

Minding the Gap: Connexin40 at the Heart of Renin Release

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A key component of the kidney's ability to maintain body fluid homeostasis resides in one of its endocrine functions: the production of renin. Control of renin release by renal juxtaglomerular (JG) cells serves to regulate the renin-angiotensin system,¹ which is of critical importance for extracellular fluid volume and BP regulation. Physiologic control of renin release is influenced by three major variables: renal sympathetic nerve activity, sodium chloride delivery to the macula densa, and renal perfusion pressure. Although the nature of the renal baroreceptor has been deliberated for nearly 40 years,² the molecular mechanisms underlying pressure control of renin release have remained elusive. Previous work by Kurtz and colleagues^{3–5} and others⁶ has established a key role for connexin proteins in this process. Much has been learned from transgenic mouse models with alterations in connexins, including globally-deficient connexin40 (Cx40) knockout mice,^{5,6,7} renin cell-specific Cx40 knockout mice,³ and now from mice expressing a novel point mutation in Cx40, as reported in this issue of *JASN*.⁸ Disruption of Cx40 leads to loss of pressure control of renin secretion and development of hypertension.^{6,5,3}

In this issue of *JASN*, Lubkemeier *et al.*⁸ report their findings in a new transgenic mouse model that expresses a missense mutation in exon 2 of the connexin40 gene (Cx40A96S). This same loss-of-function mutation was previously identified in a human patient with idiopathic atrial fibrillation.⁹ A gap junction-forming protein, Cx40, is the main connexin in JG cells of the kidney.¹⁰ Homozygous Cx40A96S mice are hypertensive, with markedly elevated plasma renin concentrations (sixfold increase) compared to wild type (WT) controls. Cx40A96S mice express the mutated Cx40 protein in the kidney in a pattern similar to WT mice, yet are not able to adjust JG cell renin release in response to changes in renal perfusion pressure, presumably

due to a lack of functional gap junctions within the juxtaglomerular apparatus (JGA). Using the isolated perfused kidney model, the authors find there is loss of pressure-dependent control of renin secretion, likely due to aberrant localization of renin-producing cells outside the medial layer of afferent arterioles. Furthermore, when the Cx40A96S mutation was expressed in HeLa cells, there was almost complete loss of cell-cell coupling compared with WT Cx40, paralleling the results described in N2A cells by Gollob *et al.*⁹

Proper Cx40 function lies at the heart of renin regulation, and loss of this key component of the gap junction results in renin-dependent hypertension. These studies, together with previous observations from Cx40-deficient mice, indicate that intact intercellular communication through connexin-based gap junctions is vital to the proper regulation of renin release by both perfusion pressure and the macula densa mechanism but not sympathetic stimulation. This further begs the question of which intercellular signaling molecules traverse these gap junctions to regulate renin secretion. Many key mediators of renin release, including cAMP,¹¹ Ca²⁺,¹² and ATP^{13,14} may pass through gap junctions, facilitating communication between cells of the JGA to stimulate or inhibit renin expression and release. The nature of the precise intercellular signaling mechanisms that control the basal and stimulated secretion of renin is an exciting area awaiting further investigation.

Another intriguing phenotype of mice lacking functional Cx40 is aberrant localization of renin-producing cells. In normal adult animals, renin cells are localized within the medial layer of the most distal portion of the afferent arteriole. Chronic stimulation of renin synthesis increases the number of renin-producing cells, through proximal recruitment of cells within the afferent arteriolar wall.¹⁵ Interestingly, both Cx40A96S mice and mice with renin cell-specific deletion of Cx40 maintain the ability to recruit additional renin-producing cells in response to salt depletion and treatment with an angiotensin converting enzyme (ACE) inhibitor, while those with global deletion of Cx40 do not.^{3,5,6} These observations suggest that gap junctional coupling is not required for recruitment of additional renin cells during homeostatic challenges, but it appears to be necessary for proper localization of these cells both under basal conditions and during prolonged renin stimulation. It is also possible that a structural or scaffolding function of Cx40 hemi-channels in nonrenin cells¹⁶ may be required for this process. Endothelial Cx40 is not required for recruitment or localization, as *Tie2-Cre* Cx40^{fl/fl} mice display appropriate renin cell localization and stimulated recruitment.³ Thus, while proper localization and recruitment of renin cells require functional Cx40, these two processes appear to be regulated independently.

While the true nature of the renal baroreceptor remains to be fully elucidated, it is clear that connexin proteins are an

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essential component of this important regulatory mechanism. Whether baroreceptor function is restricted to renin cells or other cell types within the JGA, and whether proper localization of renin cells within the afferent arteriole directly impacts this function, are questions that remain to be answered. These interesting new observations by Lubkemeier *et al.* lend support to the view that the JGA is an integrated unit whose function depends upon precisely coordinated activity of its component cells. Cx40 gap junctions facilitate the cell-to-cell flow of physiologic information that ensures proper control of renin release for maintenance of fluid homeostasis.

Expression of vascular connexins in the human renal cortex is quite similar to that in rodents,¹⁷ and numerous mutations in human Cx40 have been identified in patients with cardiovascular disease.⁵ Therefore, assessment of the physiologic effects of the Cx40A96S mutation in mice furthers our understanding of renin regulation and BP control in humans. Lubkemeier *et al.* demonstrate, for the first time, that defective regulation of renin in mice lacking functional Cx40 is primarily due to loss of gap junctional coupling in renin-secreting cells. In fact, the patient with the A96S mutation, identified by Gollob *et al.*,⁹ also had hypertension in addition to atrial fibrillation, suggesting a common underlying mechanism. Taken together, these findings bring to light the possibility that mutations in the *Cx40* gene, such as the one modeled in this paper, may contribute to renin-dependent hypertension in humans.

DISCLOSURES

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See related article, “The Connexin40 A96S Mutation Causes Renin-Dependent Hypertension,” on pages 1031–1040.

Pores for Thought: New Strategies to Re-energize Stressed Mitochondria in Acute Kidney Injury

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Ischemia-reperfusion injury (IRI) is a major cause of acute kidney injury (AKI) in both native and transplanted organs. Given that AKI is associated with significant patient morbidity and mortality and the development of long-term chronic kidney disease, there is an urgent need to develop new preventive or treatment strategies to improve outcomes and relieve the financial burden of AKI on health care systems. In this issue of *JASN*, Szeto *et al.*¹ describe a novel agent that is specifically

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