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Review

Cell junction proteins: Crossing the glomerular filtration barrier in diabetic nephropathy

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ABSTRACT

Diabetic nephropathy as a deleterious complication of diabetes mellitus and an important cause of end-stage renal failure is characterized by changes in the molecular and cellular levels. Cell-cell communication via the gap and tight junctions are involved in the pathogenesis of diseases such as diabetes and kidney failure. Studying cell junctions including gap junctions, tight junctions, and anchoring junctions within the nephron can be used as an early sign of diabetic nephropathy. Furthermore, cell junctions may be an upcoming target by pharmacological methods to improve treatments of diabetic nephropathy and pave the way to introduce promising therapeutic strategies based on cell-cell communications effects and its translation into clinical studies for the treatment of diabetic nephropathy.

Contents

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1. Introduction

Diabetic nephropathy (DN) or diabetic kidney disease is the most prevalent acquired reason of diabetes disease (both type 1 and type 2), which results in end-stage renal disease (ESRD) and eventually the renal replacement therapy [60]. Based on the accessible evidence, the pathogenesis of DN is multifactorial. Diabetic nephropathy is a risk factor for bacterial infections [74,81,101]. The incidence of DN can be owing to the interaction between both genetic and environmental factors in diabetic patients. It should be considered that some of the morphological and functional abnormalities like glomerular hyperfiltration [95], natriuresis [73], and proteinuria [111] are the momentous consequences of DN.

Glomerular hyperfiltration is a well-established mechanism involved in DN and glomerular vessels. A deteriorated vascular resistance of the afferent arteriole can be a proposed reason for glomerular hyperfiltration [75]. Natriuresis is another distinguishing subsequence of DN, which is the process of sodium excretion by the action of kidneys in the urine. Natriuresis not only can decrease sodium level in the blood but also can reduce blood volume [103].

The glomerular filtration barrier (GFB) is critical for the ultrafiltration process and composed of three cellular layers including glomerular basement membrane (GBM), highly specialized podocytes, and the fenestrated endothelium. The podocytes and their specific junctions, called slit diaphragm (SD) form the backbone of this assembly. The presence of excess proteins in the urine referred to as proteinuria, specifies a defective GFB and a crucial parameter for the progression of DN, which is specifically related to inflammation [51]. Recent clinical studies have been displayed that this complication is a representation of the underlying glomerular injury as well as the contribution of tubular and interstitial damage via abnormal filtration of proteins and activation of cellular responses to the renal injury itself [22,85].

Dysregulation of cell junction intercellular communication is a causative factor in DN. The clarification of the simultaneous interactions between glomerular endothelial cells, podocytes, and GBM sets the platform for a greater understanding of the pathophysiology of kidney dysfunction in DN [65]. This review outlines growing evidence that cell junctions offer a viable future therapeutic target for the control and treatment of DN.

2. Pathophysiology of DN

Hyperglycemia induces inflammation, oxidative stress, and glomerular hyperfiltration. Higher intracellular glucose influences different signaling pathways including an increase in TGF-β, activation of the renin-angiotensin-aldosteronesystem (RAAS), protein kinase C/diacylglycerol pathways, polyol pathway, hexosamine pathway, advanced glycation end-product (AGEs) accumulation, and increased reactive oxygen species (ROS) [58,93]. These events cause various abnormal responses in different renal cells including endothelium, podocyte, mesangial, and tubular cells [58].

In the glomerular endothelial cells, diabetes affects the production of angiopoietin 2, nitric oxide, and glycocalyx, leading to endothelial injury as well as reduced fenestration and charge barrier. In podocytes, reduced expression of VEGF (vascular endothelial growth factor) and insulin signaling, Wnt signaling, angiotensin II, AGEs, and an increase in mTOR (mechanistic target of rapamycin) signaling cause changes in either the function, structure, or their number in the glomerulus; resulting in podocyte hypertrophy, epithelial-mesenchymal transdifferentiation (EMT), apoptosis, and detachment [8,15,58]. Additionally, in tubular cells, inflammation, hypoxia, and fibrosis cause changes in the ECM (extracellular matrix) and tubulointerstitial fibrosis [2,58]. DN eventually results in disruption of the GFB, thickened GBM, high capillary permeability, glomerular hypertrophy, mesangial expansion, and kidney fibrosis [2]. Since these cell types in the kidney are tightly connected, dysregulation of cell junctions and dysfunctions in one section can spread to other cells and promote diabetic kidney disease [58].

3. General features of cell junctions

In this section, we outline the general features of cell junctions including tight, gap, and anchor junctions.

3.1. Tight junction general

Tight junctions (TJs), also known as zonula occludens (ZO-1 and ZO-2), are protein structures regulating the exchange of substances via the paracellular pathway. Transmembrane proteins (e.g., occludin [99], junctional adhesion molecules (JAMs) [47], and claudins [109]) and scaffolding proteins (cingulin, ZO-1, -2, -3, MAGI-1, -2, -3) that connect the integral membrane proteins to the actin cytoskeleton are localized at TJs [23,82].

Occludin was identified as the first integral membrane protein by Furuse et al., possessing four transmembrane domains: two extracellular loops and long amino- and carboxy-terminal cytoplasmic domains [24]. The expression of occluding occurs in the tubular sections of a nephron. Since this membrane protein is virtually expressed by all epithelial cells, its physiological role is not confined to the tight junction. It could be involved in cell polarity, directional migration and wound healing as well [19].

JAMs, a group of glycoproteins with two immunoglobulin-like domains, are another major tight junction proteins that were detected not only in the tight junctions of endothelial and epithelial cells but also on the membrane of circulating leukocytes and platelets [20]. JAM proteins family contains five member including JAM-A, JAM-B, JAM-C, JAM4 and JAML. They are associated with immunoglobulin superfamily. Their structure contains 4 main parts. The extracellular part consists of a short N-terminal signal peptide and two extracellular Ig-like loops that are connected by a single membrane-spanning segment to a short cytoplasmic tail. The cytoplasmic tail itself consists of consensus phosphorylation sites and a C-terminal PDZ (PSD-95/Discs-Large/ZO-1)-binding motif [59]. It is well documented that JAMs are important in regulating cell polarity, leukocyte/platelet-endothelium interactions, and inflammatory responses [76]. Claudins, a family of tetraspan proteins at the range of 20–28 kDa, are generally referred to as the major expressed components glomerulus with a pivotal role in paracellular charge selectivity between epithelial cells. These proteins are categorized as barriers or pore proteins since their expression can increase or reduce the ionic permeability of epithelial, respectively. The former is expressed in tighter distal sections, while the latter is accompanied by leakier tubule sections [97]. These proteins possess four transmembrane domains: two extracellular loops, amino- and carboxy-terminal cytoplasmic domains and a short cytoplasmic turn [67]. A sequence of approximately 50 amino acids with a common motif (-GLWCC; PROSITE ID: PS01346) constructs the first extracellular loop (ECL1) of claudin [3], and also intercalating negative [14] and positive [52] charges, participating in paracellular ion selectivity via electrostatic effects. The second extracellular loop (ECL2) usually comprise of 25 amino acids mediating trans-claudin interactions and also claudin interactions with the *Clostridium perfringens* enterotoxin through a predicted helix-turn-helix motif [66]. The small domains that are called PDZ (postsynaptic density 95/discs large/zonula occludens-1) form the C-terminal domain of claudin. Indeed, PDZ is 80–100 amino acids protein domains with ability binding to C-terminal residues of partner proteins, which can regulate interactions with the submembrane scaffold protein, ZO-1 as well as correct localization in the tight junction (24). Claudin polymerization into TJs strands require ZO-1 [40].

3.2. Gap junctions

Gap junctions are specific intercellular connections and are composed of two adjacent connexons or hemichannels on neighboring cells. Connexons are the assembly of six connexins that form a 1–2 nm diameter aqueous pore which allows a bidirectional flow of ions and small molecules [1,30]. Connexins, as transmembrane proteins, perform a vital role in the development of intercellular connections. Until now, 21 genes have been introduced, which are related to connexins family. The mentioned genes have been named based on their molecular weight and it is assumed that every cell in the whole body has a partial expression of these genes. Expression of CX32 has been seen in several cells, such as cardiomyocytes, nephrocytes, hepatocytes, and some other specialized cells. While CX62 expression takes place only in retinal tissue [68]. Insertion and spatial arrangements of connexin polypeptides in the bilayer cell membrane are similar to other membrane-bound proteins [53]. Connexins have a remarkable production and destruction frequent cycle that brings the precise regulation of channel activity and gap junction-mediated cell communication [53]. All connexins illustrate the same structural topographies in which two extracellular loops connect four transmembrane helices, also one intracellular loop, cytoplasmic - NH_2 and -COOH terminal regions have been seen in the connexins' structure. The -NH_2 terminal tail with a calmodulin-binding motif plays the main role in membrane insertion of connexin proteins. The conductivity levels of these channels have determined by some of the post-translation alternations such as phosphorylation of the N-terminal tail and C-terminal region on each serine/threonine/tyrosine residues. Additionally, the ratio of production/destruction of gap junctions is another influential factor in the permeability of these channels [54].

As a result of the existence of various connexin isoforms, connexons can be each homomeric or heteromeric. Hemichannels are single structures in the cell membrane formed by six connexons, which lack the same structure in the adjust membrane [30]. Permeability to a diversity of small metabolites is a feature of hemichannels, which facilitates the performance of paracrine signaling [69]. Depending on the type of isoform involved in the gap junction structure, the diameter and charge of the pore will vary, which brings the selectivity feature for gap junction. For example, the presence of CX43 in the structure of gap junction increases permeability to AMP, ADP, and ATP, while gap junctions with CX32 display a higher tendency for adenosine [38]. It should be noted that the conductivity properties of gap junctions are not only determined by diverse isoform, but also determined by environmental factors including pH, Ca^{2+}, and post-translational modification. Despite much knowledge about gap junctions, the details of oligomerization and membrane insertion of gap junction (random or directed) are unknown. However, gap junction insertion is facilitated by ECM proteins, cadherins, integrins, and laminins [17].

3.3. Anchoring junctions

Anchoring junctions are comprised of adherens junctions (AJs), desmosomes, and hemidesmosomes and are crucial constructions in the preservation of tissue hemostasis. Catenins are bridges between AJs and cellular cytoskeleton, actin, and cadherins form their transmembrane core. Cadherins of opposing cells are trans-oligomerized through the interaction of calcium ion and the ectodomain of cadherin. Flexible hinges separate the motifs present in the extracellular parts of cadherins [100]. Cell adhesions are formed as a result of the interaction between the N-terminal domains of cadherins from neighboring cells. Armadillo proteins including α-catenin and β-catenin maintain the stability of cadherin clusters [83]. Fig. 1 illustrates the schematic structure of junctional proteins.

4. Slit diaphragms

Slit diaphragms are specialized cell-cell junctions of mature podocytes. SDs are contributed to control protein permeability across the GFB. Any changes in these junctions lead to proteinuria. Slit diaphragms are regarded as specialized adherens and tight junctions. Since SDs have some morphological features with adherens junctions (having typical adherens proteins including catenins, P-cadherin, and FAT), they can be considered as modified adherens junctions (Fig. 2) [77]. These adherens junctions comprise typical adherens molecules and unique membrane proteins (e.g., podocin, nephrin, and Neph1–3) that exert unique permeability. Moreover, tight junction-associated proteins are existed at SDs and are linked with nephrin [23].

Fukasawa et al. proposed an interaction map for the podocyte cell junction and SD proteins [23]. Through a direct interaction between ZO-1 and Neph1, the SD and tight junction proteins are connected

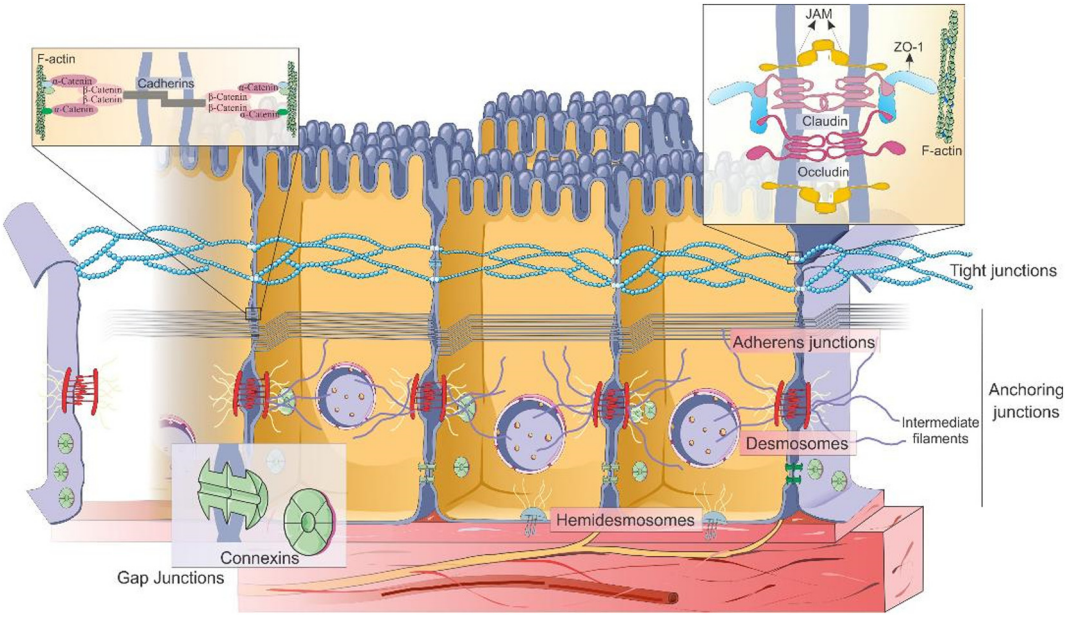

Fig. 1. Cellular junction proteins. Occludin, junctional adhesion molecules (JAMs), claudins and scaffolding proteins such as ZO-1 are located in tight junctions. Adherens junctions, desmosomes, and hemi-desmosomes in Anchoring junctions and connexins are core proteins of gap junctions.

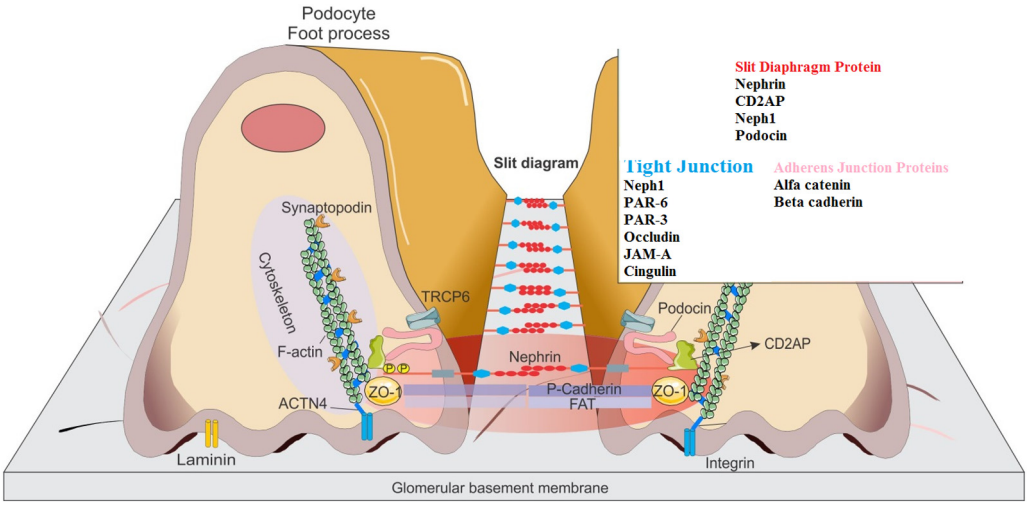

Fig. 2. Communication map for the podoctye cell junction and slit diaphragm (SD) proteins. Adjacent foot processes and the intermediate SD.

together. Moreover, another possible interaction between JAM-A and nephrin may occur through PAR-3 and PAR-6. The detachment of SDs and tight junction proteins from the cytoskeletal actin is a common figure of the podocyte's response to damage. However, there are no direct interactions between the adherens junction and SDs proteins; indirectly, α-catenin is linked to Neph1 and CD2AP through actin and ZO-1, respectively [23].

The upregulation of claudin-1 gene expression in mature podocytes results in proteinuria. Claudin-1 directly interacts with the SD components such as nephrin and podocin and this association may facilitate slit diaphragm tight junction transition [29]. Furthermore, the deprivation of nephrin or Ca^{2+} content disrupts cell junction, abrogates cell contact, and triggers EMT and chronic nephropathies through the β-Catenin/NF-kappa B activation [26]. Based on an experimental study on diabetic mice, blockade of cannabinoid receptor-1, expressed in glomerular podocytes, abolishes albuminuria and prevents down-regulation of nephrin, podocin and ZO-1 [6].

5. Tight junction in diabetic nephropathy

It has been found that glomerular and tubular epithelial cells can regulate the various solutes such as organic/inorganic materials and consequently affect extracellular fluid homeostasis [12,45]. Indeed, the tight junction adjusts the paracellular transport of solutes and water [49].

According to the published reports, several factors are contributing to the pathogenesis of DN like reduced production of nitric oxide as well as enhanced activity of protein kinase C, causing the overproduction of ROS [90]. It should be noted that ROS species play a crucial role in the structural and functional abnormalities of TJs. Two mechanisms, overproduction and also reduced metabolism of ROS species contribute to the pathogenesis of kidney disease in diabetic patients. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is one of the major sources of ROS generation [88]. Expression of NADPH oxidase plentifully occurs in some segments of the kidney such as renal vessel, glomerular mesangial cells, podocytes, distal tubule, and the macula densa [84,108].

In a performed research on the rats with DN, NADPH oxidase expression was observed in the kidney [89]. The authors of this study were reported that an angiotensin-converting enzyme inhibitor/an angiotensin receptor blocker possessed a significant suppressor effect on renal NADPH oxidase, ROS production, and microalbuminuria. In this regard, apocynin was employed as an NADPH oxidase inhibitor to moderate the renal O_2^- generation and circumvent proteinuria as well. Actually, apocynin could be possessed an inhibitory effect on glomerular mesangial function and also glomerular protein permeability in diabetes disease. In conclusion, oxidative stress can impair TJ integrity between cells [5].

Induction of oxidative stress mainly in the glomeruli and proximal tubules in a type 1 diabetes model, indicated that the expression of special proteins such as claudin-5 in the glomerulus and occludin and claudin-2 in proximal tubule decreases, while the expression ofclaudin-4 and -8 increases in the distal tubule. Furthermore, ZO-1 protein is redistributed from membrane to cytosol. A decrease in claudin-2 and -5 causes an increase of natriuresis and proteinuria, respectively [61].

The destructive influence of high glucose on the epithelial paracellular barrier is not related to its osmotic effect on the tight junction. In a cultured renal epithelial cell line, an increase of osmolality with mannitol solution enhanced the tight junction- mediated tubular barrier. It increases the tight junction and cellular content of claudin-1, a barrier-forming claudin, whereas decreases claudin-2, a pore-forming claudin. In contrast, high glucose, another osmotic agent, disrupts the tubular epithelial barrier function [9]. This damaging impact in glomerular endothelial cells might be related to the activation of RhoA/ROCK signaling pathway [70,102,107], and disruption in expression and translocation of occluding [46,70,102,107] and ZO-1 function [46,70,102]. Furthermore, high glucose-related activation of Rho/ROCK signaling evokes a fundamental role in diabetic retinal microvascular endothelial dysfunction by inducing the expression of tight junction proteins [57]. Some agents such as simvastatin [70], ginseng total saponin [31], Rutin [102] and sinomenine [107] alleviate glomerular endothelial cells hypermeability in diabetes condition by inhibition of RhoA/ROCK1 signaling. Furthermore, the administration of All-trans retinoic acid prevents loss of occludin and claudin-2 and-5 by decreasing oxidative stress [62].

Zonula occludens-1 evokes a fundamental role in regulating podocytes function. High glucose, angiotensin II [79], and angiopoietin-like protein 2 impose podocyte dysfunction via activation of focal adhesion kinase [43], translocation of zonula occludens-1 from the membrane to the cytosol and then increase of albumin permeability [43,79]. Angiopoietin-like protein 2 is a pro-inflammatory protein that is secreted by endothelial cells especially in the stressed cells. There is a direct association between its serum level and the progression of DN [43].

ADAM17, a disintegrin and metalloenzyme family member, mediates the activation of the epidermal growth factor receptor (EGFR) pathway and regulates podocytes permeability. Bradykinin evokes antiproteinuric effects by stimulation of this pathway [18].

6. Endothelial cell-selective adhesion molecule and diabetic nephropathy

Endothelial cell-selective adhesion molecule (ESAM), an expressed surface protein by endothelial cells, belongs to the immunoglobulin superfamily that possesses a key role in the mediation of cell-cell adhesion and regulation of vascular permeability as well [98]. It has been reported that the expression of ESAM is concentrated in the kidney glomeruli.

Based on both in vitro and in vivo studies, hyperglycemia decreases the ESAM expression and increases glomerular endothelial permeability and albuminuria [32]. Endothelial dysfunction in diabetic patients causes elevation of the soluble form of this immunoglobulin and its level is directly correlated with diabetes duration and inflammation [44]. Alteration in endothelial cells including the expansion of tight junctions and lessen in fenestration numbers are consequences of this phenomenon, proposing the vital role of this adhesion molecule to adjust the function of the glomerular barrier. Additionally, the authors indicated that in spite of the considerable reduction in ESAM in the first 4 weeks, no difference did detect in ESAM expression in comparison to the control group. Based on the obtained data in this research, ESAM is important for the control of glomerular permeability and possibly downregulation of ESAM leads to promote the level of urinary albumin excretion; this incidence, which is called microalbuminuria, is a principal manifestation of DN [64].

Despite the meditation role of ESAM in hemophilic interaction between endothelial cells, its capability in the regulation of glomerular permeability is still controversial. In order to assess the pathogenesis of albuminuria in DN, Ishida and et al., investigated the expression as well as the functional role of ESAM in a murine model of hyperglycemia. The observed results in this study exhibited significant expression of ESAM in the glomerular endothelial cells and subsequently a considerable reduction in the diabetic mice. The ESAM expression in the cultured endothelial cell with a high level of glucose (35 mmol/L) had a remarkable decrease compared to the normal glucose group (5 mmol/L). Albuminuria was examined through ESAM$^{-/-}$ mice for approval of these data in vivo. According to the observations of this study, urinary albumin to creatinine ratio in ESAM$^{-/-}$ mice was higher than in ESAM$^{+/+}$ mice. The achieved images using transmission electron microscopy demonstrated a reduction in the glomerular endothelial fenestration. Moreover, the endothelial tight junction was irregularly broader in ESAM$^{-/-}$ mice rather than ESAM$^{+/+}$ mice. In brief, the findings of this study introduced ESAM as a new regulator for albumin extravasation that possesses the initiation role of DN in the hyperglycemic conditions [48].

7. Gap junctions in diabetic nephropathy

High incidence of gap junction-related diseases, which can be caused by mutations of associated structural proteins, suggest that functional gap junctions are critical for cell function [72]. Some studies confirmed that the footprint of connexins can be seen in some diseases such as ischemia, inflammation, and both renin-induced and essential hypertension [21,80,96]. Furthermore, in diabetes condition, there is a parallel correlation between hyperglycemia and decreased gap junction expression, which mediates microvascular complications in diabetes [104]. Several studies have shown the effects of hyperglycemia on gap junction malfunction, as increased blood glucose declines gap junction conductance in different cells such as retinal pericytes [7], endothelial cells [55], and epithelial cells [94].

Different animal models have also investigated the role of gap junctions in DN. For instance, Zucker lean (ZL) and the Zucker diabetic fatty (ZDF) rat model of type 2 diabetes have been utilized to elucidate the connection between gap junctional communications and renal function. ZL animals exhibit lower plasma glucose, renal blood flow, and glomerular filtration rate I in comparison to ZDF rats. Also, the phosphorylation of Cx-43 in ZL is lower than ZDF animals. Moreover, immunohistochemical analyses have revealed that renin-secreting cells show a significant reduction in the density of abundance of Cx-37. Renal auto-regulation was substantially disturbed in ZDF animals but it was conserved in ZL rats [92].

Altered expression and/or function of connexin are connected with the development and progress of diabetic-related secondary microvascular complications. In this regard, expression of CD43 has been decreased in elevated glucose condition that leads to apoptosis and decreases cell communication [7]. It seems that cardiovascular complications as the main risk factor in subjects with diabetes may be linked with loss of gap junction intercellular communication (GJIC) due to deficiency of CX43 in vascular cells, so, loss of CX43 impairs ventricular induction [42]. In overall, it is documented that several diabetes complications such as nephropathy [38] and retinopathy [66] have been intervened by loss of connexin-mediated GJIC5. According to the studies on the kidney, it has been realized are expressed nine Cxs (Cx-26, -30.3, -31, -2, -37, -40, -43, -45, and -46) in the kidney [56,110]. Studies on rat revealed that Cx-37, -40, and, -43 mRNA in preglomerular renal microvasculature and Cx-37 mRNA in smooth muscle cells have high expression levels [38]. The mentioned CXs in the preglomerular vessels have a vital physiological effect on functional couples between two abutting nephrons that supplied by a common interlobular artery [27]. While, Cx-43 expression is merely seen in the postglomerular renal microvascular network [16]. One of the initial important injuries in the DN is early histological changes in glomerular system such as hyperfiltration and hyperperfusion that are detectable before the beginning of assessable clinical variation. Also, further significant structural alterations including thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial extension occur in the next stages [28]. The mentioned pathophysiological changes of glomerulus are associated with changes in Cxs. In this regard, decreased resistance in both afferent and efferent arterioles of the glomerulus is related to increase and decrease of Cx-40 in afferent and efferent arterioles, respectively [100]. The decreased resistance in these arterioles has been shown to trigger glomerular hyperfiltration in the first stage of DN. According to the above contents, alterations in some specific Cxs are associated with damaged autoregulation and following glomerular hyperfiltration. Animal models of hypertension as well as the established role of preglomerular vessels Cx-40 on hypertension have revealed an association between blood-pressure related renin release and Cx-40. Takenaka et al. [6], also evaluated the impact of CXs alterations on glomerular hyperfiltration in Zucker diabetic fatty (ZDF) rats, according to the results of this study, CX-37 has been decreased in renin secreting cells and phosphorylation of Cx-43 has been increased (an event that interfered with gap junction functioning) that leads to glomerular hyperfiltration [4]. Malfunction of glomerular mesangial cells that can be seen around the renal blood vessels, also is involved in the DN. It is reported by Hillis [34] that Cx-37 and Cx-40 increased and Cx-43 decreased in both extra- and intramesangial cells in diabetic rats. Further research by Hillis [45] revealed that increased levels of glucose in diabetes condition declined Cx-43 and induced the elderly in the glomerular mesangial cells.

The bold effect of Cxs on DN also, has been studied on human kidney cells in culture; however, more clinical applications are needed for determining the role of CXs on human DN. It is noticeable that Cx-43 can have a defensive effect on renal injury. Researches on human collecting duct cell lines by Hills team [36] showed that there was a linear correlation between glucose concentration and Cx-43 levels. Increased glucose levels induced an increase in Cx-43 levels and cellular communication by gap junction. It is also shown that calcium transients have been increased in response to high glucose. In conclusion, it is supposed that Cx-43 has a protective effect on collecting duct against diabetic nephropathy induced injuries. According to the Sawai et al. [86] disease progression in DN and levels of failure in kidney function are related to decreasing level of Cx-43 in podocytes. In line with the study of Sawai, Cx-43 has been applied as a marker for evaluation of nephropathy progression and severity in human.

Tubulointerstitial fibrosis is a frequent outcome detected in diabetic patients. The increment of extracellular matrix deposits, generation of fibrotic scars, and disturbed renal function are characteristics of fibrosis [35]. Diabetes or the presence of high glucose increases the secretion of TGF-β1 from the proximal tubule cells, which in turn induces EMT [37] by upregulation of mesenchymal markers such as N-cadherin and vimentin and attenuation of the expression of epithelial markers including E-cadherin. This event is concurrent with the disruption of gap junctions in renal tissue. Gap junction are activated in response to moderate energy depletion in proximal tubule cells resulting in cell death [13]. Furthermore, hyperglycemia induces podocytopathy through the upregulation of transforming growth factors that stimulate mature podocytes to dedifferentiation and effacement types. This pathoadaptive change evokes albuminuria, glomerulosclerosis, and podocytopenia [33].

Other signaling pathways have also been contributed to the mechanisms of fibrosis generation in diabetes. Nuclear factor E2-related factor 2/anti-oxidant response element (Nrf2/ARE) signaling pathway is a prominent cellular defense mechanism against the oxidative circumstances. The expression of Cx-43 has been shown to diminish renal fibrosis in hyperglycemic conditions through the c-Src pathway [105]. The anti-oxidative specifications of Cx-43 have been proposed to have a role in this context. In a study conducted by Chen et al. the potential anti-fibrotic role of Cx-43 in renal system has been examined in relation to the Nrf2/ARE pathway. It was shown that diabetic animals had a decreased Cx-43 expression, while the activity of c-Src was elevated in the kidney tissue. Moreover, upregulation of Cx-43 in high glucose treated glomerular mesangial cells (GMCs) prohibited the secretion of TGF-β1, intercellular adhesion molecule-1 (ICAM-1), and fibronectin proteins. The results of this study indicated that Cx-43 attenuates ROS formation through activation of Nrf2/ARE signaling in diabetic conditions. Overexpression of CX-43 was simultaneous within the blockade of c-Src which in turn promoted the activity of Nrf2 that reduces fibrosis-related protein expression in high glucose-treated GMCs [10].

It has been shown that astaxanthin alleviates DN by upregulation of Cx-43 and further effects in Nrf2/ARE signaling. The results of this study demonstrated that astaxanthin enhances the expression of Cx-43 and stimulates the Nrf2/ARE signaling in both high glucose-treated GMCs and db/db mice. Astaxanthin could significantly plunge the interaction between Nrf2 and c-Src that result in the accumulation of Nrf2 in the nucleus. Thus, this compound has a potential role in the alleviation of renal fibrosis in a Cx-related cascade [11].

Some other studies have investigated the role of gap junctions in the progression of kidney disease. Hills et al. have explored the expression of Cx-43 and Cx-26 in human primary proximal tubule epithelial cells (hPTECs) of DN-suffered patients. Also, they have utilized epithelial cells from human renal proximal tubules (HK2) and have cultured them in high glucose medium. The results indicated that diabetic condition enhances the connexin expression, decreases total gap junctional communications, and increases paracrine ATP release which in turn surges the secretion of fibronectin and interlukin-6 [39]. Thus, gap junctional cell-cell communications are potential target of intervention in DN and its manifestations. A clinical study evaluated the amount of Cx-43 expression in podocytes of overt DN. The patients showed a down-regulated Cx-43 pattern, while normal controls had a linear expression profile. The magnitude of Cx-43 heterogeneity was in line with the level of renal function failure [86].

Micro-vascular complications and inflammatory response have a pivotal role in the pathogenesis of DN. The up-regulation of different inflammatory/pro-inflammatory mediators such as endoplasmic reticulum stress, NADPH oxidase, peroxisome proliferator-activated receptor alpha as well as the down-regulation of Cx-43 have been observed during the diabetes in the kidney tissue [41]. These pathological events have been prohibited using some therapeutic agents in vivo. For instance, argirein, a novel compound which consists of L-arginine and rhein molecules, has been reported to reverse the micro-vascular damages in streptozotocin-treated animals. Rhein possesses anti-inflammatory properties [25]. Argirein has not only decreased the level of NADPH oxidase and PKR-like eukaryotic initiation factor 2α kinase (as known inflammatory factors) but also has enhanced the expression of CX-43 in the diabetic kidney [41].

8. Anchoring junctions in diabetic nephropathy

The foot processes of adjacent cells from several podocytes generate the SD which is a porous structure. The presence of ZO proteins at the cytoplasmic domain of this diagram proposed a tight junction pattern for this structure [50]. However, new advances showed that SD is more likely an AJ due to the presence of P-cadherin [78]. Cadherins mediate signaling pathways in different pathologies. Cadherins are classified into three groups: epithelia (E-cadherins), placental (P-cadherins) and neural (N-cadherins) [91]. E-cadherin is mainly expressed in the epithelial cell, while both E-cadherin and P-cadherins are expressed by glomerular tissue [78]. However, little is known about their role in this tissue. Recent evidence has shown that E-cadherin has a more abundant expression in the glomeruli and it is up-regulated during proliferative glomerulonephritis [63]. P-cadherin mainly acts as a basic platform in the SD [78]. Xu et al. investigated the expression of p-cadherin during diabetic conditions in vivo and in vitro. They demonstrated that diabetes in vivo and high-glucose-treated podocytes revealed a plummeted expression of P-cadherin mRNA and protein in which protein kinase C is involved. Furthermore, the decline in the expression of P-cadherin is linked to initial alterations of DN and might be involved in the development of proteinuria [106].

In human renal proximal tubular epithelial cell culture, hyperglycemia induces renal tubular epithelial ROCK1 [71], vimentin, α-smooth muscle actin, fibroblast-specific protein-1 and matrix metalloproteinase-2 expression [46], and blocks tubular epithelial E-cadherin level [46,87] that stimulates epithelial-mesenchymal transformation and glomerular endothelial dysfunction and albuminuria.

9. Conclusion

DN is one of the most vital concerns associated with type 1 diabetic patients. Because cell junction proteins are expressed in kidney cells and participate in myriads of cell processes and tissue repair, it is rational to speculate about the possibility of dysfunctions in these proteins as the contributors to kidney disease. The available data indicate that dysfunctions of junction-associated cell–cell communication in glomerular endothelial cells, podocytes, and GBM may have an important mechanistic role in kidney diseases, including DN. Cell junctions have promising role in future target therapy for the control and treatment of DN.

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Declaration of competing interest

None.

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