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The role of gap junction protein 43 in acute kidney injury

Dan Xia[1,2,a], Hong Li[1,b], Hongbao Liu[2,c,*]

[1]Shaanxi University of Chinese Medicine, Xianyang, 712046, China
[2]Department of Nephrology, Tangdu Hospital, Fourth Military Medical University, Xi'an, 710038, China
[a]2393236365@qq.com, [b]sxefyy.lh@163.com, [c]xjsnlhb@fmmu.edu.cn
[*]Corresponding author

Abstract: *Acute kidney injury (AKI) refers to a clinical syndrome caused by various factors that rapidly decrease renal function in a short period of time. In severe cases, it can progress to renal failure and even death. At present, there is no effective clinical treatment method for AKI. The pathogenic mechanism of AKI is relatively complex, with studies confirming its involvement in the pathological process of AKI, including inflammatory response, cell apoptosis, necrotic apoptosis, and ferroptosis. Connexin43 (Cx43) is a channel protein that participates in various signaling pathways and plays a role in promoting inflammation, apoptosis, necroptosis, and ferroptosis. Cx43 has recently been established as a participant in the development of kidney disease. It has been found that the expression of Cx43 changes in AKI induced by lipopolysaccharide, cisplatin, perfluorooctane sulfonic acid, and other etiologies. Therefore, inhibiting the expression of Cx43 is of great significance for the treatment of AKI. This article provides a systematic review of the structural functions, signaling pathways involved, and roles of Cx43 in acute kidney injury, and discusses the potential prospects for future treatment of acute kidney injury based on Cx43.*

Keywords: *CX43, acute kidney injury, signaling pathway*

1. Introduction

Acute kidney injury (AKI) refers to a sudden or continuous decline in renal function caused by various causes, mainly manifested as a sudden decrease in glomerular filtration rate, the accumulation of metabolic waste and toxins in the body, and in severe cases, it can develop renal failure or even death[1]. The pathogenesis of AKI is related to inflammation, apoptosis, necrosis, etc. The current treatment measures for AKI, apart from kidney replacement therapy and symptomatic support therapy[2], do not yet have more effective treatment methods. Therefore, finding more targeted and effective treatment methods for AKI patients is a problem that we need to solve.

Gap junctions (Gjs) are membrane channels composed of a series of connexins (Cxs), and each complete membrane channel is completed by the docking of half channels on two adjacent cell membranes. A half channel is a homologous or heterologous hexamer structure composed of six linker protein subunits, with a hydrophilic tubule with a pore size of about 1.5nm formed in the center, allowing direct exchange of ions and small molecular weight substances between adjacent cells, such as calcium ions, sodium ions, second messengers, and metabolites, forming gap junction intercellular communication (GJIC) that mediates the transmission of electrical and chemical signals between cells, The metabolic coupling that ensures the transmission of electrical signals and material exchange between cells is a key node in regulating cell proliferation, differentiation, and the homeostasis of the environment within tissues and organs [3,4].

Cxs is the basic unit that makes up Gjs, and currently there are 21 and 20 subtypes found in humans and mice, respectively. Among them, Cx43 (Connexin43, Cx43) is the most widely expressed and extensively studied subtype[5]. Extensive research has shown that Cx43 not only plays a role in cellular communication, but also mediates gene transcription, cytoskeleton dynamics, ATP exocytosis, vesicle release, and cellular stress [6]. Research has shown that Cx43 plays an important role in acute kidney injury (AKI) induced by various etiologies, mediating multiple signaling pathways and participating in pathological processes such as inflammatory response, cell apoptosis, necrotic apoptosis, and ferroptosis. However, the specific mechanism is currently unclear. At present, multiple studies have shown that inhibiting Cx43 expression can alleviate the pathological symptoms of AKI, and using it as a target for

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the treatment of AKI has good clinical application prospects. This article will review the role of Cx43 in the pathogenesis of different types of AKI mentioned above, and discuss the potential prospects of targeting Cx43 in the treatment of acute kidney injury in the future.

2. Structure and Function of Cx43

Cx43 is encoded by the gene GJA1 (gap junction protein alpha1), located in the chromosome 6 arm 22.32 (6q22.31), with a length of 3.0kb and composed of 382 amino acids. The protein encoded by Cx43 has a molecular weight of 43kDa, hence its name. Cx43 contains four transmembrane domains, two extracellular rings, one cytoplasmic ring, an intracellular amino terminal, and a carboxyl terminal [7,8]. The main difference between Cx43 and other Cxs subtypes lies in the differences in the cytoplasmic ring and carboxyl terminal amino acid sequences. The carboxyl terminus (CT) of Cx43 has approximately 150 amino acids, and its rich amino acid composition makes CT a potential target for interacting with other proteins and kinases. There are multiple post transcriptional modifications and protein binding sites that regulate the endocytosis, degradation, and channel gating of Cx43. The CT of Cx43 interacts with various protein kinases to regulate physiological processes such as cell growth, differentiation, and migration [9]. The half channel composed of six Cx43 subunits is docked with the half channel on adjacent cell membranes to form Gjs. In addition to regulating the physiological functions mentioned above, in pathological situations, Gjs can amplify cell death through bystander effect, that is, Gjs mediates GJIC to transmit death information to adjacent cells. Many studies have found that Cx43 half channels (HCs) not only open during the formation of Gjs, but also under pathological conditions such as oxidative stress, inflammation, and pH decrease, forming a direct connection between the cytoplasm and the extracellular environment, allowing free passage of sodium and potassium ions, causing cell swelling and overloading of intracellular calcium ions. At the same time, cells release small molecules such as ATP, glutathione, and glutamate, depleting their energy reserves. This leads to cell damage [10]. In recent years, the mechanism of Cx43 in inflammatory response, cell apoptosis, necrotic apoptosis, and ferroptosis has received widespread attention from the scientific community.

3. The role of Cx43 in acute kidney injury

In kidney tissue, Cx43 is mainly located in the renal vascular system, mesangial cells, and collecting ducts[11]. The expression and distribution of Cx43 are closely related to the occurrence of various types of AKI. Cx43 participates in the occurrence and development of AKI by mediating various signaling pathways, which may involve the following mechanisms.

3.1 Promote inflammatory response

Systemic inflammatory response is the main characteristic of lipopolysaccharide (LPS) induced acute kidney injury, and inflammatory mediators play an important role in the inflammatory response. More and more studies have shown that NLRP3 inflammasomes are involved in regulating the process of renal inflammatory response and are key to the production of inflammatory mediators [12]. Therefore, targeted inhibition of NLRP3 inflammasome activation can serve as a new treatment method for preventing and treating inflammatory kidney disease.

Many studies have confirmed a close relationship between Cx43 and renal inflammatory response. In 1998, Cobo et al. First found an increase in Cx43 expression in the kidneys of rats injected with LPS. Genes containing Cx43 promoter activity were transfected into rat renal tubular epithelial cells. After incubation with serum containing LPS, it was found that the promoter activity of Cx43 was enhanced, indicating that upregulation of Cx43 is a part of LPS induced inflammatory responses [13]. In a study on the effect of Fangji Poria cocos on LPS induced AKI [14], it was found that downregulation of Cx43 expression can enhance the protective effect of Fangji Poria cocos on the kidneys, and the specific mechanism may be related to reducing LPS induced inflammatory response and cell apoptosis. The above studies indicate that the inflammatory response is an important component of Cx43's involvement in LPS induced AKI. Recently, Yanru et al[15]. Conducted in vivo and in vitro experimental studies to clarify the role of Cx43 in the mediating inflammatory response and its involvement in the pathogenesis of acute kidney injury induced by lipopolysaccharide, and to explore the mechanism and pathway of Cx43 mediated inflammatory response. They found that the mechanism by which Cx43 participates in the inflammatory response is complex and may be related to the activation of NLRP3 inflammasomes, while Cx43 participates in regulating the activation of NLRP3 inflammasomes through various mechanisms.

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Firstly, considering that reactive oxygen species ROS are the central factor mediating the activation of inflammasomes, oxidative stress and NADPH oxidase play important roles in the activation process of inflammasomes. Mitogen activated protein kinases (MAPKs) activated by oxidative stress, including p38, ERK, and JKN kinases, play a mediating role in the activation process of inflammasomes. From these aspects, it was found that in the macrophage model induced by lipopolysaccharide, Cx43 expression increased, while oxidative stress-related indicators, NADPH oxidase expression, and mitogen activated protein kinases (MAPKs) expression were upregulated. By downregulating the expression of Cx43 through genetics, cell transfection, or inhibitors, the above indicators are correspondingly downregulated. Subsequently, studies have shown that NLRP3 inflammasomes, NADPH oxidase, and oxidative stress are involved in lipopolysaccharide-induced acute kidney injury. Based on this, an animal and cell model of lipopolysaccharide-induced acute kidney injury was established. It was found that CX43 can participate in the activation of inflammasomes through cell communication mediated ROS generation, NADPH oxidase expression, and oxidative stress activation. The above research results confirm that the activation of NLRP3 inflammasomes is related to the upregulation of Cx43 expression, which promotes the activation of NLRP3 inflammasomes by mediating intracellular redox states [15]. The specific mechanism by which Cx43 regulates the intracellular redox status may be related to its formation of a half channel. Under harmful conditions such as lipopolysaccharide stimulation, the Cx43 half channel of cells opens, allowing for the free passage of $Na^+$and K^+ions, leading to Ga^{2+}overload [16]and promoting ROS formation [17]. ROS is an important mechanism for oxidative stress and activation of inflammasomes. At the same time, oxidative stress is also involved in the activation of NLRP3 inflammasomes, which in turn expands inflammatory damage [15]. And some studies have found that inhibiting Cx43 expression can alleviate oxidative stress and inflammatory reactions caused by lipopolysaccharides and other toxins after liver transplantation by mediating ROS content [18,19]. At the same time, studies have shown that the opening of the Cx43 half channel can induce ATP release and form an autocrine feedback loop to amplify and sustain inflammatory responses [20], while ATP release can also exacerbate intracellular oxidative stress and increase intracellular ROS content. Again, under sepsis conditions, the half channel formed by Cx43 on the cell membrane is open, mediating Ga^{2+}signaling and ATP release, and then inducing the activation of NLRP3 inflammasomes by regulating the intracellular ROS content and oxidative stress state, ultimately leading to an inflammatory response.

In summary, the above studies indicate that Cx43 is a key participant in the activation of inflammasomes and renal inflammatory diseases, providing strong evidence for targeted inhibition of Cx43 in the treatment of sepsis related AKI.

3.2 Promote cell apoptosis

Apoptosis is a kind of programmed cell death regulated by genes, and physiological apoptosis is an important mechanism to maintain the stability of tissues and organs. However, under the stimulation of pathological deleterious factors, an imbalance in apoptosis can lead to excessive cell death, thereby affecting the structure and function of tissues and organs [21]. The pathways of inducing apoptosis include endogenous mitochondrial pathway, exogenous death receptor pathway and perforin/granzyme pathway. Caspase-3 is the intersection of three pathways and plays an important role in apoptosis. BCL-2 family proteins play an important regulatory role in the mitochondrial pathway of apoptosis. A decrease in the BCL-2-BAX ratio promotes apoptosis, whereas the Tumor necrosis factor receptor family binds to its corresponding ligands to initiate an external pathway of apoptosis [22]. Many studies have proved that apoptosis is an important mechanism of nephrotoxic injury, especially renal tubular injury. Reducing apoptosis can prevent acute renal injury, acute kidney injury caused by lipopolysaccharide, perfluorooctane sulfonate, cisplatin, etc. [23-25].

Recent studies have found[26]that in both in vivo and in vitro models of pfos-induced acute kidney injury, PFOS mediates mitochondrial damage by inducing oxidative stress, this eventually leads to mitochondrial-mediated apoptosis pathway activation, while CX43 expression is upregulated in the model, suggesting that CX43 may be a molecular mechanism mediating apoptosis. The results showed that down-regulation of CX43 could decrease the expression of apoptosis-related protein Caspase 3 (Caspase-3) and increase the ratio of Bcl-1 to BAX. In addition, it has also been found [27]that Cisplatin can be involved in the initiation of apoptosis by upregulating CX43, and that inhibition of CX43 expression in a cisplatin-induced acute kidney injury model can attenuate the apoptotic state; The expression of apoptosis-related proteins caspase-3 and Bax decreased, while the expression of BCL-2 increased.

These results suggest that CX43 may participate in the pathological process of acute kidney injury by regulating apoptosis, and its mechanism may be related to the mitochondrial-mediated apoptosis pathway.

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CX43 may activate Caspase-3 by regulating the expression of BCL-2 family proteins, leading to apoptosis. Although the specific mechanism by which CX43 regulates apoptosis is not well understood, existing studies provide strong evidence for using CX43 as a target for the treatment of toxic kidney injury.

3.3 Promote necroptosis

Necroptosis is a kind of programmed necrosis, it mainly depends on the activation of receptor-interacting serine/threonine kinase 1 (Ripk1), receptor-interacting serine/threonine kinase 3 (Ripk3) and mixed lineage kinase-like domain (MLKL), it has nothing to do with Caspase [28] . In recent years, many studies have confirmed that necroptosis plays an important role in acute kidney injury, including drug, ischemia-reperfusion injury and contrast agent-induced acute kidney injury. Therefore, inhibition of necrotic apoptosis is of great significance in the treatment of acute kidney injury.

A recent study found[18] that CX43 is involved in kidney damage after liver transplantation and mediates necroptosis by regulating ROS content. The results showed that the expression of CX43 was up-regulated, ROS content was increased, and necroptosis related proteins RIPK1 and MLKL were also up-regulated in the rat and cell models of kidney injury after liver transplantation, inhibition of CX43 down-regulates the expression of necroptotic apoptosis-related proteins RIPK1 and MLKL by reducing ROS content. Therefore, CX43 can be used as a target to prevent and treat renal injury after liver transplantation. Regarding how CX43 induces necroptosis by modulating ROS content, the possible mechanism is related to the Cx43-composed semi-channel, which is open under various pathological conditions, this mediates the Ga^{2+} signaling pathway and Ga^{2+} is a key molecule involved in ROS production. In summary, when cells are in a toxic metabolic environment, it leads to the opening of CX43 semi-channels, Ga^{2+} influx, and mitochondrial ROS formation. Necroptosis is induced in one way, with the opening of cellular CX43 semi-channels leading to Ga^{2+}, and Ga^{2+} influx into cells leading to mitochondrial ROS formation, which activates Ripk1 and MLKL via CX43, ultimately leading to necroptosis[29] .

Although, there are few reports on the involvement of CX43 in acute kidney injury through necroptosis, and the specific mechanisms by which CX43 regulates necroptosis are not clear enough, we will have to continue to study in this regard in the future, however, the present results still provide strong evidence that CX43 is a novel target for the treatment of renal injury after liver transplantation.

3.4 Promote iron death

Iron Death is a novel form of cell death discovered in recent years, which is accompanied by massive iron accumulation and Lipid peroxidation, and is an iron-dependent mode of cell death [30]. One of the most important mechanisms of iron death is cysteinglutamic acid reverse transporters, which are amino acid reverse transporters present in membrane Lipid bilayer, is a heterodimer consisting of two subunits, SLC7A11 and SLC3A2, which can convert cystine and glutamate inside and outside cells in a 1:1 ratio, Transferring cystine into the cell is involved in GSH synthesis, which is affected by Glutathione peroxidase GPX4, which reduces lipid ROS and reactive nitrogen, and inhibition of cysteinglutamic acid reverse transporters, gpx4 activity is inhibited, the cell's antioxidant capacity is reduced, and eventually lipid ROS accumulation leads to iron death [31]. Recent studies have shown that iron death is involved in the process of acute renal injury induced by ischemia-reperfusion injury, folic acid, cisplatin, lipopolysaccharide, etc.[32], it is important to explore the molecular mechanism of iron death for the treatment of Aki.

Recent studies have shown that downregulation of CX43 can attenuate cisplatin-induced acute kidney injury by inhibiting iron death, suggesting for the first time a relationship between CX43 and iron death [27]. The results showed that the expression of CX43 was up-regulated in the model of cisplatin-induced acute kidney injury, while the expression of SLC7A11 and GPX4, which were related to the inhibition of iron death, were down-regulated, indicating that CX43 may down-regulate the expression of SLC7A11, thus, GSH synthesis is limited, GPX4 activity is decreased, and finally lead to iron death. Although the specific mechanism is not clear enough, it still provides new directions for the treatment of cisplatin-induced Aki.

Taken together, CX43 is upregulated in different types of acute kidney injury models, suggesting that CX43 plays an important role in the pathogenesis of Aki, and its mechanism of action may be related to the semi-channel composed of CX43. Under various predisposing factors, the renal tissue is in a pathological state, the expression of CX43 is up-regulated in renal tubular epithelial cells, and the semi-

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channel formed by CX43 is in an open state, which allows the free influx and outflow of intracellular and extracellular ions, and release ATP. At the same time, various information is transmitted to neighboring cells to enlarge the scope of damage. In the above way, CX43 participates in the inflammatory reaction, apoptosis, necroptosis and iron death of acute kidney injury. Although the exact mechanism of action remains unclear, the available evidence suggests that CX43 is potentially useful as a therapeutic target for the treatment of Aki.

4. The prospect of CX43 mimetic peptide in the treatment of Aki

CX43 is widely distributed and there is ample research evidence that CX43 plays a key role in disease, leading to the production of a number of mimicry peptides on CX43, which are classified according to their binding sites on CX43, gap26 and Gap27, which bind to the extracellular loop of CX43 cells, act by inhibiting gap junction formation, while Gap19, which bind to the cytoplasmic loop of CX43 cells, acts by blocking gap junction half-channel opening[33]. In recent years, these mimetic peptides have been widely used in animal and cell experiments. In the study of acute kidney injury induced by different drugs, the pathological symptoms of acute kidney injury models using CX43 mimetic peptides were alleviated, these results suggest that CX43 mimetic peptide has a potential therapeutic effect on acute renal injury, suggesting that CX43 may play an important role in the treatment of acute renal injury.

5. Conclusion and prospect

In conclusion, a growing body of research evidence shows that CX43 plays an important role in acute kidney injury, and its mechanism of action involves a complex network of signaling pathways. However, there is relatively little data from relevant studies at present, and the mechanism of CX43 in Aki remains unclear, and more studies exploring the role of CX43 in the kidney are needed in the future. There are limited clinical methods to treat acute kidney injury. It is a promising challenge to treat an acute kidney injury with CX43 as a new target, we can target CX43 to treat acute kidney injury and apply it to clinical practice on the premise of knowing the mechanism of signal pathway mediated by CX43.

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