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Organelles in focus

Podocyte energy metabolism and glomerular diseases

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ABSTRACT

Mitochondria are crucial organelles that produce and deliver adenosine triphosphate (ATP), by which all cellular processes are driven. Although the mechanisms that control mitochondrial biogenesis, function and dynamics are complex process and vary among different cell types, recent studies provided many new discoveries in this field. Podocyte injury is a crucial step in the development of a large number of glomerular diseases. Glomerular podocytes are unique cells with complex foot processes that cover the outer layer of the glomerular basement membrane, and are the principle cells composing filtration barriers of glomerular capillaries. Little is known on the modalities and the regulation of podocyte's energetics as well as the type of energy substrate primarily used for their activity, recent studies revealed that dysfunction of energy transduction in podocytes may underlie the podocyte injury associated with numerous glomerular diseases. We herein review and discuss the importance of a fine regulation of energy metabolism in podocytes for maintaining their cellular structure and related kidney function. In the future, understanding these mechanisms will open up new areas of treatment for glomerular diseases.

1. Introduction

Mitochondria are crucial organelles not only for ensuring the energy supply by producing adenosine triphosphate (ATP), but also for other important biological processes, such as ion homeostasis (Cardoso et al., 2010), the production and scavenging of reactive oxygen species (ROS) (Lenaz, 2012) and cell death (apoptosis) (Spencer and Sorger, 2011). Therefore, mitochondrial dysfunction is now thought to be associated not only with monogenic mitochondrial disorders (Koopman et al., 2012), but also with many common diseases, such as diabetes (Szendroedi et al., 2011), obesity (Tseng et al., 2010), Alzheimer's disease (Coskun et al., 2012), cancer (Jose and Rossignol, 2013), aging (Bratic and Trifunovic, 2010; Bishop et al., 2010) and several others (Schapira, 2012). Recently, it was revealed that mitochondria are also involved in the inflammatory response to injury and in the innate immune response (Zhang et al., 2010a,b; West et al., 2011). Therefore, it seems possible that mitochondrial dysfunction could also be associated with glomerulonephritis, such as lupus nephritis, anti-neutrophil cytoplasmic antibody (ANCA)-related glomerulonephritis, and IgA nephropathy.

In the past, a considerable number of papers showed the involvement of mitochondria in kidney diseases. However, most of them were focused on kidney tubular cells (Soltoff, 1986; Hall and Unwin, 2007; Zhan et al., 2013; Hickey et al., 2011; Gall et al., 2012) with a tissue specific energy demand related to ion transports (Praetorius and Leipziger, 2010; Hamm et al., 2010; Ishibashi et al., 2011). Otherwise, several studies assessed the mechanisms of glomerular or tubular damage through reactive oxygen species (ROS) production or apoptosis (Chacko et al., 2010; Zhu et al., 2011; Zhang et al., 2006; Susztak et al., 2006). Indeed, direct ROS production by mitochondria, which can also induce further ROS by other sources such as NADPH oxidases (Dikalov, 2011), should play important roles in podocyte injury as described previously. However, in this review, we focus on the modalities of podocyte energy transduction, because accumulating evidences indicate that mitochondria are essential for maintaining podocyte homeostasis and their failure could lead to podocyte damage.

2. Glomerular podocytes

2.1. An overview of the structure and function of podocytes

The primary urine is made in the glomeruli. The glomerulus is a ball of capillaries surrounded by the Bowman's capsule. Each glomerulus is composed by four types of cells. These are parietal epithelial cells (Bowman's cells), visceral epithelial cells, mesangial cells and endothelial cells. The visceral epithelial cells

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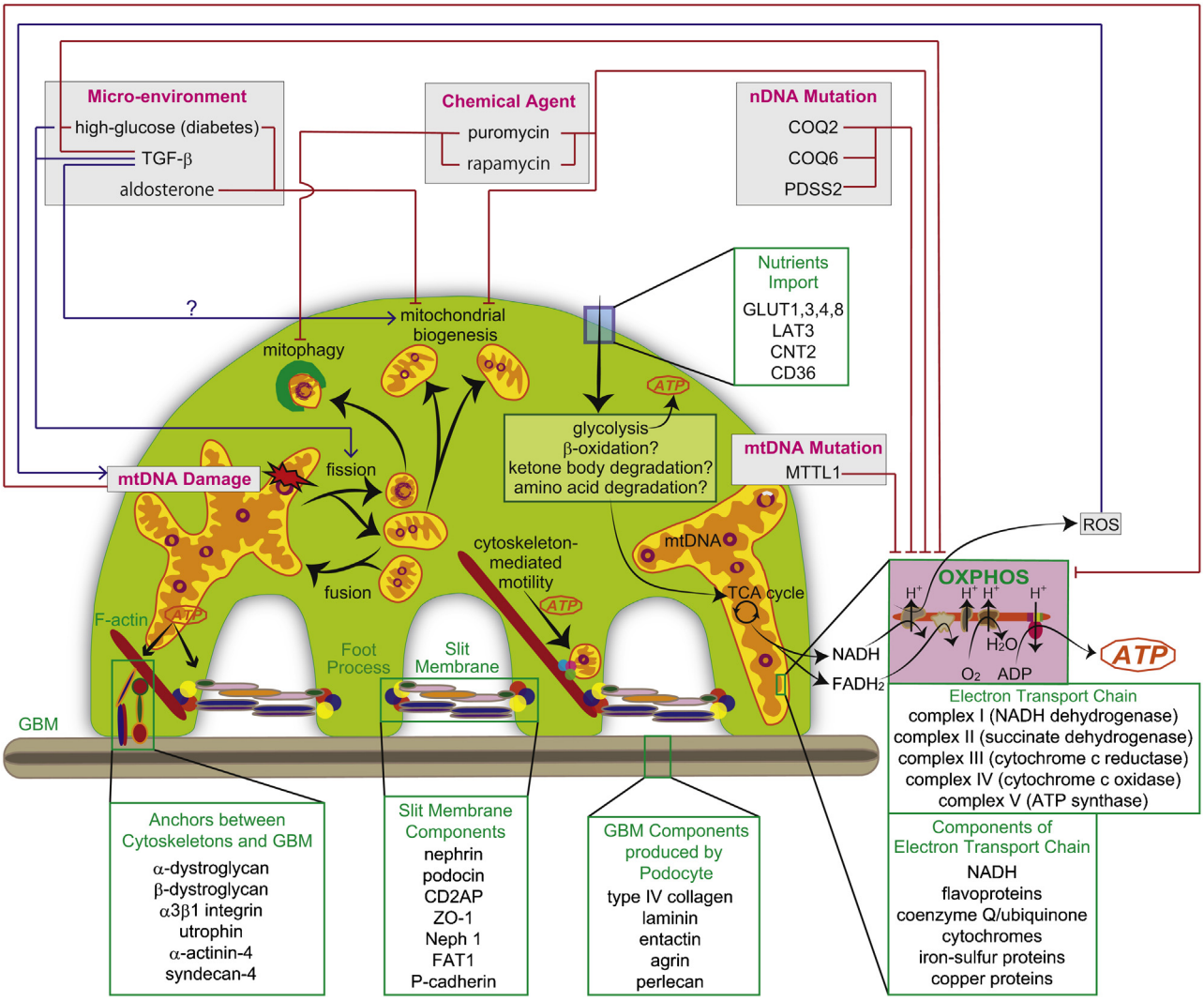

Fig. 1. A schematic diagram of a glomerular podocyte and its energy metabolism. In this figure, molecules which are important for maintaining the foot process structure and function are summarized. To maintain these podocytes' structures and functions, their energy metabolism should be controlled by precisely orchestrated steps, which are now largely unknown. Here, possible mechanisms of podocyte energy metabolism are shown. In addition, gene mutations, chemical agents and microenvironmental perturbations in energy metabolism can result in podocyte injury.

are the largest cells in the glomerulus, and are also designated podocytes because their cell body emits octopus-like processes. Podocytes have three major structural regions: the cell body, cell processes and foot processes. The cell body of podocytes never attaches to the glomerular basement membrane (GBM) under normal conditions, and only its foot processes are adjacent to the GBM (Pavenstädt et al., 2003) (Fig. 1). The podocyte's cell body contains a nucleus, rough endoplasmic reticulum, Golgi apparatus, lysosomes, mitochondria, and other organelles (Fig. 2). The foot process is the most characteristic structure of podocytes. Specialized junctions between interdigitating foot processes, known as the slit diaphragm, and junctions between the foot processes and the GBM, known as the focal adhesion complex, are crucial for maintaining the glomerular integrity and functions (Endlich et al., 2001; 10: 331–340, Pavenstädt et al., 2003; Rigothier et al., 2012; Sachs and Sonnenberg, 2013) (Fig. 1). Slit diaphragms, which play roles as size barriers for filtration, are composed of ZO-1, nephrin, NEPH1, podocin, CD2AP, FAT1 and P-cadherin. All of these diaphragm components are synthesized by podocytes (Fig. 1). Nephrin is a zipper-like protein that plays a functional role in the structure of the slit diaphragm (Tryggvason and Wartiovaara, 2001).

The GBM serves not only as a size barrier, but also as a charge barrier, in cooperation with the endothelial glycocalyx. The GBM is generated as two different layers produced by glomerular endothelial cells and podocytes. These two layers fuse to form the GBM. Because the GBM requires a constant turnover of cells to maintain its flexibility and dynamics, podocytes have to continuously add and assemble matrix components, including type IV collagen, laminin, entactin, agrin and perlecan, to the GBM (Miner, 1999) (Fig. 1). In this manner, the podocytes synthesize the GBM components and slit diaphragm proteins. Therefore, podocyte injury can result in proteinuria as a result of the destruction of these filtration barriers (Greka and Mundel, 2012a,b).

In addition, rich microfilaments are essential for the connection of foot processes to the GBM and slit diaphragm through unique molecular complexes (Pavenstädt et al., 2003). For example, α3 β1-integrin, syndecan-4 and α- and β-dystroglycans anchor foot processes to the GBM (Sachs and Sonnenberg, 2013) (Fig. 1). Slit diaphragms are also associated with the actin cytoskeleton by molecular complexes, as summarized in Fig. 1. If these slit diaphragm component proteins or anchor proteins to the GBM are lost, the foot process cannot maintain its structure or function,