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REVIEW

Autophagy, Pyroptosis and Ferroptosis are Rising Stars in the Pathogenesis of Diabetic Nephropathy

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Abstract: Diabetic nephropathy (DN) is one of the most common microvascular complications in diabetes and can potentially develop into end-stage renal disease. Its pathogenesis is complex and not fully understood. Podocytes, glomerular endothelial cells (GECs), glomerular mesangial cells (GMCs) and renal tubular epithelial cells (TECs) play important roles in the normal function of glomerulus and renal tubules, and their injury is involved in the progression of DN. Although our understanding of the mechanisms leading to DN has substantially improved, we still need to find more effective therapeutic targets. Autophagy, pyroptosis and ferroptosis are programmed cell death processes that are associated with inflammation and are closely related to a variety of diseases. Recently, a growing number of studies have reported that autophagy, pyroptosis and ferroptosis regulate the function of podocytes, GECs, GMCs and TECs. This review highlights the contributions of autophagy, pyroptosis, and ferroptosis to DN injury in these cells, offering potential therapeutic targets for DN treatment.

Keywords: diabetic nephropathy, autophagy, pyroptosis, ferroptosis, inflammation

Introduction

With the development of society and changes in lifestyle, the prevalence of diabetes has been steadily rising in recent years.[1,2] The statistics from the International Diabetes Federation show that in 2021, the number of diabetic patients worldwide reached 536 million.[3] The prevalence of diabetic complications is also increasing. As one of the most common microvascular complications of diabetes, the prevalence of diabetic nephropathy (DN) in the late stages of diabetes is almost 50%.[4,5] Due to these trends, DN has become a serious public health problem in the world.[6]

DN is a complex and chronic disease characterized by glomerular hyperfiltration, hyperperfusion, thickening of the glomerular basement membrane, glomerular capillary injury, mesangial expansion, and microalbuminuria.[7,8] In the early stages of DN, the volume of the kidney increases and the glomerular filtration rate increases. As the disease progresses to the middle stages, the basement membrane thickens and the mesangial matrix increases. This leads to glomerular nodular and diffuse lesions, arteriolar hyaline degeneration, further thickening of the glomerular basement membrane, and progressive stenosis of the glomerular capillary cavity. In the late stages, glomerular and tubulointerstitial fibrosis occurs, resulting in glomerular atrophy and ultimately renal failure. Multiple studies have shown that the regulation of inflammation, endoplasmic reticulum stress (ERS), oxidative stress and other related proteins plays crucial roles in the progression of DN.[8–13] Furthermore, certain regulatory factors can promote the transformation of endothelial cells into mesenchymal cells, a process known as epithelial-mesenchymal transition (EMT). This process plays a significant role in the development of renal fibrosis in DN. Additionally, recent studies have highlighted the dysfunction of cell junction proteins in podocytes, glomerular endothelial cells (GECs), glomerular mesangial cells (GMCs), and renal tubular epithelial cells (TECs) as key players in DN pathogenesis.[14–17] Despite ongoing research, the pathogenesis of DN remains incompletely understood due to its complexity. Therefore, elucidating the underlying mechanisms of DN and identifying therapeutic targets have both emerged as crucial strategies for effective DN treatment.

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Autophagy, an intracellular degradation process, plays a pivotal role in maintaining cellular homeostasis.[18,19] It is involved in the pathogenesis of numerous diseases, including diabetes,[20] DN,[9] and cardiovascular disease.[19] Pyroptosis, a distinct form of programmed cell death, differs from apoptosis both morphologically and mechanistically. It is characterized by the formation of inflammasomes and the production of pro-inflammatory caspases.[21–23] Pyroptosis has been implicated in a range of diseases, including atherosclerosis, diabetes, and DN.[10,24] Ferroptosis, another type of programmed cell death, is characterized by iron-dependent accumulation of lipid hydroperoxides to lethal levels.[25]

The role of inflammation in the onset and progression of DN is well-documented.[7,12] Inflammation markers such as C-reactive protein, kidney injury molecule-1, serum uric acid, monocyte/lymphocyte ratio in hemogram, systemic inflammatory index, and uric acid/HDL cholesterol ratio have been associated with DN.[25–29] Autophagy, a cellular process that maintains homeostasis, has been shown to suppress inflammation, thereby protecting the kidney.[30] On the other hand, both pyroptosis and ferroptosis are forms of programmed cell death that are associated with inflammation.[31] Diabetes mellitus and its microvascular complications are associated with high burden of inflammation.[32,33] Given the central role of inflammation in DN, it is logical to investigate autophagy, pyroptosis, and ferroptosis in the context of this disease. Elucidating the contributions of these cellular processes in DN may offer valuable insights into potential therapeutic strategies for managing this condition. Besides, recent studies indicate that autophagy, pyroptosis, and ferroptosis of podocytes, GECs, GMCs, and TECs are involved in the occurrence and development of DN. A thorough examination of the uniqueness and correlation among autophagy, pyroptosis, and ferroptosis in the injury pathways of these cell types could lead to the identification of novel therapeutic targets for the prevention and treatment of DN.

Autophagy and DN

The autophagy process is essential for maintaining the homeostatic balance of cellular components, as it regulates their synthesis, degradation, and recirculation. This multistep regulation is orchestrated by various signaling pathways, including phosphatidylinositol 3-kinase (PI3K) -AKT-mTOR signal pathways, AMP-activated protein kinase (AMPK) signal pathway and nuclear factor kappa-B (NF-κB) signal cascades.[18] Under physiological conditions, an appropriate amount of autophagy maintains the stability of its structure and function. However under pathological conditions, autophagy dysregulation can lead to cellular dysfunction and contribute to the development of various diseases, including DN,[9] cardiovascular disease,[19] diabetes[20] and others.

The main pathological features of DN are podocytes, GECs, GMCs, TECs injury, which eventually develops into glomerular and tubulointerstitial fibrosis.[10] These injuries are driven by various mechanisms such as glucolipotoxicity, inflammation, apoptosis, oxidative stress, and mitochondrial dysfunction.[7,10] Autophagy plays a crucial role in maintaining intracellular homeostasis, and its dysfunction has been implicated in the pathogenesis of DN. Notably, glucagon like peptide-1 (GLP-1) has been shown to alleviate kidney damage in DN rats by promoting autophagy through the activation of the PI3K/AKT/mTOR pathway.[34] Similarly, oral butyrate has been found to alleviate damage in diabetic rats, possibly by enhancing autophagy via the AMPK/mTOR signaling pathway.[35] These studies provide evidence that autophagy plays a key role in the progression of DN and that modulating autophagy may offer therapeutic potential for reducing renal damage. Therefore, in this section, we aim to review and discuss the recent research progress on autophagy in podocytes, GECs, GMCs, and TECs. We focus on elucidating the role of autophagy in the progression of DN and exploring potential therapeutic targets.

Autophagy and Podocytes

Podocytes, as highly specialized glomerular epithelial cells, play a crucial role in maintaining glomerular structure and function. The initial pathological manifestation of DN often involves a decrease in podocyte number, followed by their detachment, which further exacerbates glomerular injury. It is reported that autophagy dysfunction is one of the important mechanisms causing homeostatic imbalance in podocytes. Regulating podocyte autophagy can protect against glomerular injury and improve renal function.[36,37] SPAG5-AS1 gene knockout can inhibit apoptosis and induce autophagy via suppressing AKT/mTOR pathway, reducing podocyte injury induced by high glucose (HG).[38] Adipose-derived stem cell-derived exosomes enhance the expression of miR-486, thereby inhibiting the Smad1/mTOR signaling pathway, and enhancing autophagy flux to reduce podocyte damage.[39] Besides, studies have shown that multiple drugs can improve

DN by promoting podocyte autophagy. Exogenous spermine ameliorates podocyte autophagy by regulating the AMPK/mTOR signaling pathway, alleviates podocyte injury, and improves serum creatinine, urea and urinary albumin excretion in diabetic rats.[36] Curcumin and ursolic acid induce podocyte autophagy and alleviate renal oxidative stress through PI3K/AKT/mTOR pathway, thereby improving renal function in diabetic rats.[37,40] Astragaloside-IV via the SIRT1/NF-κB pathway induces autophagy to inhibit glucose-induced EMT of podocytes and to improve function in DN mice.[41] Collectively these studies suggest that improving podocyte autophagy can serve as an important target for the treatment of DN.[36,37]

Autophagy and Glomerular Endothelial Cells

GECs, as a crucial component of the glomerular filtration barrier, play a pivotal role in maintaining renal health. Upon injury, GECs exhibit an elevated level of proteinuria, indicating compromised glomerular function. This injury further exacerbates autophagy and senescence, leading to dysfunction of GECs. Such dysfunction has been implicated in the pathogenesis of renal microvascular disease and may promote the development of DN.

The electron microscopy findings indicate that in streptozotocin-induced diabetic rats, there is a significant decrease in both the volume and numerical densities of autophagic vacuoles in proximal tubular cells compared to the control group.[42] Yoshibayashi et al suggest that autophagy-deficient mice can lead to GECs injury and severe proteinuria.[43] In ATG5-deficient diabetic mice, proteinuria levels are significantly elevated compared to controls. The electron microscope results show that the cytoplasmic structure of GECs is disordered and vacuolized, which further proves that GECs autophagy deficiency aggravated the DN process.[44] Inhibition of autophagy diminishes GEC viability. Additionally, heat-aggregated gamma globulin inhibits GECs autophagy through the AKT/mTOR pathway, further compromising cell survival and exacerbating renal injury.[45] Cinacalcet elevates intracellular Ca^{2+} concentration and activates Ca^{2+}/calmodulin-dependent protein kinase β, leading to the phosphorylation of liver kinase B1 and downstream signaling. This cascade ultimately enhances autophagy, reduces oxidative stress and apoptosis, and protects GECs and DN in mice exposed to HG.[46] Spironolactone mitigates podocyte adhesive capacity damage induced by mechanical stress by blocking the PI3K/AKT/mTOR pathway and restoring autophagy activity.[47] These findings collectively underscore the crucial role of autophagy in maintaining the structural and functional integrity of GECs.

Autophagy and Glomerular Mesangial Cells

The death and aging of GMCs indeed exacerbate the progression of DN. HG can stimulate human GMCs proliferation, extracellular matrix accumulation, and oxidative stress.[48] Astragaloside-IV, a compound that targeting the silent information regulator 1 (SIRT1)-NF-κB pathway, has been shown to induce autophagy and enhance GMCs viability, improving glomerular morphology and renal fibrosis in DN mice.[49] On the other hand, aging can inhibit autophagy and promote GMCs senescence through the RAGE/STAT5 pathway.[50] Metformin effectively ameliorates glycolipid metabolism and renal damage in diabetic rats by activating the AMPK/SIRT1-FOXO1 pathway. This activation not only alleviates oxidative stress but also enhances autophagy, slowing down the abnormal proliferation of HG cultured GMCs.[51] Fibroblast growth factor 21 ameliorates autophagy levels, thus preventing mesangial cells overproliferation via the AMPK/mTOR pathway.[52] Trigonelline induces autophagy to protect mesangial cells in response to HG via activating the miR-5189-5p-AMPK pathway.[53] Ginkgetin alleviates HG-induced GMCs oxidative stress injury, inflammation, and extracellular matrix deposition through AMPK/mTOR signal pathway mediated autophagy.[54] Collectively, these findings suggest that targeting autophagy and its associated signaling pathways may provide therapeutic strategies for mitigating GMCs death and the progression of DN.

Autophagy and Renal Tubular Epithelial Cells

Oxidative stress, inflammation, ERS and hypoxia can cause TECs damage, leading to renal interstitial fibrosis and the decline of renal function.[55–60] This damage is further exacerbated by the dysregulation of autophagy, as observed in the proximal tubules of streptozotocin-induced diabetic models and HG-induced Human renal glomerular endothelial cells (HRGECs) HK-2 cells.[61] ATG7 knockout mice, which exhibit defective autophagy in renal proximal epithelial tubular cells, result in increased renal cell damage.[62] In HG-cultured NRK-52E cells and DN mice, the inhibition of ATF4 can

ameliorate DN tubulointerstitial fibrosis by improving autophagy flux and decreasing collagen type-IV levels.[14] Cotreatment with molybdenum and autophagy inhibitor 3-methyladenine (3-MA) significantly increase lactate dehydrogenase release, reactive oxygen species (ROS) level, and cell injury, indicating that autophagy inhibition can exacerbate TECs damage and further worsen renal function.[63] Metformin promotes autophagy of TECs through AMPK, thereby reducing tubular interstitial fibrosis.[64] Besides, traditional medicine Red Ginseng has been shown to reduce the expression of TGF-β1 and kidney injury molecule-1 by inducing autophagy, and then alleviate renal inflammation and fibrosis caused by hyperglycemia.[65] Collectively, these findings suggest that autophagy plays a crucial role in maintaining TEC health and preventing renal fibrosis. Therapeutic strategies aimed at restoring or enhancing autophagy may offer new avenues for treating renal damage and dysfunction.

Podocytes, GECs, GMCs and TECs damage are all involved in DN progression. Damage to these cell types plays a significant role in the development and progression of DN. These studies indicate that inhibition of autophagy aggravates renal injury and promotes the progression of DN. Fortunately, some drugs have shown that regulating autophagy can improve renal function in DN. For instance, Metformin can improve renal function by promoting autophagy.[51,64] GLP-1 analog liraglutide can upregulate autophagy in vivo and in vitro through the AMPK/mTOR signaling pathway.[66] Subcutaneous injection of insulin with liraglutide alleviates oxidative stress and activates autophagy, which not only restored renal morphology but also significantly improved renal hemodynamics.[67] Given the substantial interest in developing therapies that enhance autophagy as means of treating DN, further study of autophagy in this setting may lead to fruitful results.

Pyroptosis and DN

Pyroptosis can be activated by Caspase-1 and induce an inflammatory response, leading to cell membrane rupture and dissolution. The molecular mechanisms of pyroptosis[21] mainly include classical cell pyroptosis mediated by Caspase-1, non-classical pyroptosis mediated by Caspase-11/-4/-5 and by Caspase-3. The activation of Caspase-1 is the core of the classical pyroptosis pathway, a defence mechanism against pathogenic microbial infection, and an important part of the natural immune system. Caspase-11/-4/-5 can directly recognize and bind lipopolysaccharide (LPS) and act on GSDMD (gasdermin d) to release active N-terminal domain (GSDMD-N); In addition, Caspase-11 also activates the inflammasomes of nod like receptor protein-3 (NLRP3) and downstream caspase-1, resulting in the release of inflammatory factors and promoting pyroptosis. Caspase-1 mediates pyroptosis by activating GSDMD. Inflammasomes are produced during pyroptosis, which can induce tumor pyroptosis and inhibit tumor cell proliferation. Pyroptosis is a physiological state that can promote the immune response against infection, but excessively activate pyroptosis leads to GSDMD activation and numerous inflammatory cytokines such as interleukin (IL)-1β and IL-18 release, which can cause cell death, tissue damage, organ failure, and even cause diabetes, cause irreversible damage to the body.[11,21–24]

Pyroptosis has been implicated in a wide range of diseases such as diabetes, DN and infectious diseases.[11,21,24] The expression of Caspase-1 and GSDMD in renal tissue of DN mice increased significantly.[68] A series of researches have indicated that inhibiting pyroptosis can reduce the damage to podocytes,[68] GECs,[69] GMCs[70] and TECs.[71]

Pyroptosis and Podocytes

Podocyte injury plays a crucial role in the early stages of DN. The expression of Caspase-11, Caspase-4 and GSDMD-N in podocytes is increased significantly in DN mice, the loss and fusion of podocyte foot processes, and elevated inflammatory cytokines IL-1β and IL-18, suggesting increased podocyte pyroptosis in DN.[72,73] Similar results are obtained in vitro models of DN.[72] Knockout of Caspase-11, Caspase-4 or GSDMD gene can attenuate the above changes in diabetic mice, proposing that inhibiting pyroptosis can ameliorate podocyte damage in DN.[73] Moreover, studies have shown that multiple drugs can improve DN not only by promoting podocyte autophagy but also by alleviating podocyte pyroptosis. High-glucose can induce mouse podocyte line MPC5 cells pyroptosis and oxidative stress.[74] Further, atorvastatin protects MPC-5 cells from pyroptosis and downregulates the level of renal oxidative stress through MALAT1/miR-200c/NRF2 signal pathway.[75] Carnosine can significantly reverse the albuminuria and histopathological lesions damage of the DN mouse model and reduce renal inflammation and pyroptosis via the targeting of Caspase-1.[68] The administration of geniposide to DN mice through AMPK/SIRT1/NF-κB pathway inhibits podocyte pyroptosis,

oxidative stress and inflammation, and reduces glomerular basement membrane thickening and inflammatory cell infiltration, thereby inhibiting the development of DN.[75] In vitro studies have shown that high fat can induce NLRP3 dependent pyroptosis of podocytes. Ginsenoside Rg1 inhibits pyroptosis through the mTOR/NF-κB/NLRP3 axis and protects podocytes from damage induced by hyperlipidemia.[76] Total flavones of Abelmoschus Manihot (TFA) have been widely used to treat DN. Further research reveals that TFA can ameliorate podocytes pyroptosis under diabetic conditions by regulating METTL3-dependent methyladenosine modification and downregulating NLRP3-inflammasome formation and PTEN/PI3K/AKT axis.[77] All these results suggest that podocyte pyroptosis is involved in the development of DN.

Pyroptosis and Glomerular Endothelial Cells

The whole process of DN is accompanied by GECs injury. Hyperglycemia, inflammation, ERS and oxidative stress can lead to endothelial cell injury. High-glucose can induce pyroptosis of human endothelial cells, accompanied by an increase in NLRP3 inflammatory bodies.[78] This finding is further supported by another study, which demonstrates that high-glucose/LPS and ATP enhance the release of pyroptosis-related factors IL-18 and IL-1β in GECs.[69] Besides, the deletion of GSDMD reduces pyroptosis and kidney injury both in-vivo and in-vitro.[69] Gu et al reported that high-glucose increases GSDMD-N and IL-1β, IL-18, which induces GECs pyroptosis.[79] And sodium butyrate can improve GECs pyroptosis under diabetic conditions through Caspase1-GSDMD typical pyroptosis pathway.[79] Hirudin has been found to ameliorate renal injury in DN. Further studies show that Hirudin significantly ameliorates the GECs injury by inhibiting GSDMD-mediated pyroptosis.[69] Collectively, these findings suggest that GEC pyroptosis plays a pivotal role in the pathogenesis of DN. Therapeutic strategies that target GEC pyroptosis may offer promising avenues for the treatment of this debilitating disease.

Pyroptosis and Glomerular Mesangial Cells

Another study shows that streptozotocin-induced diabetic rats exhibit increased expression of Caspase-1, NLRP3, and IL-1β.[70] This is consistent with the latest findings that high-glucose promotes the expression of Caspase-1, NLRP3, and IL-1β in GMCs.[70,80] Sodium butyrate, through the NF-κB signaling pathway, reduces LPS and high-glucose-induced IL-1β expression in GMCs.[79] These results suggest that GMCs pyroptosis is involved in the development of DN.

Pyroptosis and Renal Tubular Epithelial Cells

Hyperglycemia, proteinuria and oxidative stress can aggravate renal tubular injury.[7,81,82] Changes such as apoptosis and interstitial fibrosis of TECs further lead to the decline of renal function and aggravate the process of DN.[10] In diabetic rats, renal function is significantly impaired, accompanied by NLRP3-dependent pyroptosis, while high-glucose-induced expression of TECs pyroptosis-related proteins is increased.[11,83] Reducing the expression of pyroptosis-associated protein can reduce the damage to renal function.[11] High-glucose increases the expression of NLRP3, Caspase-1 and IL-1β and IL-18 in HK-2 cells, promotes TECs pyroptosis and induces renal tubular injury.[71] Another study is verified that high-glucose could induce NLRP3, Caspase-1, and IL-1β expression in HK-2 cells. In addition, high-glucose also induced the expression of pyroptosis-related executive protein GSDMD.[84] Inhibition of ROS/NLRP3/Caspase-1 mediated pyroptosis can reduce cadmium-induced apoptosis of duck TECs, suggesting that inhibition of pyroptosis can reduce TECs injury.[85] Selective Caspase-1 inhibitors VX-765 ameliorates ballooned cell membrane, decreases the expression of GSDMD cleavage, and the release of inflammatory cytokines in high-glucose induced HK-2 cells. On the other hand, VX-765 treatment can improve renal function, inhibit inflammatory cell infiltration and pyroptosis-related protein expression. Therefore VX-765 can downregulate collagen I and fibronectin deposition in DN mice to alleviate tubulointerstitial fibrosis.[15] Pyroptosis upregulated TECs adhesion protein 1 (VCAM1) expression under high-glucose, while disulfiram treatment abrogating pyroptosis inhibited VCAM1 expression, inflammation and fibrosis in HK-2 cells. Disulfiram might improve fibrosis in DN by targeting renal tubular pyroptosis and VCAM1 expression.[16] The above studies show that pyroptosis is closely related to TECs injury, and inhibition of TECs pyroptosis is expected to become an important target for reducing DN, suggesting that pyroptosis can be an important target for treating DN.

In summary, the pyroptosis of podocytes, GECs, GMCs and TECs is significantly activated in the diabetic state, and inhibiting pyroptosis can prevent the progression of DN, it can effectively inhibit the development of DN. The specific

targets of action and related pathways have yet to be further explored, and the mechanism of pyroptosis itself also needs to be explored. In the future, we may be able to find a cure for diabetic nephropathy with pyroptosis as the target.

Ferroptosis and DN

Ferroptosis is a new type of programmed cell death which has attracted widespread attention in recent years. It mainly refers to cell death caused by excessive accumulation of lipid peroxides under iron-dependent overload. Multiple factors are involved in the occurrence of ferroptosis including iron metabolism disorders, Cystine/glutamate reverse transporter/ glutathione (GSH)/glutathione peroxidase 4 (GPX4) pathway abnormality, oxidative stress, lipid peroxidation, tumor suppressor p53 targeted induction.

Ferroptosis is involved in many diseases such as diabetes,[86] diabetic cardiomyopathy,[87] DN[88] and diabetic retinopathy.[89] HG and palmitate trigger ferroptosis in mouse pancreatic β cells and mouse islets through decreased the level of expression of GPX4 and increased the level of expression of anti-acyl-CoA synthetase long-chain family member 4(ACSL4) while metformin is effective in inhibiting pancreatic β cells and mouse islets ferroptosis through regulation of the GPX4/ACSL4 axis.[86] Palmitate induces cardiomyocytes ferroptosis, astragaloside IV ameliorated myocardial injury and improved contractile function, attenuated lipid deposition, and decreased the expression level of ferroptosis-related factors in DCM rats and cellular ferroptosis.[87] Ferroptosis is increased in HG-treated HK-2 cells. ACSL4 is increased in kidney tissues of DN mice.[88] HG stimulation increased those of MDA, ROS, GSSG, and Fe in HRECs.[89] Mounting studies suggest that ferroptosis plays an important role in kidney cells injury and is one of the key mechanisms to induce DN, supporting that ferroptosis could be a potential therapeutic target for DN.[90,91] The marker of ferroptosis, GPX4, is decreased in db/db mice and T2D patients, which means ferroptosis plays a pathophysiologic role in DN,[68] which means ferroptosis might serve as a target for treating DN. In this section, we mainly separately discuss the role of ferroptosis in podocytes, GECs, GMCs and TECs.

Ferroptosis and Podocytes

HG induces podocytes injury by stimulating podocyte ferroptosis.[92] Besides, high fructose feeding and intraperitoneal injection of STZ is helpful for establishing DN model.[93] High fructose consumption induces podocyte ferroptosis in glomerular injury (main features include low-expression of ferroptosis protein markers SLC7A11 and GPX4, lipid peroxidation accumulation and cell death).[94] Accumulating evidence suggests that some medicines can modulate ferroptosis in podocytes and show great potential for improving DN. Ginkgolide B alleviates ferroptosis in palmitic acid-high-glucose induced podocytes and DN mice through inhibiting GPX4 ubiquitination to improve DN.[95] Germacrone possesses anti-inflammation, anti-apoptotic and antioxidative effects. Germacrone plays a pivotal role in the progression of DN. Recent study reveals that germacrone mediates the improvement of DN through regulating ferroptosis by targeting miR-188- 3p/GPX4 signaling axis.[96]

Ferroptosis and Glomerular Endothelial Cells

More and more studies have shown that HG induces ferroptosis of endothelial cells participates in diabetes retinopathy,[89] diabetes atherosclerosis,[97] diabetic wounds,[98] and diabetes-related limb ischemia.[99] Previous studies have shown that glomerular endothelial cells ferroptosis plays an important role in the pathophysiological process of DN.[100–102] HG induced ferroptosis in an in vitro model of DN by increasing iron concentration in HRGECs. Traditional Chinese medicine, Schisandrin A attenuates ferroptosis in HG induced HRGECs.[100] Another study also suggests that high glucose-induces ferroptosis in HUVECs, as evidenced by the protective effect of the ferroptosis inhibitors, deferoxamine and ferrostatin-1, resulting in increased lipid ROS and decreased cell viability.[101]

Ferroptosis and Glomerular Mesangial Cells

Previous study has shown that ferroptosis activated in DN patients and in mesangial cells in response to HG.[102] The research results indicate that the release of serum ferritin, LDH and ferroptosis-related proteins ACSL4, GPX4 are elevated in DN patients and HG-induced renal mesangial cells.[102] Besides, galactose deficient IgA1 leads to ferroptosis in human mesangial cells by inhibiting PPARα and FABP1 expression. Levels of GPX4 were decreased in

immunoglobulin A nephropathy renal tissue, which means ferroptosis plays a key role in the processes of IgA nephropathy.[103] Senescence is closely related to DN.[104,105] Aging causes iron overload in renal tubules. Salidroside is a phenylpropanoid glycoside and acts as an anti-oxidative, anti-inflammatory, anti-aging, and alleviates renal interstitial fibrosis. Studies have suggested that salidroside delays renal aging and inhibits aging-related glomerular fibrosis by inhibiting ferroptosis in SAMP8 mice.[106] Ferroptosis inhibitor ferrostatin-1 increased the expression of GPX4 in the mouse kidneys.[106]

Ferroptosis and Renal Tubular Epithelial Cells

HG injures rat renal tubular epithelial NRK-52E cells by triggering ferroptosis as demonstrated by the accumulation of iron content and down-regulation of GPX4, SLC7A11, indicators of ferroptosis.[107] Another study also suggests that the GPX4 protein expression and GSH activity levels are decreased in HG induced HK-2 cells. Circular ASAP2 through SLC7A11 decreases the inflammation and ferroptosis in DN.[108] Traditional Chinese Medicine glabridin ameliorates DN via suppressing ferroptosis in diabetic rats' kidney and HG-induced NRK-52E cells.[107]

The above studies have explained the important role of ferroptosis regulated by related signaling pathways in the occurrence and development of DN at different cellular levels, indicating that the interaction between different cells in kidney tissue may provide clues to the pathogenesis of DN and targeting ferroptosis could provide a new way to prevent and treat DN.

Conclusions

In recent years, autophagy, pyroptosis and ferroptosis have attracted increasing attention, and have become a research focus in DN and other diseases. Besides, some drugs such as metformin and a large number of Chinese herbal medicines can improve DN by regulating autophagy, pyroptosis and ferroptosis, further proving that autophagy, pyroptosis and ferroptosis can be used as a star target for treating DN. However, the specific mechanism still needs to be further studied. Therefore, seeking targets that can act on autophagy and pyroptosis of podocytes, GECs, GMCs and TECs at the same time is expected to become a breakthrough in the treatment of DN.

Abbreviations

AMPK, AMP-activated protein kinase; DN, diabetic nephropathy; EMT, epithelial-mesenchymal transition; ERS, endoplasmic reticulum stress; GECs, glomerular endothelial cells; GMCs, glomerular mesangial cells; GSDMD, gasdermin d; HK-2, human renal tubular cell lines; IL, interleukin; PI3K, phosphatidylinositol 3-kinase; TECs, renal tubular epithelial cells; NLRP3, nod like receptor protein-3; ROS, reactive oxygen species; SIRT1, silent information regulator 1; VCAM1, vascular cell adhesion protein 1; 3-MA, 3-methyladenine.

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Disclosure

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