal epithelium lines Bowman space (urinary space), the cavity in which plasma ultrafiltrate first collects. The glomerular capillary wall is the filtration unit and consists of the following structures (Figs. 1 and 2):

- A thin layer of fenestrated *endothelial cells*, each fenestra being 70 to 100 nm in diameter.
- A *glomerular basement membrane* (GBM) with a thick, electron-dense central layer, the *lamina densa*, and thinner, electron-lucent peripheral layers, the *lamina rara interna* and *lamina rara externa*. The GBM consists of collagen (mostly type IV), laminin, polyanionic proteoglycans, fibronectin, and several other glycoproteins
- *Podocytes*, which are structurally complex cells that possess interdigitating processes embedded in and adherent to the lamina rara externa of the basement membrane. Adjacent *foot processes* are separated by 20- to 30-nm-wide *filtration slits*, which are bridged by a thin slit diaphragm composed in large part of nephrin.
- The glomerular tuft is supported by *mesangial cells* lying between the capillaries. Basement membrane–like mesangial matrix forms a meshwork through which the mesangial cells

are scattered. These cells, of mesenchymal origin, are contractile and are capable of proliferation, of laying down collagen and other matrix components, and of secreting a number of biologically active mediators.

Normally, the glomerular filtration system is extraordinarily permeable to water and small solutes and almost completely impermeable to molecules of the size and molecular charge of albumin (a 70,000-kDa protein). This selective permeability, called glomerular barrier function, discriminates among protein molecules according to their size (the larger, the less permeable), their charge (the more cationic, the more permeable), and their configuration. The characteristics of the normal barrier depend on the complex structure of the capillary wall, the integrity of the GBM, and the many anionic molecules present within the wall, including the acidic proteoglycans of the GBM and the sialoglycoproteins of epithelial and endothelial cell coats.

The podocyte is also crucial to the maintenance of glomerular barrier function. Podocyte slit diaphragms are important diffusion barriers for plasma proteins, and podocytes are also largely responsible for synthesis of GBM components.

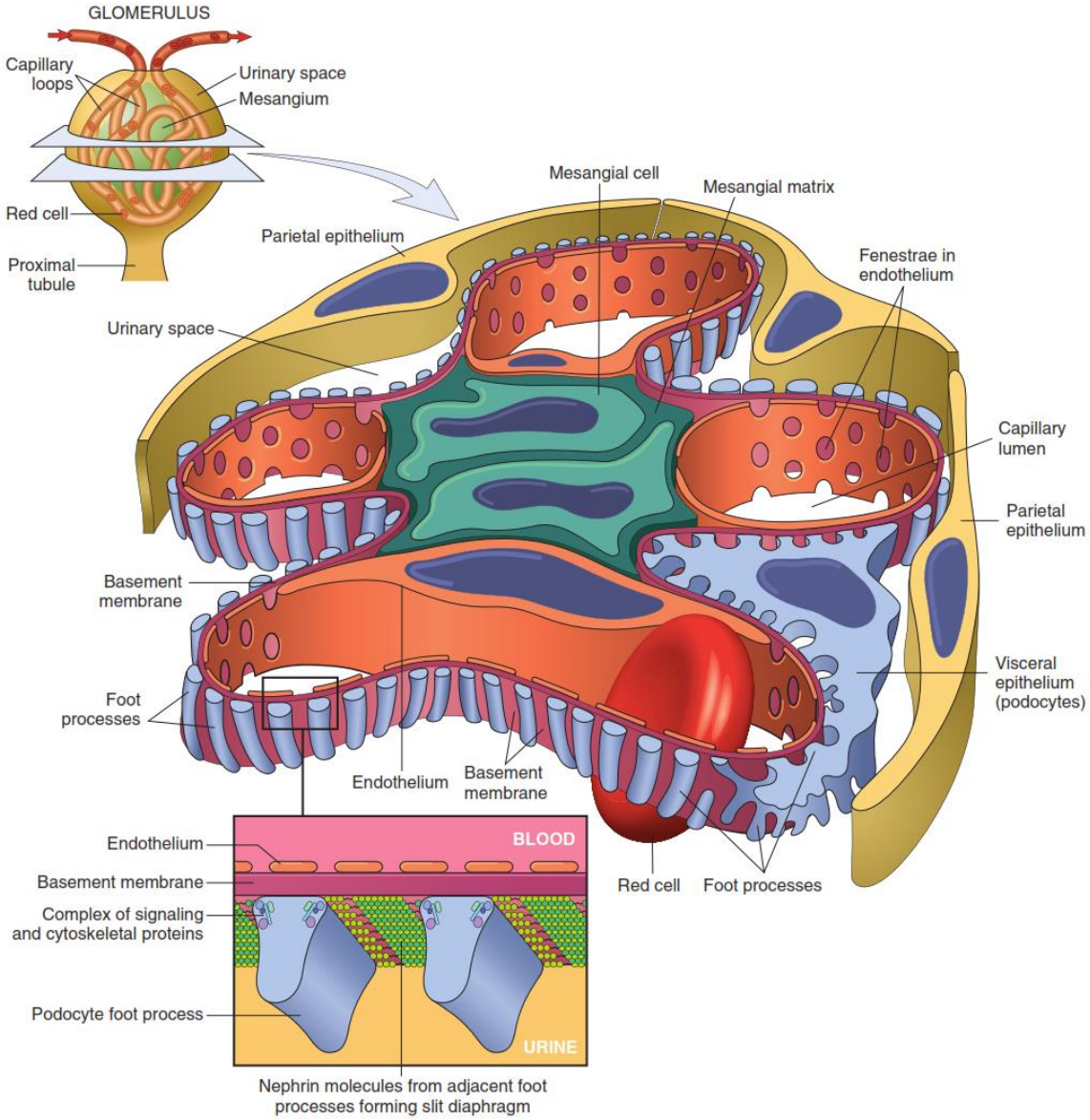

Figure 13–1 Schematic diagram of a lobe of a normal glomerulus.

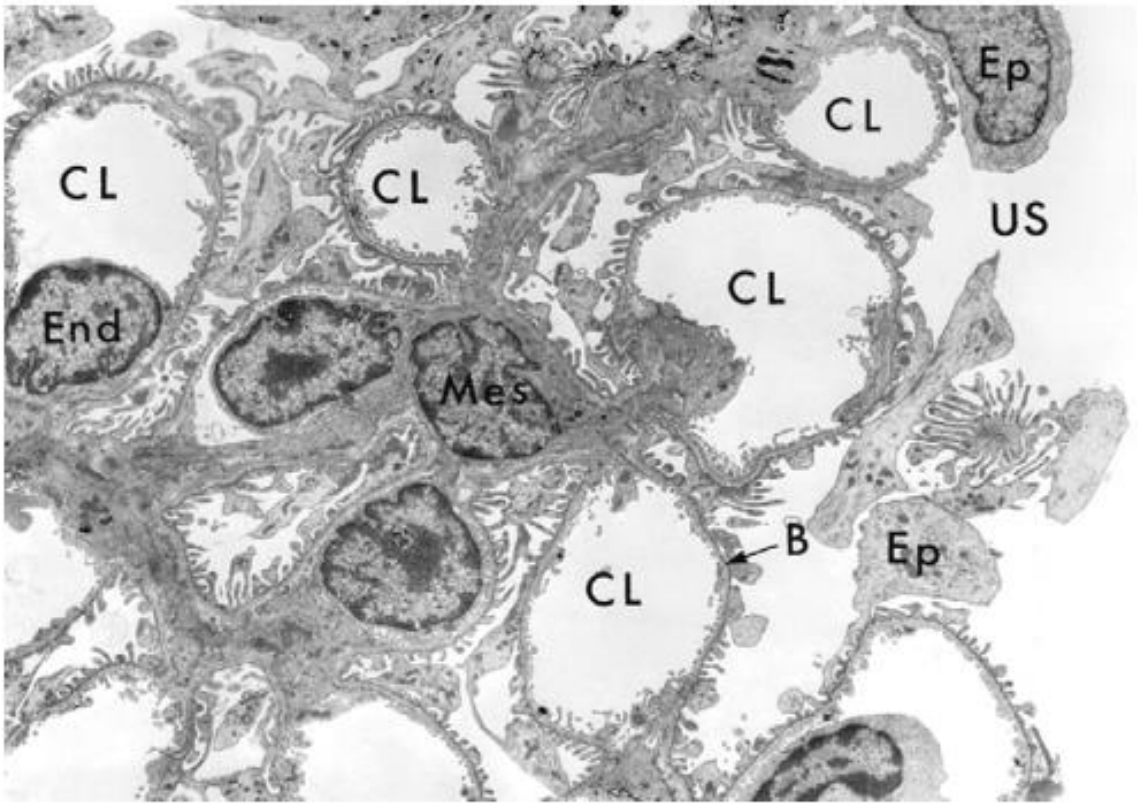

Figure 13–2 Low-power electron micrograph of rat glomerulus. B, basement membrane; CL, capillary lumen; End, endothelium; Ep, visceral epithelial cells (podocytes) with foot processes; Mes, mesangium; US, urinary space.

Glomeruli may be injured by diverse mechanisms and in the course of a number of systemic diseases. Immunologically mediated diseases such as systemic lupus erythematosus, vascular disorders such as hypertension and hemolytic uremic syndrome, metabolic diseases such as diabetes mellitus, and some purely hereditary conditions such as **Alport syndrome** often affect the glomerulus. These are termed **secondary glomerular diseases** to differentiate them from those in which the kidney is the only or

predominant organ involved. The latter constitute the various types of **primary glomerular diseases**.

Table 1 Glomerular Disease

Primary glomerular diseases
Minimal-change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Acute post infectious GN
Membranoproliferative GN
IgA nephropathy
Glomerulopathies Secondary to Systemic Diseases
Lupus nephritis (systemic lupus erythematosus)
Diabetic nephropathy
Amyloidosis
GN secondary to multiple myeloma
Goodpasture syndrome
Microscopic polyangiitis
Wegener granulomatosis
Henoch-Schonlein purpura
Bacterial endocarditis–related GN
Thrombotic microangiopathy
Hereditary Disorders
Alport syndrome
Fabry disease
Podocyte/slit-diaphragm protein mutations

Mechanisms of Glomerular Injury and Disease

Although little is known about the etiologic agents or triggering events, it is clear that immune mechanisms underlie most types of primary glomerular diseases and many of the secondary glomerular diseases. Under experimental conditions, glomerulonephritis (GN) can be readily induced by antibodies, and deposits of immuno globulins, often with various components of complement, are found frequently in patients with GN. Cell-mediated immune mechanisms may also play a role in certain glomerular diseases.

Two forms of antibody-associated injury have been established:

1. Injury resulting from deposition of soluble circulating antigen-antibody complexes in the glomerulus and
2. Injury by antibodies reacting in situ within the glomerulus, either with insoluble fixed (intrinsic) glomerular antigens or with molecules planted within the glomerulus. In addition, antibodies directed against glomerular cell components may cause glomerular injury. These pathways are not mutually exclusive, and in humans all may contribute to injury.