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REVIEW ARTICLE

Role of autophagy and histone deacetylases in diabetic nephropathy: Current status and future perspectives

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Abstract The prevalence of diabetes and its complications is increasing at an alarming rate in both developed and deve1oping nations. The emerging evidences highlighted that both genetic and epigenetic mechanisms including histone modifications play a significant role in the pathogenesis of diabetic nephropathy (DN). Histone deacetylases (HDACs) and acetylation are involved in the regulation of autophagy as well as pathogenesis of DN. Both HDACs and histone acetyltransferases (HATs) play a key role in chromatin remodeling and affect the transcription of various genes involved in the cellular homeostasis, apoptosis, immunity and angiogenesis. Further, HDAC inhibitors are exert the renoprotective effects in DN and other diabetic complications. Thus, the cellular acetylation plays a crucial role in the regulation of autophagy and can be explored as a new therapeutic target for the treatment of DN. This review aimed to delineate the role of HDACs and associated molecular signaling/pathways in the regulation of autophagy with an emphasis on promising targets for the treatment of DN.

Introduction

Diabetic nephropathy (DN), a micro-vascular complication, which leads to end-stage renal disease (ESRD).[1] DN is characterized by the excessive deposition of extracellular matrix (ECM) with thickening of glomerular basement membranes and mesangial expansion in both glomerular and tubulo-interstitial compartments as well as persistent micro-albuminuria.[2,3] It is also associated with reduced renal function, podocyte damage and proteinuria.

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Approximately 30—40% of both type-1 and type-2 diabetic patients develop nephropathy, but evidences are higher in type-1 diabetic patients and ultimately lead to ESRD.[4,5] DN has several distinct phases of development. The structural and functional changes occur in the glomerulus and tubules such as glomerular hyper-filtration, hyper-perfusion, thickening of glomerular basement membrane and glomerular hypertrophy as well as mesangial expansion.[6,7] Excessive accumulation of ECM in glomerular mesangial and tubulo-interstitial compartments as well as, epithelial-to-mesenchymal transition (EMT) of renal tubular epithelial cells are the hallmark of DN.[8] In DN, the renal hemodynamic changes involve the activation of various vaso-active systems such as rennin-angiotensin-aldosterone systems (RAAS), which results in the secretion of pro-fibrotic molecules such as transforming growth factor β1 (TGF-β1), advanced glycosylated end-products (AGEs), activation protein kinase C (PKC) and acceleration of the aldose reductase pathway increases systemic and intra-glomerular pressure, thereby hyper-perfusion, hyper-filtration and other functional changes, which lead to leakage of proteins from the glomerular capillaries.[8,9] Further, DN is also associated with podocytes damage; which are terminally differentiated highly specialized epithelial cells. It plays an important role in maintaining the integrity of glomerular filtration barrier and acts as a critical size and charge barrier to prevent proteinuria.[10] Thus, DN is associated with compromised renal function, podocyte damage and subsequent proteinuria, which ultimately lead to ESRD.

Several mechanisms such as oxidative stress, inflammation, genetic and epigenetic alterations as well as autophagy are contributed in the pathogenesis of DN.[11—13] However, the exact role of autophagy has not been studied in DN. Autophagy is a catabolic cellular process by which cells degrade and recycle the dysfunctional proteins and damaged organelles to maintain the cellular homeostasis under stress conditions such as starvation, hypoxia, endoplasmic reticulum (ER)-stress and hyperglycemia.[14,15] Several reports highlighted that the dysfunctional proteins and organelles are accumulated in DN due to reduce autophagy.[16,17] Further, deficiency of autophagy leads to chronic kidney injury, which is associated with ischemia-reperfusion, hypoxia and DN.[18—20]

Recent studies emphasized that the epigenetic mechanisms like histone modifications (acetylation), DNA methylation and microRNA play a significant role in the development and progression of DN.[21,22] Histone deacetylases (HDACs) are the enzymes, which remove the acetyl group from lysine residues of histone proteins, while histone acetyltransferases (HATs) add the acetyl group on the histone and ultimately regulate the gene expression.[23,24] HDACs are involved in several biochemical pathways and contribute in the pathogenesis and progression of DN.[25—27] HDAC1 has been found to trigger fibroblast activation, proliferation and chemokine production in the interstitial renal fibroblasts and tubular epithelial cells.[22] Recently, it has been reported that HDAC2/4/5 are up-regulated in both experimental and clinical DN and play a critical role in its progression by reducing autophagy.[23,28] Moreover, podocytes exposed to high glucose and transforming growth factor-β1 (TGF-β1) increased the expression of HDAC4, suggesting its contribution in DN.[23,29] On the other hand, HDAC inhibitors possess the renoprotective and anti-fibrotic activities against various pathophysiological insults in diabetes, which confirm that HDACs play a central role in DN.[21,30,31] Further, valproic acid showed renoprotective effect in DN by decreasing the expression of HDAC4/5 and improving autophagy through HDAC inhibition and histone acetylation.[32] The kidney of STZ-induced diabetic rats, db/db mice and TGF-β1-treated NRK52-E cells showed marked elevation of HDAC-2 activity, which increased the expression of fibronectin and SMA, while decreased the expression of E-cadherin.[33] Moreover, HDAC inhibitors also exert beneficial effects in various nephrotic and non-nephrotic pathological conditions through chromatin-dependent and independent mechanisms.[31,34—37] Considering the recent literature, it is clearly evident that HDACs and autophagy are the key contributors in the pathogenesis and progression of DN (Table 1). This review provides the novel insights on the role of HDACs, cellular acetylation and the associated molecular signaling/pathways, which modulate the autophagy and DN with an emphasis on promising therapeutic targets.

Autophagy: an overview

Autophagy is a cellular catabolic process, which degrades and recycles the unwanted proteins and organelles in cell to maintain cellular homeostasis under stress and pathological conditions.[36,38,39] In the other words, autophagy recycles the intracellular energy resources in response to nutrient depletion, removes the cytotoxic proteins and organelles under physiological conditions (Fig. 1).[14,40] Every cell has a unique feature to sense the nutrients availability and produce a specific response via adenosine monophosphate (AMP)-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR) and sirtuins (SIRTs) mediated nutrient sensing pathways for the cellular homeostasis.[41—43] Apart from this, cellular energy level regulates autophagy through the nutrient-sensing signaling depending on cell requirement.[19,44] Depletion of energy level activates autophagy by the inhibition of mTOR or activation of AMPK and SIRT1, to degrade the unnecessary cellular components, thereby providing energy and other substrate to the cell.[43—46] The above pathways regulate the efficient nutrient utilization by autophagy for the cell growth and survival (Fig. 2). In general, these pathways are directly and indirectly involved in the pathogenesis of diabetes, cancer and obesity. Further, nutrient regulatory pathway modulates the post-translational modifications including HDAC-mediated de-acetylation of various target proteins of autophagy as well as many physiological processes.[45,47,48]

The process of autophagy involves a series of dynamic membrane rearrangements regulated by a set of ATG proteins.[49] This comprise of four protein complexes, which constitute core molecular machinery i.e., the kinase complex ATG1—ATG13 (initiator), phosphatidylinositol-3 kinase (PI3K) complex I (BECN1, ATG14, PIK3C3/VPS34 and PIK3R4/VPS15) as well as two ubiquitin-like protein conjugation complexes i.e, ATG12—ATG5-ATG16L1 and LC3—PE.[24,50] In brief, the process of autophagy is accomplished in the following steps.