CBP and p300 in renin homeostasis: can they drive the fate?

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Renin is the rate-limiting enzyme in the renin-angiotensin system that is responsible for the control of blood pressure and fluid homeostasis. In the adult mammalian kidney, renin is synthesized, stored, and released by the juxtaglomerular (JG) cells, which are confined to the vascular wall of the afferent arteriole at the entrance of the glomerulus. To reach its final differentiated state, a renin-expressing cell “travels” a long way, leaving its memory imprinted: in the embryo, renin precursor cells are present in the metanephric mesenchyme and give rise to JG cells and to arteriolar smooth muscle cells even before vessel development has occurred and before the hemodynamic role of renin is required. Later, in the fetus, renin-containing cells are present in the large intrarenal arteries and in the glomerular interstitium. As maturation continues, the number of renin-containing cells diminishes to a few into the classical adult JG distribution. When homeostasis is imbalanced or threatened, as in the case of a low salt intake, the number of renin-expressing cells along the preglomerular arteries increases, resembling the fetal pattern. This phenomenon is usually called recruitment, and it is thought to provide additional plasma renin to maintain salt balance and blood pressure.

The work of Sequeira Lopez, Gomez, et al. (9) and other investigators (2) established that smooth muscle cells in the afferent arteriole retain the plasticity to synthesize renin during the recruitment process. The signaling and molecular mechanisms involved in recruitment of renin-expressing cells have remained obscure. It is unequivocally established that cAMP plays an important role in renin regulation. Increases in intracellular cAMP induce renin release from the JG cells (6), stabilize renin mRNA (1), and increase the expression of renin (3). The reacquisition of renin expression may be, in part, mediated by the second messenger cAMP. Recently, Pentz, Gomez, et al. (8) began to identify the mechanism and role of cAMP in governing the fate of renin-containing cell recruitment. They generated mouse models in which cells of the renin lineage that expressed renin during development were labeled with cyan fluorescent protein (CFP), while cells actively expressing renin were labeled with yellow fluorescent protein (YFP). They elegantly demonstrated that cAMP stimulation of preglomerular smooth muscle cells from the renin cell lineage (CFP-positive cells) results in reexpression of renin (YFP-positive cells). This finding shows that the smooth muscle cells that retain the plasticity to reexpress renin are those that expressed renin earlier during development. Importantly, they also showed that cAMP-induced recruitment of smooth muscle cells into renin-expressing cells requires histone acetylation and chromatin remodeling of the cAMP responsive element (CRE) region of the renin gene promoter.

The CRE region in the renin promoter is known to be essential in renin gene transcription (7). In other cells, the regulation of this promoter region by cAMP involves the complex interaction of CRE-binding protein with coactivators (5). CRE-binding protein (CBP) and/or p300, which facilitate access of the transcription factor TFIIIB and initiate transcription (4). In addition, the coactivators CBP and p300 have been described to possess histone acetyltransferase activity and, therefore, may play a role in chromatin remodeling (5). On the basis of their previous results, Gomez et al. (1a) extended their finding implicating the cAMP pathway in the recruitment process and maintenance of JG cell identity in vitro to an in vivo mouse model. Gomez et al. very elegantly demonstrate that JG cell CBP and p300 are required for maintenance of JG cell identity, renin expression, and overall kidney development. They generated transgenic mice, where CBP, p300, or both are deleted, specifically in the JG cells, by crossing floxed CBP and/or floxed p300 mice with their previously described renin cre-recombinase mice (9). They report that renin expression and kidney structure are not altered by homozygous deletion of CBP (CBP<sup>fl/fl</sup>;Ren<sup>cre/cre</sup>) or p300 (p300<sup>fl/fl</sup>;Ren<sup>cre/cre</sup>) individually. However, dual deletion of these coactivators from renin-expressing cells (double-homozygous CBP<sup>fl/fl</sup>;p300<sup>fl/fl</sup>;Ren<sup>cre/cre</sup>) severely decreased renin expression and the number of renin-positive JG cells and caused severe disruption of kidney development. This was reflected by reduced kidney growth, extensive fibrosis, and significant structural alteration of the kidneys. In addition, reduced kidney growth and altered morphology were accentuated in the triple-homozygous (CBP<sup>fl/fl</sup>;p300<sup>fl/fl</sup>;Ren<sup>cre/cre</sup>) animals, where both renin alleles are deleted, in addition to CBP and p300.

Taken together, these data show an essential role of CBP and p300 in renin expression and JG cell development in vivo. The data also emphasize the essential role of the cAMP-dependent regulation of the CRE promoter region, which drives renin expression during development and also during adult life. The data show, for the first time, the important function of CBP and p300 in the development of kidney function in vivo, since whole animal knockout of any of these genes is lethal.

All good science leads to novel and exciting questions. The previous work by Pentz, Gomez, et al. (8) suggests that renin expression per se in a population of cells during development is linked to the acquisition of renin cell memory and plasticity. However, the molecular mechanisms that drive the fate for JG cell identity are unclear. Since the triple-homozygous (CBP<sup>fl/fl</sup>;p300<sup>fl/fl</sup>;Ren<sup>cre/cre</sup>) animals presumably did not express renin during development, can CBP/p300-dependent regulation of gene expression be sufficient to predistine the acquisition of renin cell memory? If so, a threat to homeostasis (that would induce recruitment in wild-type mice) should be impaired in double-homozygous (CBP<sup>fl/fl</sup>;p300<sup>fl/fl</sup>;Ren<sup>cre/cre</sup>) animals, emphasizing the relevance of CBP/p300 and cAMP signaling in renin cell lineage conditioning. In my opinion, Gomez et al. (1a) have challenged the philosophical thought that “fate” cannot be changed.
GRANTS

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REFERENCES