Mechanistic Basis for Autophagy in Diabetic Kidney Disease

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Diabetic kidney disease (DKD), or diabetic nephropathy (DN), is a common but severe complication in diabetic patients. The disorder mainly consists of persistent proteinuria with progressive worsening of renal function, and can ultimately cause irreversible kidney damage. Studies have provided new insights into the connection between autophagy, a physiological metabolic process known to maintain cellular homeostasis, and the pathophysiological pathways of DKD. Typically, autophagic activity plays a role in DKD progression mainly by promoting an inflammatory response to tissue damage, while both overactivated and downregulated autophagy worsen disease outcomes in different stages of DKD.

Keywords: autophagy ; diabetic kidney disease ; diabetic nephropathy ; nutrient-sensing ; macrophage ; phenotypic change ; epigenetic

1. Introduction

Diabetic kidney disease (DKD), or diabetic nephropathy (DN), is a common but severe complication in diabetic patients. The disorder mainly consists of persistent proteinuria with progressive worsening of renal function, and can ultimately cause irreversible kidney damage [1]. As the leading cause of end-stage kidney disease (ESKD), DKD is associated with increased morbidity and mortality in diabetes patients, and thus poses a considerable threat to healthcare systems across the globe. It has been estimated that of the global population of type 2 diabetes mellitus (T2DM) patients, over 35–40 percent eventually develop DKD [2]. Several risk factors for DKD have been identified, most of which are related to the underlying metabolic syndrome. Genetic components also play a role in the development of the disease, and a persisted hyperglycemic state remains an important contributing factor to the progression of DKD [3]. The pathophysiological mechanism of DKD arises from the interaction between various metabolic pathways, including reactive oxygen species (ROS) and advanced glycation end-products (AGEs) [2][4][5]. This mechanism triggers abnormal downstream cellular responses, which in turn lead to gross vascular injury and renal cell damage.

Considering the high prevalence of DKD and the large population of T2DM patients at risk, updates on the understanding and management of the disorder are essential. Clinically, blood glucose/pressure control and renin-angiotensin-aldosterone system (RAAS) medications are supported by strong evidence for halting the development and progression of DKD. However, much is unknown about the underlying mechanism and stage-specific strategy for DKD. Over the years, researchers have identified numerous pathways that are related to the pathophysiology of DKD, with oxidative stress and metabolic imbalance caused by a persisted hyperglycemic state taking center stage. These pathways include the mitogen-activated kinases (MAPK) pathway, which leads to podocyte apoptosis and extracellular matrix deposition, and pathways that are heavily involved in inflammation, such as the Janus kinase-signal transducers and activators of transcription (JAK/STAT) and nuclear factor kappa-B (NF-κB) pathways [3]. Together, these pathways contribute to the complex regulatory network of DKD.

Autophagy is known to be an important mechanism for maintaining intracellular homeostasis. The process plays a wide variety of physiological roles, and dysregulation of autophagy can cause irreparable tissue damage [6]. There are three subtypes of autophagy: microautophagy, macroautophagy, and chaperone-mediated autophagy. Macroautophagy is the most prevalent form of the three, and thus will be referred to as autophagy hereafter unless otherwise specified. The process of autophagy can be divided into several stages: first, the initiation of autophagy due to stress stimulation; next, the formation of phagophores and encapsulation of intracellular components into autophagosomes; and last, the fusion of autophagosomes with lysosomes, which form autophagolysosomes that ultimately go through the degradation process [7]. Multiple genes and signaling pathways can interfere with this process, and are closely related to the microenvironment the cells are in.

In light of its role in various diseases, increasing evidence indicates that the regulation of autophagy plays a complex role in the progression of DKD, and conversely that the modulation of autophagy in DKD may have potential as a therapeutic target in the future.

2. An Increased Understanding of Nutrient-Sensing and Downstream Pathways

Due to a constant hyperglycemic state, the nutrient-sensing AMPK and mTOR signaling pathways have established their role in influencing DM-induced pathological changes [8][9][10]. The downregulation of AMPK signaling in DN leads to decreased autophagic activity and worse outcomes [11], while the mTOR signaling pathway, which is overactivated in DN, blocks the initiation of autophagy [12][13]. Recently, the JAK/STAT signaling pathway has been shown to be closely related to energy expenditure while also being regulated by AMPK signaling [14][15]. Previous studies have demonstrated the potential of hindering DN development via regulating JAK/STAT signaling; the pathway's effect on autophagy regulation has also been shown in chronic myeloid leukemia cells [16][17]. However, reports regarding the impact of the JAK/STAT pathway on autophagy in kidney cells is lacking. A recent update by Chen et. al. found that in a DKD mice model the JAK/STAT signaling pathway was activated in podocytes under hyperglycemic conditions, and MAP1LC3 (LC3) expression, which serves as a proxy for autophagic activity, was downregulated, leading to subsequent cellular apoptosis and DKD progression [18]. By inhibiting the JAK/STAT signaling pathway in cell models via the JAK inhibitor ruxolitinib, impaired autophagic flux was restored. Another pathway closely related to nutrient-sensing, the p53 signaling axis, was recently introduced as a regulator of autophagic signaling [19]. Activated p53 signaling under DKD models was found to impair autophagy response in renal tubular cells via the unc-51-like autophagy-activating kinase 1 (ULK1) pathway [20], and in podocytes via the nutrient-sensing Sirtuin-1 (SIRT1) pathway, leading to subsequent DKD progression [21]. Together, these results indicate that impaired autophagic activity from dysregulated nutrient-sensing pathways can promote the development of DKD.

Researchers are still looking to further investigate the cellular response to hyperglycemic states, specifically with regards to the involvement of common energy-containing nucleotides such as adenosine triphosphate (ATP), adenosine diphosphate (ADP), uridine triphosphate (UTP), and uridine diphosphate (UDP) [22]. Under hyperglycemic conditions, these nucleotides can be released extracellularly, and can subsequently trigger cellular purinergic P2 (P2Y) receptors. Among the eight known subtypes of P2Y receptors, P2Y2R was found to be prominently expressed in renal glomerular, mesangial, podocyte, and tubular cells. These updates expand the known scope of nutrient-sensing pathways, demonstrating their involvement in the autophagy-DKD axis.

3. Autophagic Activity Affects Macrophage Phenotypic Change

The current understanding of upstream pathways of DKD helps in identifying potential therapeutic targets, as well as predicting the effect of interrupting the involved signaling axes. Additionally, the downstream effects of autophagy and how the process complicates the development of DKD progression is of equal significance, as this information can assist researchers in identifying the various effects of autophagic regulation.

Within the pathophysiology of DKD, the dysregulation of autophagic activity itself contributes to the impaired repair of renal cells under stress. Another important physiological repair mechanism arises from the effect of macrophages [23]. The migration and adhesion of macrophages to diabetic kidney tissue is known to play a major role in DKD progression, as it leads to the release of cytokines and chemokines, which subsequently induce inflammatory damage to the kidney. Interestingly, studies have connected macrophage functionality with autophagic activity. It was found that a hyperglycemic state not only affects autophagic activity in kidney cells but also reduces the number of autophagosomes in RAW264.7 cells, a mouse macrophage cell line [24]. The inhibition of autophagy in macrophages was accompanied with an increased expression of P62, which promoted the adhesion and migration capacity of macrophages. This same pattern of autophagic and P62 upregulation can also be seen in the renal tissues of a DN rat model. This is also, in part, related to the fact that macrophage autophagy can inhibit M1 pro-inflammatory macrophage polarization, which, in turn, can alleviate the progression of tissue damage [25]. M2 macrophages were also found to be able to secrete autophagy-activating exosomal miR-25-3p, and ameliorate high glucose-induced podocyte injury, adding to the complex relationship between macrophages and autophagy [26]. Yuan et al. reported that the interaction between autophagy and macrophage phenotypic change may be the underlying mechanism behind the beneficial effects of mesenchymal stem cell (MSC) treatment [27]. By treating DN mice via MSC vein infection, their data showed a restoration of autophagic activity and an inhibited inflammatory response in macrophages, which alleviated renal injuries. The researchers also identified activation of transcription factor EB (TFEB) as the mechanism behind the effects of the MSC treatment. TFEB nuclear localization was significantly increased after MSC treatment in RAW 264.7 cells, which elicited the polarization of M2 macrophages. A

better understanding of the interactions between autophagy, DKD, and macrophage function may provide us with a fresh outlook on the effects of autophagy outside of kidney tissue, and the other intercellular events that are a part of DKD progression.

4. New Prospects in Gene and Epigenetic Regulation

The final aspect concerning the regulatory pathways of autophagy in DKD that wish to highlight in this section is the role of epigenetics. With precision medicine being the future trend in healthcare, the recognition of the specific genetic components of disease has become increasingly crucial. Epigenetic mechanisms such as histone modifications and microRNA regulation are believed to assist in physiological adjustments to environmental conditions. Components of epigenetic modulation, including noncoding RNAs (ncRNAs), histone deacetylases (HDACs), and DNA methylation, were all found to play a unique role in DKD progression [28][29]. Studies have shown that persistent inflammation and cytokine exposure under diabetic conditions leads to epigenetic modifications, and ultimately induces lasting open chromatin structures at pathological gene sites, a possible mechanism for “metabolic memory” [30]. Numerous miRNAs are involved in autophagic suppression under diabetic conditions, with some achieving their effect by taking part in some of the aforementioned signaling events [31][32]. Reversing the effects of these miRNAs, then, is expected to reduce glomerular mesangial hypertrophy in early stages of DN in animal models, which may be a viable therapeutic strategy in the future.

In addition to the effect of miRNAs, HDACs have also been identified as an important family of enzymes that take part in numerous physiological processes, including diabetes and insulin resistance [33]. In the case of DKD, it was established that HDACs can promote fibrosis and chemokine production in kidney cells. Further research found that different isoforms of HDACs may also exert individual effects on autophagy in DKD [34][35]. HDACs 4 and 5 were among the earliest enzymes within the family that were found to play an inhibitory effect on autophagy; in fact, suppressed autophagic activity and increased inflammation were both observed. Adding to this connection, Liang et al. showed that HDAC6, an HDAC that is predominantly located in the cytoplasm and is related to the stability of microtubules, was activated in T2DM patients, db/db mice models, and advanced glycation end products (AGE)-treated podocytes [36]. Their further results indicated that the podocytes suffered from subsequently enhanced motility and suppressed autophagy, leading to DN progression, which could be rescued by tubacin, an HDAC6-specific inhibitor. A number of medications such as valproic acid—a widely used anti-epileptic drug—have been recognized as possessing HDAC-inhibiting effects [37]. Although specific medications that target epigenetic mechanisms may not currently be readily available, the advancement of pharmaceutical technology, tailored gene therapy, and epigenetic interventions may provide an exciting avenue for treating DKD in the future.

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