NEPHROLOGY

Openventio PUBLISHERS

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-104

Opinion

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Volume 1 : Issue 2
Article Ref. #: 1000NPOJ1104

Article History
Received: May 11th, 2015
Accepted: June 25th, 2015
Published: June 26th, 2015

Citation
Chen XM, Huang C, Pollock CA. Current opinion in the treatment of diabetic nephropathy. *Nephrol Open J*. 2015; 1(2): 20-24. doi: 10.17140/NPOJ-1-104

Current Opinion in the Treatment of Diabetic Nephropathy

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KEYWORDS: Diabetic nephropathy; Autophagy; MicroRNA; Chronic inflammation; Nlrp3; mTOR; AMPK and Sirt1.

Diabetic nephropathy is a leading cause of end-stage renal failure. Approximately 20-40% patients with diabetes mellitus will develop nephropathy with a significant proportion requiring regular dialysis or kidney transplantation. The International Diabetes Federation estimates that 366 million people had diabetes worldwide in 2011 and 552 million people will have this disease by 2030.[1] The increasing incidence of diabetes elevates diabetic nephropathy to one of the most important current public health issues, representing a significant burden on the health system.[2] Despite current interventional strategies being intensively implemented, the number of patients with diabetes requiring renal replacement therapy for end-stage renal disease is growing.[3] Current treatments of diabetic nephropathy slow its progression,[3] so the optimal therapeutic strategy to arrest or reverse the nephropathy is needed urgently. As multiple risk factors and their interactions promote the development of diabetic nephropathy, targeting a single factor may be ineffective in the treatment of this disease; thus, optimal treatments by targeting multiple factors need to be developed to arrest or reverse the diabetic nephropathy.

The classical features of diabetic kidney include glomerular and tubular basement membrane thickening, and mesangial and interstitial expansion. There is deposition of extracellular matrix in both glomerular and interstitial compartments.[4] Due to increased matrix protein production and decreased protein degradation, over accumulation of collagen type I, III and IV, and fibronectin occurs in the mesangium and interstitium, which leads to decreased glomerular filtration, tubular injury and interstitial fibrosis. The mechanisms of the diabetic nephropathy have been largely investigated. It was well documented that chronic hyperglycaemia interferes with various intracellular processes including activation of protein kinase C, leads to generation of Advanced glycation end-products (AGEs) and reactive oxygen species, of inflammatory cytokines and chemokines and changes in cellular signaling pathways leading to dysregulation of transcription factors controlling the extracellular matrix homeostasis.[5-7] However, diabetic nephropathy is complex and multifactorial and the current therapies are largely ineffective, therefore there is increasing urgency to identify novel therapeutic targets that will allow more precise control over disease development and progression.

Current treatments of diabetic nephropathy involve the strict control of metabolic and hemodynamic abnormalities.[8,9] Glycaemic control, reducing albuminuria and management of hypertension are commonly used to limit the progress of diabetic nephropathy.[9] Despite of these strategies, the number of patients with diabetes that ultimately develop end-stage renal disease remains high. Novel agents to inhibit AGE-RAGE, PKC, TGFβ, oxidative stress, and fibrosis are under investigation.[8] In recent years, inflammatory pathways and inflammasome activation in renal disease has been recognised.[10,11] Micro-RNA based therapies have shown promise in ameliorating chronic renal disease;[12-16] and dysregulation of autophagy in the development of diabetic nephropathy has been reported.[17-21]

ISSN 2380-0445 Open Journal http://dx.doi.org/10.17140/NPOJ-1-104

CHRONIC INFLAMMATION IN DIABETIC NEPHROPATHY

Inflammation plays a central role in the progression of diabetic kidney disease.[11] Molecules integral to the inflammation pathways in diabetic kidney disease include transcription factors, pro-inflammatory cytokines, chemokines, adhesion molecules, Toll-like receptors, adipokines and nuclear receptors, which are all novel molecular targets for the treatment of diabetic kidney disease.[11] Comprehensive genomic profiling in diabetic kidneys identified the central role of proinflammatory pathways and the identified pathological gene assemblies resulting in renal inflammation, apoptosis and cell cycle arrest in progressive diabetic kidney disease.[22,23] Inflammasomes are key signaling platforms that detect pathogenic microorganisms and sterile stressors, and that activate the highly pro-inflammatory cytokines IL-1β and IL-18.[24] Nlrp3 is one such inflammasome that, once activated, Nlrp3 inflammasome activates caspase-1 and mediates the processing and release of cytokine IL-1β, amplifies the inflammatory response.[25] Once activated**,** Nlrp3 recruits the adapter ASC (apoptosis-related speck-like protein containing a caspase recruitment domain), which in turn recruits procaspase-1. Procaspase-1 auto catalyzes its cleavage and activation, resulting in maturation of the precursor forms of IL-1β and IL-18 into active proinflammatory cytokines and initiation of pyroptotic cell death.[26] The Nlrp3 inflammasome has been implicated in the pathogenesis of a wide variety of diseases including renal fibrosis. The Nlrp3 inflammasome has previously been reported to promote renal inflammation and contribute to chronic kidney disease.[27] Activation of the Nlrp3-inflammasome has been previously demonstrated in *in vitro* studies in endothelial cells and podocytes, in patients with diabetes, and in mouse models of diabetes.[28] It has been well summarized the recent findings: the Nlrp3 inflammasome is not limited by the traditional microbial stimuli of innate immunity and its connection with autophagy, apoptosis, fibrosis, and pro-inflammatory cytokines has broader implications for a variety of kidney diseases.[29] In a wide spectrum of glomerular and tubulointerstitial diseases, the Nlrp3 inflammasome is upregulated in both classical immune cells such as infiltrating macrophages and resident dendritic cells as well as in renal tubular epithelial cells, and even podocytes.[29] Inhibition of the Nlrp3 inflammasome ameliorates renal injury in a variety of animal models.[29] The deleterious effect of albuminuria on the proximal tubular epithelium and podocytes is, in part, mediated by inflammasome activation.[29] Therefore, developing strategies to target Nlrp3 inflammasome in diabetic nephropathy are warranted.

miRNAs IN DIABETIC NEPHROPATHY (DN)

Several miRNAs were reported to participate in the pathogenesis of DN, while others showed renal protective effects in diabetic nephropathy. To date, some miRNAs are displaying therapeutic potential with several in pre-clinical development. Thus, targeting miRNAs that are involved in diabetic nephropathy may have a good prospect in the treatment of the disease.[30,31] It was reported that the specific reduction of renal miR-192 decreases renal fibrosis and improves proteinuria, lending support for the possibility of an anti-miRNA-based translational approach to the treatment of diabetic nephropathy.[32] TGF-β1, a cytokine playing a central role in the development of diabetic nephropathy, reduced expression of the miR-29a/b/c/family, which targets collagen gene expression, and increased expression of ECM proteins.[33] miR-200a and miR-141 significantly impact on the development and progression of TGFβ-dependent EMT and fibrosis *in vitro* and *in vivo*.[34] It was also reported that overexpression of miR-21 in kidney cells enhanced, but knockdown of miR-21 suppressed, high-glucose-induced production of fibrotic and inflammatory markers. Thus inhibition of miR-21 might be an effective therapy for diabetic nephropathy.[35] One study has demonstrated that miR-21 overexpression can contribute to TGF-β1-induced EMT by inhibiting target smad7, and that targeting miR-21 may be a better alternative to directly suppress TGF-β1-mediated fibrosis in diabetic nephropathy.[36] Despite there are controversial reports about the role of miR-21 and miR-192 in the diabetic nephropathy,[37,38] miRNA-based therapies still hold great promise in ameliorating diabetic nephropathy. To date, the major obstacle to the therapeutic use of miRNAs is the delivery method. Systemic delivery of miRNAs or antagonistic miRs have been widely used, but lead to off-target effects, as this methodology may change the function of miRNAs in organs other than where pathology is targeted. To tackle this problem, kidney targeted delivery of exogenous miRNA is essential in the treatment of diabetic nephropathy.

AUTOPHAGY IN DIABETIC NEPHROPATHY

The development of metabolic diseases, such as type 2 diabetes and its complications are associated with alterations in several nutrient-sensing pathways.[17] One such nutrient-sensing pathway involves the mammalian Target of Rapamycin (mTOR), AMP-activated protein kinase (AMPK), and oxidized NAD- (NAD+-) dependent histone deacetylase (SIRT1), which are also recognized as important regulatory factors of autophagy under nutrient-depleted conditions.[17] Thus alteration of these pathways under diabetic conditions may impair the autophagic stress response, which may be involved in the development of diabetic nephropathy.[17] Indeed, treatment with rapamycin, an inhibitor of mTORC1, limits the development of diabetic nephropathy induced by Streptozotocin (STZ) in rats, which implicates a potential pathogenic role of the mTOR pathway in diabetic nephropathy.[39] One of the major upstream regulators of mTOR is AMP activated protein kinase (AMPK), a critical energy sensor. Many studies have shown that AMPK phosphorylation and activity are reduced in the renal cortex of kidneys from STZ-induced diabetic rats and db/db mice, while AMPK activators, resveratrol, metformin and AICAR attenuate renal hypertrophy, renal lipid accumulation and urinary albumin excretion.[20] SIRT1 has been shown to inhibit renal cell apoptosis, inflammation and fibrosis, and regulate lipid metabolism, autophagy, blood pressure and sodium balance.[40] As reviewed,[41] autophagy can be stimulated by multiple forms of cellular stress including growth factor deprivation, hypoxia and Reactive Oxygen

Species (ROS), which are common factors implicated in diabetic nephropathy. Hence targeting the autophagic pathway to activate and restore autophagy activity may be renoprotective. Fang, et al. reported high glucose/diabetes impaired autophagy in podocytes *in vitro* and in diabetic mice.[18] Tanaka, et al. present a compelling case for the need for studies addressing the roles of autophagy in diabetic nephropathy as these pathways are likely to be eminently suitable targets for novel therapeutic approaches.[17] Mitophagy dysfunction also contributes to the development of diabetic nephropathy. Mitochondria are the main energy-producing organelles in mammalian cells, but they also play a central role in cell injury and death signalling. Mitochondria are known to be a major intracellular source of ROS.[42] Under pathological conditions such as diabetes, uncoupling of oxidative phosphorylation and loss of mitochondrial membrane integrity induce excessive ROS production from the respiratory chain, while excessive ROS leads to further mitochondrial dysfunction and disruption.[43] Oxidative damage and the associated mitochondrial dysfunction may result in energy depletion, accumulation of cytotoxic mediators and cell death. Mitophagy, a biological process of autophagic removal of damaged mitochondria, is important as dysfunctional mitochondria may enhance cellular oxidative stress, generate apoptotic signals, and induce cell death. To date, autophagy is the sole known mechanism for mitochondrial turnover. Fragmented mitochondria are engulfed by autophogasomes *via* mitophagy and emerging evidence has suggested mitochondrial fragmentation is characteristic of renal diseases, including diabetic nephropathy.[42] In response to reduced cellular ATP, AMPK is activated, which phosphorylates ULK1 and ULK2 (two Atg1 homologues) to activate both general autophagy and mitophagy. In response to stress, induction of mitophagy results in selective clearance of damaged mitochondria in cells. Autophagic removal of damaged mitochondria requires two steps: induction of general autophagy and priming of damaged mitochondria for selective autophagic recognition, mediated either by the Pink1-Parkin signalling pathway or the mitophagic receptors Nix and Bnip3.[44] Dysfunction of mitochondria in diabetic kidneys has been well reviewed.[42,45] Studies from animal models indicate that disturbances in mitochondrial homeostasis are central to the pathogenesis of diabetic kidney disease.[46] Collectively, functionally restoring the autophagy and mitophagy in kidney may be an effective strategy to arrest the progression of diabetic nephropathy. However, to date there is not specific pharmacological activator or inducer of autophagy and mitophagy available.

In conclusion, the complications of diabetes mellitus, such as nephropathy, parallel its rapidly increasing incidence with resultant devastating personal and societal impacts. A successful continuum between innovative discovery science and rigorous translation of research findings is required to limit the development, and improve the outcomes of patients with existing diabetic nephropathy. However, diabetic kidney disease is complex and multifactorial and the current therapies are largely ineffective, therefore there is increasing urgency to identify novel therapeutic targets that will allow more precise control over disease development and progression. In addition to optimal control of hyperglycaemia, hypertension and albuminuria, novel strategies to target chronic inflammatory signalling pathways, restore function of autophagy and mitophagy, and kidney-specific deliver miRNA in kidney would be future directions for the treatment of diabetic nephropathy.

CONFLICTS OF INTEREST

We declare there are no conflicts of interest.

ACKNOWLEDGMENT

This work was supported by the Juvenile Diabetes Research Foundation International.

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