Connections in chronic kidney disease: connexin 43 and connexin 37 interaction

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The prevalence of chronic kidney disease is rising sharply worldwide and affects 13.1% of the population in the US (3). Patients with chronic kidney disease represent a population not only at risk of progression to end-organ failure but also at higher risk for cardiovascular diseases (22). Although inflammation is beneficial for host wound healing and defense toward infection, excessive or altered inflammation often leads to a wide range of tissue injury and human disease, including cardiovascular and kidney disease (13, 20, 29). Inflammation causes oxidative stress by promoting the release of reactive oxygen and other reactive species by inflammatory cells, and this process contributes to tissue injury. Infiltration of inflammatory cells and increased expression of proinflammatory factors are crucial in the development of renal injury (20, 29). Renal tubule cells produce both cytokines and chemokines that are secreted across the apical and basolateral membranes and contribute to the development and progression of interstitial inflammation and glomerular and tubular injury (4, 23, 35).

Cell-to-cell communication, which occurs via gap junctions, is important to cell viability. However, gap junctions have been shown to be disrupted by inflammation (21) and oxidative stress (27). Paired connexins (connexons) play an important role in gap-junctional intercellular communication while unpaired connexins allow communication between the cytosol and extracellular environment. The most common connexins in the renal vasculature are connexin 37 (Cx37), Cx40, Cx43, and Cx45. Cx26, Cx30, Cx30.3, Cx32, and Cx43 are also expressed in renal tubules (12). Several connexins have been implicated in the development of cardiovascular disease, including hypertension and kidney and heart disease (1, 2, 7, 8, 10–12, 14, 15, 17, 18, 24, 25, 28, 30–34).

Cx40 is expressed to a greater extent than Cx45 in renin-producing juxtaglomerular cells while the converse is true in vascular smooth muscle cells. Deletion of Cx40 in renin-producing but not in endothelial cells resulted in hyperreninemia and hypertension (17, 30). Kurt et al. (17) also reported that there is a “reciprocal expression of Cx40 and Cx45 during phenotypical changes in renin-secreting cells”. Toubas et al. (27a) now report in an issue of the American Journal of Physiology-Renal Physiology that in the renal cortex of control mice there is negligible expression of Cx43 while Cx37 is abundantly expressed. However, in three different experimental models of chronic renal disease in mice, i.e., RenTg, anti-glomerular basement membrane glomerulonephritis, and unilateral renal obstruction, there is an early increase in Cx43 expression and a decrease in Cx37 expression in the renal cortex of these mice. The increase in the Cx43-to-Cx37 ratio is associated with an increase in cell adhesion molecules, vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), followed by inflammatory cell infiltration, with an increased expression of monocyte chemoattractant protein-1 (MCP-1). The increase in Cx43 expression is important in the inflammatory response because deletion of one allele of Cx43 blunted the increase in VCAM-1 expression. Cx37 may counter the effect of Cx43 that could be gleaned from the acceleration of atherosclerosis in Cx37 null mice (8).

The imbalance of renal cortical (Ref. 27a, this report) and vascular Cx43 and Cx37 expression may contribute to the

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Fig. 1. Gap junctions and transforming growth factor (TGF)-β counterregulate each other. Connexin 43 (Cx43), the major gap junction protein in the myocardium, which is also expressed in renal tubules, may positively regulate TGF-β. The response gene to complement 32 (RGC-32) and SMAD 3, downstream targets of TGF-β, regulate Snail, which is important in the epithelial-mesenchymal transition (EMT) of renal proximal tubule cells. Snail-mediated EMT decreases Cx43 expression, resulting in a negative feedback loop. In some tissues, e.g., kidney, an increase in the Cx43-to-Cx37 ratio could be a regulator of renal fibrosis (27a). Whether this interaction also regulates the expression of TGF-β remains to be determined.
initiation of inflammation (18). However, the balance between Cx43 and Cx37 may play different roles in different tissues and diseases. Thus Cx43 expression is decreased but interstitial collagen fiber is increased in the corpus cavernosum of spontaneously hypertensive rats and rats with chronic renal failure (7). The epithelial-mesenchymal transition (EMT) in embryonic stem cells or human lens is associated with decreased expression of Cx43 (28, 31). However, in agreement with the current study, renal Cx43 mRNA expression is increased 5 days after unilateral ureteral obstruction (25) and myocardial EMT (1). In hypertensive two-kidney, one-clip (2K1C) rats, Cx43 is increased in the unclipped but not the clipped kidney (10). Cx43 mRNA in the heart is not altered 4 wk after 2K1C, DOCA-salt hypertension, or \( N^\omega \)-nitro-L-arginine methyl ester (L-NAME; nitric oxide inhibitor) hypertension. However, Cx43 protein expression is increased in the aorta of rats with 2K1C or DOCA-salt hypertension but decreased in rats with L-NAME hypertension (11). Cx43 has also been reported to be highly expressed in inflammatory, damaged renal tubule, interstitial cells in human kidneys (14), and podocytes of rats with puromycin aminonucleoside nephrosis (32). What makes the kidney and heart different from the other organs, in terms of Cx43 expression? What is responsible for the differential regulation of Cx43 in different organs? Is it related to differential cell expression (2, 13, 33)? More intriguingly, does the differential expression of Cx43 in the same tissue occur with different diseases (11)?

Gap junctions can be regulated by transforming growth factor-\( \beta \) (TGF-\( \beta \)) and vice versa (15). Cx43, the major gap junction protein in the myocardium, may positively regulate TGF-\( \beta \) because deficiency of Cx43 is associated with a decrease in TGF-\( \beta \) signaling (1, 34) (Fig. 1). We have reported that the response gene to complement 32 (RGC-32) is a downstream target of TGF-\( \beta \) signaling, which mediates the EMT in renal proximal tubule cells (9, 16, 19). The SMAD cascade is not implicated in the TGF-\( \beta \) effect on Cx43 expression in the mammary gland (26). However, in cardiomyocytes, Cx43 positively regulates TGF-\( \beta \) by releasing Smads from microtubules (5). SMAD3 also interacts with RGC-32, Slug, and Snail to cause EMT (9). Snail1-mediated EMT results in Cx43 repression (6). The interaction of these different proteins, especially the connexins, in the regulation of EMT and renal fibrosis may lead to a better understanding of how to interfere with the fibrotic process that occurs with renal inflammation and injury.

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REFERENCES


