Autophagy in Glomerular Health and Disease

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Summary: Glomerular filtration coupled to tubular reabsorption was the prerequisite for one of the most important milestones in evolution, when animals made their way from water onto land. To fulfill the enormous filtration task the filter is composed of the most sophisticated postmitotic epithelial cells—the podocytes, which have only a very limited ability to regenerate. Podocyte injury and loss owing to genetic, toxic, immunologic, or metabolic insults underlie the most common glomerular diseases. Thus, the understanding of the factors and mechanisms that help to maintain podocytes are of major clinical importance. Recently, autophagy emerged as a key mechanism to eliminate unwanted cytoplasmic materials, thereby preventing cellular damage and stress to safeguard long-lived podocytes. Here, we highlight the accumulating evidence suggesting that autophagy plays a critical role in the homeostasis of podocytes during glomerular disease and aging.
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Ultrafiltration is executed by a multilayered filtration barrier that is composed of the fenestrated glomerular endothelium, the glomerular basement membrane, and the slit diaphragm, which bridges the filtration slits between the podocyte foot processes.[1,2] These structures are maintained by four resident cell types: the endothelial cells of the glomerular capillaries; the mesangial cells, holding the glomerular capillary tuft from the inside; the podocytes, covering the capillary tuft from the outside with their primary processes and interdigitating foot processes; and the glomerular parietal epithelial cells, lining the bowman capsule.[1,2] The highly specialized podocytes are the most vulnerable component of the filtration barrier. Podocyte injury is responsible for proteinuria, and loss of podocytes by cell death or detachment is a critical step for the progression of glomerular diseases and glomerular aging (Fig. 1).[3–5] Transgenic mouse models of podocyte-selective depletion showed that loss of more than 20% of podocytes is sufficient to cause glomerulosclerosis.[6,7] Because podocytes are postmitotic cells with a very limited regenerative potential,[8,9] mechanisms such as autophagy, which control the cellular homeostasis, are essential to maintain the podocyte compartment.

Macroautophagy (hereafter referred to as *autophagy*) is the major cellular bulk degradation pathway. It serves as a quality control mechanism by inactivating misfolded proteins and nonfunctional organelles and supplies nutrients for survival. The process of autophagic degradation consists of several phases, the initiation of a double-membrane structure, called isolation membrane or phagophore, the elongation of this phagophore, the sequestration of the cargo, and the maturation to an autophagosome, which fuses with a lysosome to an autolysosome, where the cargo is degraded and nutrients are shuttled back to the cytoplasm for metabolic recycling (Fig. 2A).[10,11] For a detailed description of the molecular autophagy machinery we refer the reader to recent excellent reviews by Mizushima et al,[10] Yang and Klionsky,[11] Ravikumar et al,[12] and Choi et al.[13] In brief, the initiation of autophagy and the nucleation of the isolation membrane depends on two protein complexes: the Unc-51-like kinase 1 (ULK1)-autophagy related 13 (ATG13)-FIP200-complex, which is activated by 5′-AMP activated protein kinase (AMPK) in response to energy depletion and negatively regulated by the mammalian target of rapamycin complex 1 (mTORC1); and the beclin 1–interacting complex, comprising beclin 1, the class III phosphatidylinositol-3-kinase VPS34 (vacuolar protein sorting 34), its regulatory subunit VPS15, ATG14L, and other interacting proteins. Activation of the beclin 1–interacting complex results in the generation of phosphatidylinositol-3 (PI3) phosphate, which promotes autophagosomal membrane nucleation.[13] The elongation of the membrane depends on two ubiquitin-like conjugation systems, the ATG5-ATG12 conjugation system and the

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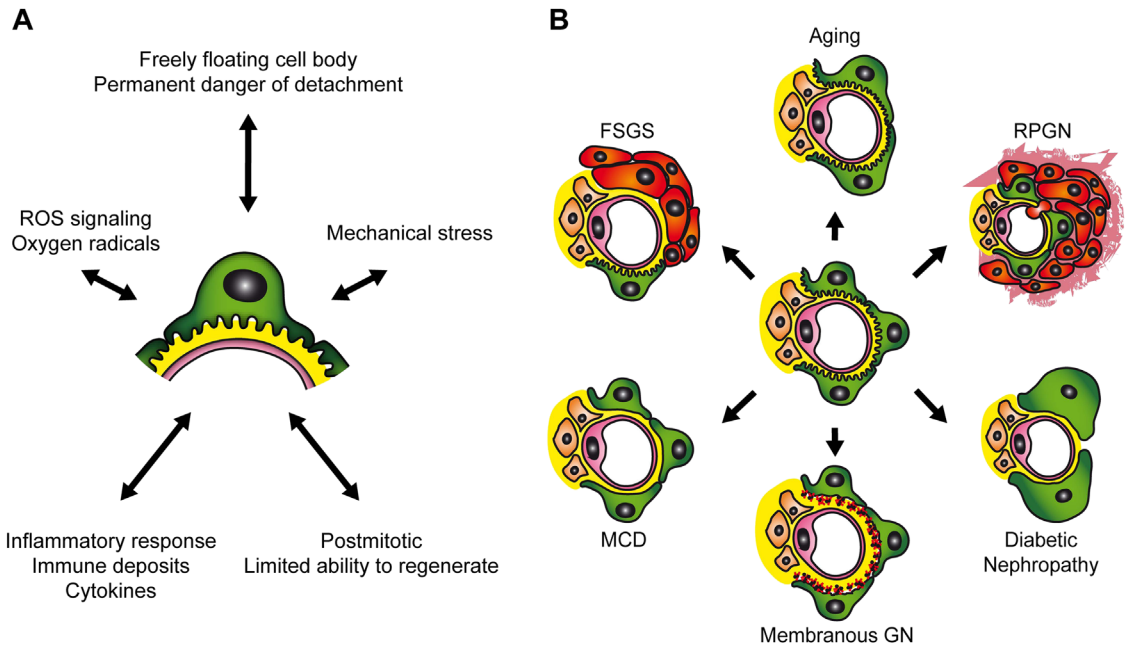

Figure 1. Podocytes are a main target of glomerular diseases. (A) Podocytes are exposed to a wide range of cellular stress events, but have only a very limited regenerative potential. (B) Injury and loss of podocytes are the key to the progression of glomerular diseases and glomerular aging. MCD, minimal change disease; ROS, reactive oxygen species; RPGN, rapid progressive glomerulonephritis.

microtubule-associated protein 1 light chain 3 (LC3)-conjugation system,[12,13] where cytosolic LC3-I is converted to LC3-II by conjugation with phosphatidylethanolamine.[14] LC3-II commonly serves as a marker for autophagosomes and can be visualized by immunofluorescence staining, appearing as dots in the cytosol, which represents autophagosomes.[15] By using LC3 as a reporter system, a green fluorescent protein (GFP)-LC3 transgenic mouse model recently enabled the in vivo monitoring of autophagy.[16] In addition, LC3-I and LC3-II can be detected by Western blot analysis, in which the lipidation of LC3-I results in a higher electrophoretic mobility.[14]

Glomerular podocytes were identified as cells with high levels of basal autophagy (Fig. 2B).[16–18] Subsequent studies recently showed a critical involvement and protective role of autophagy for glomerular maintenance, aging, and disease progression, which is summarized in this review. The understanding of the mechanisms by which autophagy can prevent glomerular disease progression may lead to the identification of new diagnostic and therapeutic approaches. In fact, agents directly acting on autophagy may offer novel opportunities for targeted therapies of glomerulopathies.

ROLE OF AUTOPHAGY FOR PODOCYTE MATURATION AND DIFFERENTIATION

Podocytes are derived from the metanephric mesenchyme and undergo a series of complex transdifferentiation processes from mesenchymal cells to highly differentiated epithelial cells. This differentiation process is accompanied by a stop in cell division,[2] and, during the late capillary loop stage, an up-regulation of autophagy.[18] The latter remains at a high basal level and becomes a characteristic hallmark of differentiated podocytes in vivo and in vitro.[16–19] Constitutive knockout of *Atg5*, however, did not result in an obvious alteration of podocyte maturation,[18] indicating that autophagy is not necessarily required for the differentiation process itself, but it is part of the podocyte's phenotypic and metabolic shift to a postmitotic secretory cell.

ROLE OF AUTOPHAGY FOR PODOCYTE MAINTENANCE

A functional block of the autophagy machinery in podocytes by deletion of *Atg5* caused a slowly progressing cellular degeneration.[18] Podocyte-specific conditional *Atg5* knockout mice (*Atg5* PcKO mice) developed aging-related albuminuria and late-onset glomerulosclerosis between 20 and 24 months of age.[18] The phenotype phenocopied typical age-related alterations, such as the formation of ubiquitin- and SQSTM1/p62-positive protein aggregates, the accumulation of lipofuscin, the occurrence of damaged mitochondria, and the increase in the total load of oxidized proteins (Fig. 2C).[18] The Calnexin signal was increased, and ultrastructural studies showed cytosolic vacuolization, apparently caused by expanded endoplasmic reticulum (ER) membranes. The compensatory

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