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Plasticity of Renin Cells in the Kidney Vasculature

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Abstract

During development, renin cells are precursors for arteriolar smooth muscle, mesangial cells, and interstitial pericytes. Those seemingly differentiated descendants retain the memory to re-express renin when there is a threat to homeostasis. Understanding how such molecular memory is constructed and regulated would be crucial to comprehend cell identity which is, in turn, intimately linked to homeostasis.

Keywords

Cell fate; Cell identity; Cell memory; Cell number; Recruitment

Juxtaglomerular (JG) cells are sensors. They synthesize and release renin in response to a decrease in renal perfusion pressure, a decrease in the concentration of sodium chloride in the macula densa, or activation of beta-adrenergic receptors [1]. Because angiotensin II suppresses renin release from JG cells, renin synthesis and release increases when the actions of angiotensin are prevented. The number of JG cells is quite small, constituting about 0.01% of the total kidney cell mass [2]. Nevertheless, under normal circumstances, release of renin by those few cells usually suffices to maintain blood pressure and fluid-electrolyte balance. However, if an adult animal is subjected to manipulations that threaten homeostasis, such as dehydration, hypotension, or hemorrhage, additional cells along the renal arterioles are called into action to synthesize and release renin. Under homeostatic threats, therefore, smooth muscle cells along the arterioles and sometimes mesangial cells and interstitial peritubular pericytes are transformed to synthesize renin [2–4••]. Thus, the ability to reestablish homeostasis is in large part determined by the number of cells that synthesize the hormone [2–5]. Interestingly, the transformation of these cells is not limited to the expression of renin: the cells adopt an epitheliod appearance, they produce granules to store renin, their endoplasmic reticulum and Golgi become prominent, their glycogen content increases, and the number of myofibrils is diminished. Underlying such remarkable morphological changes, a whole molecular program is activated. Thus, expression of renin is

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Compliance with Ethical Standards

Conflict of Interest Drs. Gomez and Sequeira Lopez declare no conflicts of interest relevant to this manuscript.

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accompanied by production of Akr1b7, an aldo-keto-reductase whose role seems to be the detoxification of harmful aldehydes produced during the high synthetic period of the cells [6••]. Expression of Akr1b7 follows that of renin throughout development and when newly transformed cells acquire the renin phenotype. In fact, expression of Akr1b7 is now considered a novel and highly reliable, renin-independent marker of cells programmed for the renin phenotype [6••]. In addition to renin and Akr1b7, the newly transformed cells express miR-330 as well as a number of genes involved in granulopoiesis, secretion, and contractility [2, 6••].

Once homeostasis is reestablished, the transformed cells stop making renin and become smooth muscle cells again. How morphological retransformation to the smooth muscle cell phenotype occurs is unclear. It is likely to involve the participation of autophagosomes to degrade granules and other structures generated during the heavy synthetic period of the renin phenotype. This hypothesis needs to be investigated. Interestingly, the ability to switch on and off the renin phenotype seems to depend on the developmental history of the transformed cells. During normal kidney development, renin cells are precursors that differentiate into arteriolar smooth muscle, mesangial cells and a subset of pericytes [2, 7••]. We found that those descendants retain the ability to synthesize renin when a physiological or pathological circumstance requires that more renin be produced to regain homeostasis [7••]. Given that the cells reenact the renin phenotype, it is not appropriate to refer to this phenomenon as “metaplastic” transformation, which implies de novo pathological transformation of one cell to another cell type not related by lineage. This implies that transformed cells that have descended from renin precursors had retained the memory to synthesize renin when confronted with a homeostatic challenge [7••]. Preservation of such memory may be a fundamental mechanism to respond to homeostatic threats without the need to incur the extra energy expenditure required with cell proliferation and/or migration. In fact no or dubious evidence has been found for cell proliferation when the number of renin-expressing cells increases in response to any of the manipulations explored so far [2]. Therefore, the term JG cell “hyperplasia” should be avoided when describing this phenomenon.

The reactivation of the renin phenotype makes use of an established developmental program whereby a molecular imprint of the renin phenotype may be left in the genome as the cells differentiate into smooth muscle cells. Upon exposure to a physiological threat, those cells, primed for action can quickly elicit the renin phenotype. The retransformation of cells has been extensively documented in vivo but it can also be observed transiently in vitro using cells derived from the renin progeny [7••]. This suggests that the reacquisition of the renin phenotype is a “built in” cell autonomous process whereby each cell retains the ability to sense and respond [2, 5, 7••, 8]. It is likely that such imprint or molecular memory resides in the organization of the cell’s chromatin genome-wide and at the locus of the renin gene. To address this question, we used a genome-wide approach to identify key epigenetic marks and unique super enhancer structures that control the identity and fate of renin cells in adult life. One may ask what are the intracellular signaling mechanisms that control the ability of cells from the renin lineage to switch back and forth between one fate and another. We have found that the cAMP/CBP/p300 pathway and the ancestral cell-to-cell communication Notch/RBP-J system are instrumental in maintaining the identity of renin cells and the ability of smooth

muscle cells to transform into renin synthesizing cells [2, 8, 9]. Further work is necessary to understand whether and how these two pathways are coordinated with one another. A number of other systems and pathways are likely to modulate renin cell identity including microRNAs, connexins, and cell-matrix interactions [2, 10].

Finally, it should be noted that the ability to reenact a cell identity phenotype and increase the number of hormone-producing cells is not exclusive of renin cells [4••, 5]. Heart cells are capable or re-expressing atrial natriuretic peptide—expressed by ventricular cells in the embryo-in a rat model of adult heart failure induced by aortocaval fistula. A similar phenomenon has also been observed with pancreatic beta cells, thyroid cells, and erythropoietin-synthesizing cells. In all of these situations, the adult recruited cells had been able to express the hormone in embryonic or fetal life, again suggesting that those adult cells retained the memory of the embryonic phenotype, which is reenacted when the organism is under physiological stress [2, 4••, 5, 7••]. Efforts directed to understand where in the genome this memory resides, how it is constructed and how it is retained throughout cell replication are under way in our laboratories.

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