Connexin40 is essential for the baroreceptor control of renin synthesis and secretion

Renin synthesis and secretion are regulated by the sodium balance of the organism via a long negative-feedback loop. They are also acutely regulated by plasma angiotensin II and intrarenal blood pressure (that is, renal perfusion pressure), which form short negative-feedback loops for renin secretion. The mechanism(s) by which renal perfusion pressure (also referred to as the renal baroreceptor) and angiotensin II regulate synthesis and secretion of renin in juxtaglomerular cells is unknown. However, the inhibitor effects of both factors are abolished if the extracellular calcium concentration is lowered toward the micromolar range. This suggests a requirement for calcium, which possibly acts as the inhibitory mediator in these two signaling pathways. It has been known that juxtaglomerular cells are strongly coupled among each other as well as to the adjacent endothelial cells via gap junctions. Yet, the functional implication of this coupling is still obscure, partially because of the lack of substances that interfere with gap junctional communication. Gap junctions are formed by the assembly of connexins (Cx), which belong to a family consisting of at least 20 members. More recently, it was demonstrated that Cx40 and Cx43 seem to be the dominating connexins expressed in the kidney. Specifically, the renin-producing juxtaglomerular cells but not the neighboring smooth muscle cells exhibited a striking expression of Cx40, which forms gap junctions between the renin-producing cells themselves as well as between the renin-producing cells and the adjacent endothelial cells or the extraglomerular mesangium.

Because Cx40-deficient mice are hypertensive and Cx40 is the dominating connexin in juxtaglomerular cells, Wagner et al. postulate in a new study that either Cx40 hemichannels or Cx40-dependent intercellular communication is crucially contributing to the regulation of renin secretion (see Figure). They found that, in the absence of Cx40, the negative control of renin secretion and synthesis by angiotensin II and by the renal baroreceptor was abrogated. Interestingly, the regulation of renin by salt balance and by the β-adrenergic receptor was maintained. Renin secretion from Cx40-deficient kidneys or wild-type kidneys treated with the nonselective gap junction blocker 18α-glycyrrhetinic acid resembled the situation in wild-type kidneys in the absence of extracellular calcium. This disturbed regulation was reflected by an enhanced plasma renin concentration despite an elevated blood pressure in Cx40-deficient mice. These findings indicate that Cx40 and probably intercellular communication via Cx40-dependent gap junctions mediate the calcium-dependent inhibitory effects of angiotensin II and of intrarenal pressure on renin secretion and synthesis. Because Cx40 gap junctions are also formed between renin-producing cells and endothelial cells, these findings suggest that the endothelium may be involved in the control of the renin system. (Circ Res 2007; 100: 556–563)

Juan Oliver

MicroRNA in diabetic kidney and its function in TGF-β-induced collagen expression

Major characteristics of diabetic nephropathy include glomerular basement membrane thickening, mesangial expansion and hypertrophy, and an accumulation of extracellular matrix proteins. Transforming growth factor-β1 (TGF-β1) levels are increased under diabetic conditions in renal cells, including mesangial cells, and do increase extracellular matrix proteins such as collagens.

To date, Smad transcription factors have been shown to be the major effectors of TGF-β signaling. In mesangial cells, collagen 1-α1 and -α2 (Col1a1 and Col1a2) and other extracellular matrix protein are regulated by TGF-β via Smads and via mitogen-activated protein kinases. However, the molecular mechanisms by which TGF-β regulates extracellular matrix protein genes still are not understood fully. The collagen gene has E-box elements (a binding site for basic helix-loop-helix proteins) in the far upstream enhancer region; an E-box repressor, βEF1, is a key inhibitor of E-cadherin and collagen type 1 and type 2 genes in several cells, but its role in mesangial cells is not known.

MicroRNAs (miRs) are short noncoding RNAs of approximately 22 nucleotides that play important roles in mammalian gene expression. They induce post-transcriptional gene repression by blocking protein translation by binding to the 3’ untranslated region of their target genes or by inducing mRNA degradation, and they therefore have the potential to

Double staining for renin and Cx40 protein indicates the coexpression of renin.

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play central roles in physiological and pathological conditions. It was recently shown that at least five miRs (miR-192, -194, -204, -215, and -216) are highly and quite exclusively expressed in the kidney, but their functions or targets are not yet known.

During microarray profiling, Kato et al. observed that TGF-β downregulated δEF1 expression in mesangial cells. In a new article, these authors have shown that this effect can lead to increased collagen expression via relief of repression at the E-box elements in the collagen gene. They also found that TGF-β downregulated expression of Smad-interacting protein 1 (SIP1), another E-box repressor belonging to the same family as δEF1. They further identified SIP1 as a target of miR-192. They also found in mesangial cells that TGF-β treatment or transfection with miR-192 decreased endogenous SIP1 expression, and that miR-192 levels in the cells were increased by TGF-β. Finally, in vivo they found that miR-192 levels were increased in glomeruli isolated from streptozotocin-injected diabetic mice as well as diabetic db/db mice, in parallel with increased TGF-β and Col1a2 levels.

These results uncover a role for miRs in the kidney and diabetic nephropathy in controlling TGF-β-induced Col1a2 expression by downregulating E-box repressors. Hence, the data demonstrate a previously uncharacterized mechanism for TGF-β-mediated collagen regulation involving a cross-talk between E-box repressors (δEF1 and SIP1) and miRs (miR-192) that could be relevant to the pathogenesis of diseases such as diabetic nephropathy. (Proc Natl Acad Sci USA 2007; 104: 3432–3437)

Juan Oliver

Extracellular carbonic anhydrase mediates increased retinal vascular permeability in diabetes

The effects of diabetes in the eye and kidney are characterized by microvascular abnormalities. Knowledge obtained in one vascular bed may have implications for the other. In the eye, diabetes induces proliferation of retinal vessels and increases retinal vascular permeability shortly after diabetes onset. Vascular endothelial growth factor (VEGF) has been considered a principal pathogenic factor in this process, although other vasopermeability factors are clearly involved.

To obtain new insights into the factors and mechanisms responsible for the increased retinal vascular permeability in diabetes, Gao et al. characterized the vitreous proteome in patients with diabetic retinopathy. Using mass spectroscopy-based proteomics, they detected 117 proteins in human vitreous and 31 proteins expressed differentially in individuals who had proliferative retinopathy and compared them with the proteins of individuals with diabetes but no retinopathy and individuals who were not diabetic. Among the 31 proteins, there were proteins involved in cell growth, metabolism, cell adhesion, and transport as well as complement activation and acute-phase response proteins. Carbonic anhydrase-I and carbonic anhydrase-II were elevated 15- and 8.2-fold, respectively.

Interestingly, the usual suspects of diabetic retinopathy, such as VEGF, were not identified. The elevated levels of extracellular carbonic anhydrase-I (CA-I) in vitreous from individuals with diabetic retinopathy suggested retinal hemorrhage and subsequent erythrocyte lysis (see Figure). Intravitreal injection of CA-I in rats increased retinal vessel leakage and caused intraretinal edema. CA-I-induced alkalization of vitreous increased kallikrein activity and its generation of factor XIIa, revealing a new pathway for contact system activation. CA-I-induced retinal edema was decreased by complement 1 inhibitor, neutralizing the antibody to prekallikrein and bradykinin receptor antagonism. Interestingly, subdural infusion of CA-I in rats increased cerebral vascular permeability, suggesting that extracellular CA-I could have broad relevance to edema. Thus, inhibition of extracellular CA-I and kallikrein-mediated innate inflammation could provide new therapeutic opportunities for the treatment of hemorrhage-induced retinal and cerebral edema. These findings have important implications for diabetic retinopathy, as well as for other diseases in which increased vascular permeability plays a prominent role. (Nat Med 2007; 13: 181–188)

Juan Oliver