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Renin cells in homeostasis, regeneration and immune defence mechanisms

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Abstract

An accumulating body of evidence suggests that renin-expressing cells have developed throughout evolution as a mechanism to preserve blood pressure and fluid volume homeostasis as well as to counteract a number of homeostatic and immunological threats. In the developing embryo, renin precursor cells emerge in multiple tissues, where they differentiate into a variety of cell types. The function of those precursors and their progeny is beginning to be unravelled. In the developing kidney, renin-expressing cells control the morphogenesis and branching of the renal arterial tree. The cells do not seem to fully differentiate but instead retain a degree of developmental plasticity or molecular memory, which enables them to regenerate injured glomeruli or to alter their phenotype to control blood pressure and fluid–electrolyte homeostasis. In haematopoietic tissues, renin-expressing cells might regulate bone marrow differentiation and participate in a circulating leukocyte renin–angiotensin system, which acts as a defence mechanism against infections or tissue injury. Furthermore, renin-expressing cells have an intricate lineage and functional relationship with erythropoietin-producing cells and are therefore central to two endocrine systems — the renin–angiotensin and erythropoietin systems — that sustain life by controlling fluid volume and composition, perfusion pressure and oxygen delivery to tissues. However, loss of the homeostatic control of these systems following dysregulation of renin-expressing cells can be detrimental, with serious pathological events.

The renin–angiotensin system (RAS) is central to the control of blood pressure and fluid–electrolyte homeostasis. A key feature of this enzymatic cascade is the tightly regulated secretion of renin by juxtaglomerular cells. Juxtaglomerular cells are able to sense and respond precisely to changes in blood pressure or extracellular fluid volume. They do so in part by communicating with adjacent cells at the juxtaglomerular apparatus, the circulation and the sympathetic nervous system. Under normal conditions, secretion of renin by juxtaglomerular cells is sufficient to maintain blood pressure and fluid homeostasis.

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However, juxtaglomerular cells are not the only cells that can produce renin (FIG. 1a). In the kidney, a subset of mesangial cells, arteriolar smooth muscle cells, interstitial pericytes and tubular cells also produce renin and serve in a local or systemic capacity to ensure blood pressure and fluid–electrolyte homeostasis. Beyond the kidney, renin precursor cells have been identified in multiple embryonic and postnatal tissues. The role of these precursors and their descendant cells in organs and tissues that are not traditionally associated with blood pressure regulation is intriguing, but data suggest that these cells have equally important functions in regeneration and immune defence mechanisms. Furthermore, an increasing body of evidence indicates that renin-expressing cells and their descendants are not terminally differentiated as originally thought. Rather, these cells demonstrate plasticity and are involved in a multiplicity of functions such as nephrovascular development and the regeneration of injured glomeruli. In addition, renin-expressing cells are linked to other fundamental homeostatic systems such as the control of red blood cells and oxygen supply to tissues, haematopoiesis and immune responses. In aggregate, renin-expressing cells seem to have acquired multiple functions designed to defend the organism against a variety of homeostatic challenges (FIG. 1b). Here, we review some of the key processes by which renin-expressing cells sustain homeostasis of various systems during development and in response to physiological or pathological threats.

Renin-expressing cells in development

In mice, cells that express renin are first observed around embryonic day 8.5 (E8.5), before the morphogenesis of most organs has been initiated^{1,2}. Thereafter, renin-expressing cells emerge in different tissues and organs, including skin, the nervous system, bone and bone marrow, pancreas, spleen, testes, eyes and a variety of other tissues³ (FIG. 1a). Before renin-expressing cells are observed in the developing metanephros, they can be seen distributed throughout the fetal adrenal glands, including within their transient fetal zone³. The adult adrenal gland is composed of cells from different embryonic sites, and lineage tracing of renin-expressing cells in the adult adrenal gland reveals radial stripes of labelled cells (derived from renin-expressing cells) running throughout the adrenal cortex as well as groups of labelled cells within the adrenal medulla. Interestingly, and as discussed in detail below, cells of the renin lineage that are present in the adult adrenal cortex possess the plasticity to re-express renin when aldosterone is blocked by deletion of aldosterone synthase or when the main source of circulating renin is removed (by bilateral nephrectomy). Such plasticity, which is also evident in cells that line the renal arterioles, is discussed in more detail below^{4–6}. The appearance of renin-expressing cells in the metanephric kidney is a relatively late event in the developmental history of these cells, occurring at around E11–12 (REF. ⁷).

The wide distribution of renin-expressing cells throughout development poses a series of questions that have remained for the most part unanswered. For instance, we do not currently know whether the transient or permanent expression of renin marks a special group of cells with specialized functions, and if so, the function of those cells. Current evidence, as discussed below, suggests that cells derived from renin progenitors maintain a degree of plasticity, but whether renin-expressing cells provide a reservoir of progenitor cells is also unknown⁷. Available evidence also suggests that renin-expressing cells have a role in the

growth and differentiation of the tissues they populate during embryonic development^{2,8}; however, the exact role of these cells in these processes requires further investigation. Insights into the transcriptional machinery of renin-expressing cells in different organs and tissues (for example, in bone marrow and kidney) might shed light on the nature and evolution of these cells, as discussed below⁹.

Vascular progenitors

In the developing mammalian kidney, precursors for the mural cells of the kidney arterioles emerge well before arterial vessels can be discerned by histological means⁸. These precursors are distributed within a loose and heterogeneous group of cells that constitute the stromal compartment¹⁰ (FIG. 2). Within the stromal compartment, forkhead box protein D1 (FOXD1)-expressing cells give rise to renin-expressing cells — including the juxtaglomerular cells — as well as vascular smooth muscle cells, mesangial cells, interstitial pericytes and interstitial fibroblasts^{10,11} (FIG. 1a). By contrast, cells in the stromal compartment that express stem cell protein (SCL; also known as TAL1) give rise to endothelial cells of the arterioles, glomeruli and peritubular capillaries¹². Following transplantation of murine embryonic kidneys at a stage (E11) in which they are devoid of any arterial blood vessels into the anterior chamber of the eye or under the renal capsule of an adult host mouse, the transplanted embryonic kidneys undergo not only nephrogenesis but also vascular development that resembles the arterial and arteriolar developmental pattern observed *in vivo*⁸. In fact, the mural cells, including renin-expressing cells, differentiate appropriately, distribute within expected sites along the renal arteriolar tree and connect to vascularized glomeruli, suggesting that stromal precursors have the capacity to assemble and form the kidney arterioles *in situ*^{8,10}. These experiments demonstrated the contribution of precursors from the adult host tissue to be non-existent, indicating that the blood vessels probably originated from the transplanted embryonic tissue through an initial process of vasculogenesis followed by angiogenesis⁸. Transplantation of an embryonic kidney under the kidney capsule of a newborn host, however, induces the development of blood vessels from both the transplanted organ and the host¹³, suggesting that progenitors from outside the kidney participate in blood vessel formation. Although the contribution of extrarenal progenitors to renal vascular development requires further study, in both of the experimental conditions described above the host kidney provided the transplanted embryonic kidneys with the appropriate differentiation signals and positional information to direct renin-expressing cells and other vascular cells to their appropriate locations along the renal arterial tree^{8,13}. The identification of these signals would represent a major step forward in understanding the mechanisms of kidney vascular development and has potential to aid in the generation of vascularized organs *in vitro*.

Renin cells in vascular development

As mentioned above, renin precursor cells in the developing metanephric kidney arise from FOXD1-expressing cells^{11,14} (FIGS 1a,2). The development of the renal arterial tree and the location of renin-expressing cells throughout this process follow an iterative, fractal-like pattern (FIG. 3). In early stages (E11–12), only a few renin-expressing cells are present and are randomly distributed in the stromal–interstitial compartment. As development progresses, the renin-expressing cells actively participate in the morphogenesis and

branching of the renal arterial tree¹⁵. As a new branch begins to form, a group of cells coalesces and forms a bulge, which elongates and matures into a new arteriolar branch¹⁵. As the renin-expressing cells mature and the vessel is consolidated, the renin-expressing cells differentiate into vascular smooth muscle cells. This process is repeated numerous times over a period of several weeks until maturation and elongation of the arterial tree is complete soon after birth². Renin-expressing cells are therefore extensively and heterogeneously distributed throughout the embryonic kidney, and this distribution pattern changes continuously until maturation of the arterial tree is complete^{16–18}. As the vessels mature and the cells differentiate into smooth muscle cells, renin-expressing cells are progressively restricted to the juxtaglomerular apparatus, where they remain throughout adult life¹⁹. The factors and mechanisms that control this developmental restriction are not well understood but are most likely associated with the mechanisms that control the differentiation of cells into smooth muscle and mesangial cells, including cAMP, FOXD1 and the Notch/recombining binding protein suppressor of hairless (RBP-J) signalling pathways. This changing pattern of renin distribution is conserved across species and has been demonstrated in every mammal examined, including rats, mice, pigs, sheep and humans^{7,20–23}. Interestingly, the ontogeny of renin distribution during mammalian development replicates the phylogenetic pattern of renin distribution in adult animals, from large arteries in fish to the classic localization of juxtaglomerular cells in mammals^{24–27}. As discussed below, the functions of renin in early development are thought to relate more to tissue morphogenesis than to regulation of arterial blood pressure and fluid–electrolyte homeostasis — functions that become extremely important in extrauterine life^{2,24,26,27}.

Regulation of renin-expressing cells in vascular development—As mentioned above, the major factors that control the differentiation and maintenance of renin-expressing juxtaglomerular cells include several components of the cAMP pathway^{28–32}, the transcription factor FOXD1 and the Notch/RBP-J pathway^{11,14,33}.

The second messenger cAMP is a well-known regulator of renin synthesis and release^{31,34–37}. Under normal physiologic circumstances, membrane-bound β -adrenergic receptors located in juxtaglomerular cells control the expression and release of renin via the generation of intracellular cAMP. Stimulation of membrane-bound β -adrenergic receptors results in activation of stimulatory G protein subunit α ($G_s\alpha$) and adenylyl cyclase, resulting in the generation of intracellular cAMP and activation of protein kinase A followed by phosphorylation of the transcription factor CREB (cAMP-responsive element-binding protein). In turn, CREB binds the cAMP-responsive element (CRE) located within the 5' regulatory regions of the renin gene (*REN*). The most prominent CRE is located within the renin enhancer. Access to CRE and binding of CREB is enabled by the histone acetyl transferases CREB-binding protein (CBP) and p300, which deposit acetyl marks in histones around the CRE, resulting in the local relaxation of chromatin and displacement of nucleosomes and providing access for CREB, which elicits transcription of *REN*. cAMP also activates other genes characteristic of the renin phenotype, including *Akr1b7*³⁸—encoding aldose reductase-related protein 1 (AKR1B7), which is highly expressed in renin-expressing cells during development and in the adult. AKR1B7 is believed to be a detoxifying enzyme that is capable of transforming harmful aldehydes into alcohols.

Expression of AKR1B7 can be used as an independent marker of renin-expressing cells, even when *REN* has been deleted^{38,39}.

Gene deletion studies have demonstrated that most of the components of the cAMP pathway are crucially involved in the differentiation and/or maintenance of renin-expressing cells. Conditional deletion of $G_s\alpha$, which is coupled to membrane-bound β -adrenergic receptors in renin cell precursors leads to a marked decrease in the number of renin-expressing cells in the vasculature accompanied by arteriolar abnormalities in early life^{29,32,40}. Furthermore, homozygous conditional deletion of both *CBP* and *p300* results in an absence of renin-expressing cells in the adult and severe nephrovascular abnormalities^{30,31}. These results clearly demonstrate the importance of the cAMP pathway in the development of renin-expressing cells and the central role of this pathway in the maintenance of kidney vascular integrity.

The Notch/RBP-J pathway is an evolutionary conserved cell-to-cell communication system involved in cell fate decisions during development^{41,42}. Renin-expressing cells possess Notch receptors, Notch ligands and the Notch transcriptional effector RBP-J³⁹. Deletion of *RBP-J* in renin-expressing cells reduced the number of renin-expressing cells and induced a remarkable change in the identity of the cells, characterized by an impaired ability to generate smooth muscle proteins and loss of their characteristic plump granular myo-epithelioid appearance, becoming thin, devoid of granules and poorly responsive to stimuli that activate renin expression^{33,43} (FIG. 4). However, deletion of *RBP-J* in more primitive *FOXD1*⁺ renin precursor cells not only reduced the number of renin-expressing cells but also resulted in thinner blood vessels and glomeruli that were devoid of mesangial cells with consequent development of glomerular aneurysms¹⁴. These studies indicate that the Notch/RBP-J pathway is crucial for the development of renin-expressing cells as well as for the appropriate differentiation of kidney arterioles and mesangial cells. The studies also indicate that loss of Notch activity in early precursors leads to a more severe phenotype than does deletion in more differentiated cells.

Further evidence of a fundamental role for the renal stromal compartment in the development of the kidney vasculature and the differentiation of renin cells is provided by ablation studies of *FOXD1*⁺ cells. Ablation of *FOXD1*⁺ cells with diphtheria toxin and global deletion of *FOXD1* induced the development of aberrant arterioles that penetrated the kidneys from abnormally developed subcapsular arteries¹¹. In addition, deletion of *FOXD1* or elimination of *FOXD1*⁺ cells led to a significant reduction in the number of renin-expressing cells, suggesting that the transcription factor *FOXD1* governs a molecular programme that controls the origin, number and orientation of the renal arterioles and the cellular endowment of the renal arterial tree¹¹. Given the complexity of these processes and their potential effects on ureteric and nephron development, further studies are required to determine how *FOXD1* controls guidance cues, cell number and the fate of the nephron and its vasculature.

The prorenin receptor—The prorenin receptor (PRR; also known as ATP6AP2) is another renin-interacting factor that is known to be involved in kidney development and may control the development of the kidney vasculature and differentiation of renin-expressing

cells^{44–47}. The presence of this receptor was anticipated several decades ago^{48,49} and was subsequently confirmed using expression cloning⁵⁰. The PRR binds both renin and prorenin: binding of prorenin generates active renin whereas binding of renin amplifies the hydrolysis of angiotensinogen to angiotensin I. However, the PRR has very low affinity for prorenin and it is unlikely that the levels of prorenin required to activate the receptor can be achieved *in vivo*⁴⁵. Interestingly, non-reninbinding partners seem to be responsible for the striking and important effects of the PRR^{44–47}. For example, the PRR is an accessory subunit of the vesicular V-ATPase and colocalizes in the plasma membrane with the Wnt receptor Frizzled (Fz) and low-density lipoprotein receptor-related protein 6 (LRP6). These proteins are essential for lysosomal functions such as endocytosis and autophagy, for various developmental processes and for cell proliferation and differentiation.

Global deletion of *PRR* is embryonically lethal, indicating its important role in development^{44,45}. The PRR is widely expressed in the developing kidney in the glomerular, tubular and vascular compartments⁴⁴. Conditional deletion of *PRR* in cell types derived from homeobox protein Hox-B7 (HOXB7)-expressing cells, such as collecting duct cells (FIG. 1a), results in kidney hypoplasia and a decreased ability to concentrate and acidify the urine⁴⁴. As expected, deletion of *PRR* in podocytes results in massive proteinuria and kidney failure⁵¹. Deletion of *PRR* in homeobox protein SIX2 (SIX2)-expressing nephron progenitor cells results in small cystic kidneys and reduced nephron numbers⁵². The PRR is also present in the kidney vasculature⁴⁴; however, its role in the development of arteriolar smooth muscle and renin-expressing cells has not been ascertained. Given the important role of PRR in developmental processes, it is very likely that the PRR is involved in the differentiation of both cell types.

Blood pressure and volume homeostasis

Anatomical and functional studies indicate that juxtaglomerular cells are sensors of the renal and extrarenal environment: they interpret and respond to signals that convey the level of perfusion pressure and the status of the extracellular fluid volume³⁷. Three major physiological mechanisms control renin synthesis and release: the concentration of sodium chloride (NaCl) in the macula densa, whereby a decrease in NaCl concentration stimulates renin synthesis and release; perfusion pressure as sensed by renal baroreceptors, whereby a decrease in perfusion pressure stimulates renin release; and β -adrenergic receptor activity, whereby activation of β -adrenergic receptors in juxtaglomerular cells by circulating or locally released catecholamines stimulates renin release. Usually, these mechanisms are activated simultaneously to fine-tune the appropriate amounts of renin released to the circulation³⁷ (FIG. 5). In addition, angiotensin II (ANGII) exerts a negative feedback inhibition on renin release; however, whether this effect is due to a direct effect of ANGII on type 1 ANGII receptors present in juxtaglomerular cells or is secondary owing to an increase in blood pressure is not entirely clear^{53–55}. In unstressed adults, secretion of renin by the few existent juxtaglomerular cells is usually sufficient to maintain a homeostatic balance of blood pressure and fluid homeostasis⁷. However, under more strenuous and persistent challenges such as chronic dehydration, persistent hypotension and/or chronic inhibition of the RAS, juxtaglomerular cells are maximally stimulated, after which additional cells along the afferent arterioles, interstitium and glomeruli (likely smooth muscle cells, interstitial

peritubular pericytes and mesangial cells) are stimulated to produce renin until the crisis passes and homeostasis is re-established^{3,7,56–64}. Thus, under strenuous circumstances, maintenance of volume and pressure homeostasis depends largely on the number of cells that can produce and release renin^{34,60,63}. Interestingly, proximal and connecting tubule epithelial cells can also re-express renin under certain conditions^{65–68}.

Mechanisms to increase renin cells

Several processes have been proposed to be responsible for the increased number of renin-expressing cells under states of physiological stress related to blood pressure and volume imbalance (FIG. 6).

Developmental memory—The most prominent mechanism involves the renewed production of renin expression by cells that are descendants of renin progenitor cells and were therefore capable of producing renin during development^{3,16,19,43,63,69}. For example, arteriolar smooth muscle cells, mesangial cells and interstitial pericytes retain the plasticity and developmental memory to express renin when confronted with a homeostatic challenge — a process that should not be confused with metaplastic transformation⁵⁶. Estimates suggest that in the kidney this process accounts for about 90% of the increase in the number of renin-producing cells following a relevant physiologic challenge³, suggesting that preservation of the developmental memory of the renin phenotype is a fundamental built-in mechanism to deal with homeostatic threats. It remains unclear whether the increased renin production involves some degree of cell proliferation; therefore, we suggest that the term juxtaglomerular cell hyperplasia be avoided until more convincing evidence is obtained^{70,71}.

We expect that reactivation of renin expression by non-renin-producing cells uses an established developmental programme whereby an epigenetic imprint that affects the spatial organization of the chromatin structure of the renin phenotype is left in the genome as the cells differentiate into smooth muscle or mesangial cells. The retransformation of these cells under conditions of stress has been extensively documented in animals, but it can also be transiently observed in vitro through the use of cells derived from the progeny of renin-expressing cells^{7,31,34,63}. This finding suggests that reacquisition of the renin phenotype is a cell autonomous process whereby each individual cell conserves its developmental memory and ability to respond to the appropriate stimuli with renin secretion^{1,69}. The ability of cells to reacquire a renin-expressing phenotype might not be limited to kidney cells. As mentioned above, cells in the developing fetal adrenal gland express renin earlier and more abundantly than in the embryonic metanephros. Studies from the early 1980s showed that bilateral nephrectomy with concomitant removal of the submandibular glands induced expression of renin in the adrenal cortex of adult mice, indicating that these cells also retain developmental memory⁶. Furthermore, adult animals harbouring a null mutation in *ALDOS*, which encodes aldosterone synthase, have renin-expressing cells — not only along the kidney arterioles but also in the adrenal gland — suggesting that the adult adrenal gland retains a group of cells that are capable of regaining the renin phenotype under stressful conditions⁵.

Two major signalling systems, the cAMP/CBP/p300 pathway and the evolutionary conserved Notch/RBP-J cell-to-cell communication system, are crucial in supporting the identity of renin-expressing cells and the ability of smooth muscle cells to re-express renin^{1,43}. How these two pathways are coordinated with one another remains to be defined. In addition to the cAMP and Notch pathways, other factors modulate the identity of renin-expressing cells, including, but not limited to, microRNAs, connexins and cell–matrix interactions^{30,31,72–75}.

Neogenesis—Another mechanism, termed ‘neogenesis’ (FIG. 6) has been demonstrated to contribute to the pool of renin-expressing cells⁷⁶. By using double transgenic mice⁷⁷, in which all cells that ever expressed renin are labelled with cell-membrane-localized enhanced green fluorescent protein (mG) fluorescence whereas cells that never expressed renin were labelled with cell-membrane-localized tdTomato (mT) fluorescence, the investigators could visualize cells that were activating *REN* for the first time and were therefore expressing mG fluorescence while temporarily retaining mT fluorescence. Thus, for a short period of time, the new renin-expressing cells were dually positive for mT and mG. In this context, ‘neogenesis’ means de novo expression of renin in a cell that has never expressed renin. The researchers found that neogenesis not only occurs during development, as expected, but also persists in adulthood and can be stimulated by pharmacological treatment with the angiotensin-converting enzyme (ACE) inhibitor, captopril, and by mesangial cell injury⁷⁶ and that this process contributes about 10% of the total number of renin-expressing cells. This mechanism could serve to maintain the pool of renin-expressing cells under normal homeostatic conditions as well as serve as a mechanism to respond to a sustained demand for renin under pathophysiological circumstances. Whether these neogenic cells came from a pool of FOXD1⁺ progenitor cells that have not yet expressed renin or from other mesenchymal cells is currently unknown. Also unknown is whether these new renin-synthesizing cells arise through direct transdifferentiation of lineage-unrelated adult cells that are already committed to a non-renin phenotype. These exciting possibilities remain to be investigated.

Prostaglandin-E₂-mediated induction of mesenchymal stem-like cells—A third process that potentially contributes to the number of renin-expressing cells is through activation of a small fraction of CD44⁺ mesenchymal stem-like cells⁷⁸. Under situations of sodium depletion, these cells are thought to be activated by the production of prostaglandin E₂ (PGE₂), which acts on the prostanoid EP4 receptors in those CD44⁺ cells to induce the migration of these cells to the juxtaglomerular apparatus where they insert themselves among the existent pool of juxtaglomerular cells⁷⁹. On arrival in the juxtaglomerular area, these cells stop producing CD44 and express renin⁷⁹. Although PGE₂–EP4 receptor interactions almost certainly have a role in renin synthesis and release, the specific participation and degree of contribution of mesenchymal stem-like cells to the pool of renin-expressing cells require further study. Of note, CD44 expression is not a true marker of mesenchymal stem cells but is usually observed as an artefact of culture conditions^{80,81}. Given that CD44 is also expressed by a variety of other cell types, including macrophages, the nature of these renal CD44 cells remains to be defined.

Consequence of increased renin expression—Regardless of the mechanism involved, cells that are induced to express renin undergo a remarkable transformation to an endocrine phenotype: the cells become plump and epithelioid; they acquire granules where renin is stored; their endoplasmic reticulum and Golgi apparatus become prominent; their glycogen content increases; and the number of myofibrils diminishes²⁰. This remarkable cellular transformation is accomplished by the activation of a molecular–epigenetic programme involving the expression of genes characteristic of the renin phenotype, such as *Akr1b7*, which, as mentioned earlier, encodes an aldo-keto reductase that is involved in the detoxification of harmful aldehydes produced during the high renin synthetic period of the cells^{38,39}. In addition, the transformed cells express miR-330. The function of this microRNA is unclear, but it has been proposed to counteract the stimulatory effects of miR125p-5b on the smooth muscle phenotype of renin-expressing cells: whereas miR-330 inhibits the expression of the smooth muscle protein smoothelin, miR-125p-5b stimulates it⁷⁵. The transformed cells also express proteins that are involved in granulopoiesis, secretion and contractility^{39,75}.

Of note, the mechanism of regulating homeostatic systems by changing the number of hormone-producing cells is not exclusive to renin-secreting cells: in a model of high-output heart failure induced by aortocaval fistula, ventricular myocardial cells re-express atrial natriuretic peptide in a pattern that resembles its normal expression in the embryonic heart⁸². Similarly, numbers of pancreatic β -cells, thyroid cells and erythropoietin (EPO)-synthesizing cells are increased to cope with the demands for insulin, thyroid hormone and EPO, respectively^{83–86}. In all these circumstances, adult cells are able to re-express a hormone expressed by that cell type during development in response to a homeostatic threat. Where in the genome this developmental memory resides, how it is constructed and how it is retained throughout cell division remain to be determined.

Renin-expressing cells and regeneration

The protective role of renin cells might not be limited to the control of circulatory and fluid homeostasis. Over the past few years, two independent groups have shown that renin cells might be directly involved in the repair and/or regeneration of glomerular tissue^{76,87–89}.

In an experimental model of mesangial proliferative glomerulonephritis⁸⁷, one study used a conditional inducible reporter to show that renin-expressing cells, presumably juxtaglomerular cells, contributed about two-thirds of the repopulated glomerular mesangial cells following mesangiolysis. Upon acquisition of the new mesangial phenotype, the cells stopped making renin and expressed markers of mesangial cells, including $\alpha 8$ integrin and platelet-derived growth factor receptor B. Similar to the processes that occur during development, it seems that in this situation the newly developed mesangial cells differentiated from renin-expressing cells that had retained their progenitor capabilities. Whether this process resulted from the re-emergence of a pre-established developmental programme or from another mechanism remains to be ascertained.

In another experimental model of anti-podocyte cytotoxic antibody-induced focal segmental glomerular sclerosis⁸⁹, cells that previously expressed renin were found to repopulate

injured podocytes and a fraction of parietal epithelial cells in the Bowman capsule. In this scenario, juxtaglomerular cells seemingly migrated and replaced the injured cells⁸⁸. Upon reaching the glomerulus, the cells stopped synthesizing renin and expressed podocyte markers, including synaptopodin, nephrin and Wilms tumour protein (WT1)⁸⁹. This intriguing finding elicits key questions. Given that podocytes are derived from SIX2⁺ progenitors rather than FOXD1⁺ progenitors, the findings suggest that adult juxtaglomerular cells are able to transdifferentiate into another, lineage-unrelated adult cell. Such transdifferentiation would require considerable rearrangement of transcriptional programmes and chromatin architecture to suppress genes that control renin cell identity and activate an entirely new epigenetic and transcriptional programme to drive the expression of podocyte identity genes. On the other hand, epithelial cells from the Bowman capsule and proximal tubules that are derived from SIX2⁺ progenitors do express renin during embryonic life and can express renin under physiological stress or pathological conditions^{20,65}; whether these epithelial cells and/or juxtaglomerular cells have the capacity to replace podocytes remains to be determined.

The nature of the signal(s) that trigger juxtaglomerular cells to migrate and transdifferentiate into podocytes or mesangial cells has not yet been identified. Furthermore, the precise mechanisms responsible for such marked cellular transformation remain to be defined. As this process has potential clinical applications for the replacement of damaged renal cell populations, one aspect that requires formal exploration is whether this repair process is a transient phenomenon or whether it is a clinically relevant process, resulting in sustained improvement in glomerular function.

Renin-expressing cells and oxygen sensing

Oxygen is essential for life. Thus, the net availability of oxygen as determined by the local balance between oxygen supply and consumption is crucial for maintaining oxygen homeostasis at the cellular and organismal levels. Although a certain degree of tissue hypoxia might be necessary for adaptation to high altitude and for tissue development and vascular growth, hypoxia can also have pathological roles in processes such as cancer and diabetes mellitus⁹⁰. Although somewhat controversial, acute hypoxia is generally acknowledged to stimulate renin synthesis and secretion^{90,91}. However, as renal denervation does not prevent renin release in response to hypoxia, the activation of renin-expressing cells could be mediated by mechanisms involving circulating catecholamine activation of the renal baroreceptor and/or the macula densa. In addition to producing renin, kidneys also produce EPO in response to hypoxia, which in turn stimulates the production of red blood cells in the bone marrow⁹². The cells that produce EPO have been identified as a specialized group of interstitial pericytes located near capillaries in the kidney cortex^{90,92}. When oxygen availability to these cells is diminished owing to either reduced oxygen delivery or increased oxygen consumption, EPO-producing interstitial pericytes, normally held in reserve, are massively recruited to produce EPO. Depending on its severity, anaemic or hypoxic conditions can increase circulating levels of EPO up to 1,000 times higher than normal^{93,94}. EPO is then rapidly delivered to the circulation. Interestingly, EPO-producing fibroblasts originate from the same FOXD1⁺ progenitor cells that give rise to renin precursors and other cells of the kidney vasculature. Interestingly, and as discussed earlier, interstitial pericytes in

mice and humans can also produce renin under certain circumstances^{62,95,96}. These findings indicate a possible functional, although unclear, relationship between EPO-producing cells and renin-producing cells. Furthermore, under normal circumstances, renin-expressing juxtaglomerular cells express hypoxia-inducible factor 2 α (HIF2 α ; also known as EPAS1), which regulates EPO production³⁹. Therefore, the mechanisms for sensing and responding to oxygen and those involved in the regulation of volume and blood pressure homeostasis seem to converge on these unique cell types that are capable of producing both EPO and renin. How these two systems cooperate to preserve homeostasis in both systems is a matter of intense investigation.

Interaction between renin and EPO systems

As mentioned above, renin-expressing cells are plastic and can switch their phenotype in response to endogenous and/or exogenous signals during both development and disease. A study of genes involved in the hypoxia response revealed an extreme example of this plasticity⁹⁷, whereby conditional deletion of the von Hippel–Lindau disease tumour suppressor (*VHL*) gene resulted in an accumulation of HIF2 α in cells derived from the renin precursor cells, including smooth muscle cells along the arterioles, juxtaglomerular cells and mesangial cells in mice⁹⁷. This dysregulation of HIF2 α induced renin descendant cells to constitutively express EPO, which was readily secreted into the circulation where it stimulated erythropoiesis in the bone marrow, causing the mice to develop secondary erythrocytosis⁹⁷ with haematocrits ranging from 60 to 70% (normal range 47–49%). The presence of circulating EPO under these conditions was presumed to have originated from descendants of renin-expressing cells⁹⁷; however, because non-renal organs, such as the liver, can produce EPO under hypoxic conditions, this hypothesis needs to be validated. Interestingly, concurrent deletion of *HIF2 α* prevented the erythrocytosis phenotype, suggesting that the plastic response was driven by HIF2 α -induced stimulation of EPO synthesis⁹⁸. The mechanism(s) underlying the shift in juxtaglomerular cells from a renin-expressing to an EPO-expressing phenotype also requires study, as it is unclear whether the suppression of renin in these cells is the result of a direct (cell autonomous) effect or an indirect systemic effect of circulating EPO. In this regard, exposure of mice with specific deletion of *VHL* in renin-expressing cells to a low-salt diet and the ACE inhibitor enalapril (two powerful stimuli for renin synthesis and release) resulted in a blunted renin response, with renin mRNA levels increased only to about one-third of those achieved in similarly treated control animals⁹⁷. Conversely, renal expression of EPO mRNA increased 46-fold in response to the physiological challenge⁹⁷. Both responses are interesting and somewhat unexpected. The reason(s) for the blunted renin response to the physiological challenge remains to be elucidated, but several possibilities — that are not mutually exclusive — are possible. Under normal circumstances, both the macula densa and the baroreceptor mechanisms are activated in response to a low-sodium diet and enalapril, potentiating the renin response. However, the normal blood pressure of *Vhl*^{−/−}REN mice⁹⁷ might blunt this renin response. The presence of normal blood pressure eliminates a powerful stimulus for renin release, as activation of the baroreceptor mechanism will not occur or will be diminished, thereby dampening the effect of sodium depletion on renin synthesis and release. Furthermore, sodium reabsorption by proximal tubular cells requires oxygen consumption. By decreasing sodium reabsorption, ACE inhibition can reduce oxygen

consumption^{99,100}, thereby exposing both renin-expressing cells and pericytes to above-normal interstitial O₂ concentrations and markedly diminishing both renin and EPO expression. The effect of oxygen exposure cannot, however, explain the mechanisms of heightened EPO activation observed in response to sodium depletion and enalapril in these mice. Further work is needed to ascertain why EPO-secreting cells respond so well to a manipulation that is known to activate renin synthesis and release. A second unexplained issue is whether the suppression of renin in mice with renin cell-specific deletion of *VHL* is due to an as yet speculative intrinsic molecular crosstalk between the *HIF2a/VHL* genes and *REN* or whether the suppression of renin is secondary to the systemic effects of EPO on the kidneys via increased blood pressure and increased sodium delivery to the macula densa, as described below^{99,100}. This consideration is important given that a secondary effect of EPO on renin expression might imply that *REN* is in fact responsive and operating normally but is simply constrained in the intensity of its response given the physiological status of the model (that is, normal blood pressure and blunted baroreceptor response in the presence of high circulating EPO levels). Alternatively, the fact that only the renin response is limited might indicate that the juxtaglomerular cells are not fully converted to an EPO phenotype and that they are expressing both hormones to a certain extent.

A clue to the issues posed above is provided by an excellent study of healthy human volunteers who were treated with recombinant human EPO (rhEPO) for 28 days¹⁰⁰. Interestingly in these volunteers, proximal tubular reabsorption of sodium was significantly decreased in response to rhEPO, consequentially enhancing the load of NaCl delivered to the macula densa and subsequently suppressing renin and aldosterone secretion¹⁰⁰, suggesting that one of the earliest responses to exogenous EPO exposure is a decrease in renin secretion mediated by signals from the macula densa¹⁰⁰. Together, these data suggest that the RAS and the EPO–oxygen-sensing system interact through various mechanisms involving cell plasticity, direct communication and indirect communication mechanisms through circulatory effects to maintain perfusion pressure and oxygen delivery to tissues in response to bleeding or hypoxia (FIG. 7).

Haematopoiesis and immunity

Numerous studies have documented the presence of components of the RAS in haematopoietic tissues, including the bone marrow, spleen and thymus, and in circulating leukocytes^{9,101,102}.

B renin cells

As described above, deletion of *Rbp-j* in mice led to a severe decrease in the number of cells expressing renin at 4 months of age. Fate tracing experiments demonstrated that the decrease in number of renin-positive cells was not due to cell death but rather to a marked change in the phenotype of these cells: the cells could not express renin, smooth muscle proteins or AKR1B^{33,43}. They were also unable to make renin granules and lost their ability to express *REN* in response to sodium depletion and captopril treatment. Physiologically, these changes were reflected by low circulating renin and decreased blood pressure^{33,43} and indicated that RBP-J controls a genetic programme that determines the endocrine-contractile phenotype of

the cells. In addition, at about 6–8 months of age these mice developed a highly penetrant form of pre-B cell leukemia⁹. This unexpected finding prompted an investigation of the responsible cell group within the bone marrow. Using a variety of approaches including fate tracing, phenotyping with flow cytometry and RNA sequencing, we found that a subset of pre-B lymphocytes in the bone marrow, spleen and circulation express renin⁹; we termed this subset B renin cells to indicate that they are renin-expressing cells of a lymphocyte pedigree. Interestingly, B renin cells in the bone marrow and spleen are proportionally at least ten times more prevalent than renin cells in the kidney and share remarkable similarities with renin cells from the kidney⁹. Both cell types are developmentally regulated and they decrease in number with maturation. In the kidney, this diminution in the number of cells is associated with the differentiation of renin progenitors into other cell types, including the smooth muscle cells of the renal arterioles and glomerular mesangial cells¹. The decrease in number of B renin cells in the bone marrow and spleen is potentially coupled with lymphocyte maturation, as suggested by the development of a pre-B cell leukaemia phenotype in mice with deletion of the cell-fate determinant *Rbp-j*⁹. B renin cells and kidney renin-expressing cells also share expression of transcription factors that are commonly associated with haematopoietic development, including RBP-J, the DNA-binding protein Ikaros (IKZF1), HIF2 α , transcription factor COE1 (EBF1) and protein C-ets 1 (ETS1)^{9,39}. Whether these similarities represent the conservation of ancestral transcriptional machineries or a true lineage relationship remains to be determined. Of note, however, both types of cells require RBP-J for appropriate maturation. As mentioned earlier, deletion of *RBP-J* in the kidney inhibits the production of renin-expressing cells and results in a change in cell phenotype^{9,33,43}. Similarly, deletion of *RBP-J* in B renin cells inhibits their differentiation, induces alterations in their cell cycle and leads to their accumulation as leukaemic blast cells. The function(s) of renin-expressing cells in haematopoietic tissues needs to be explored in further detail; however, in line with the developmental role of renin-expressing cells in the kidney, it is likely that B renin cells control marrow morphogenesis and haematopoiesis.

RAS components in circulating leukocytes

Of particular interest is the role of circulating haematopoietic cells that express components of the RAS^{101,103}. In addition to renin expression, circulating leukocytes, as well as several distinct leukocyte subtypes (such as monocytes, neutrophils and lymphocytes), express other components of the RAS, including angiotensinogen, ACE and angiotensin receptors^{101–103}.

Although the role of the RAS within leukocytes is a subject of continued study, current evidence suggests that RAS components expressed by white blood cells within the circulation and resident in tissue participate in inflammatory processes within and outside the kidney^{102–107}. Thus, the presence of RAS components within leukocytes might enable the system to exert localized, targeted effects at sites of infection and/or inflammation without the need to increase plasma levels of renin, angiotensinogen or angiotensin peptides through classical endocrine pathways, which could result in detrimental circulatory changes such as hypertension. In this manner, aggregates of leukocytes would behave as small carriers of RAS components, which could act intracellularly or extracellularly at the site of

infection without interfering with the endocrine functions of the RAS and/or affecting circulatory homeostasis^{101,103,108,109}.

The potential role of a leukocyte RAS in disease processes, such as hypertension, inflammatory vascular disease and haematopoietic neoplasia, is supported by experimental and clinical data from the past few years^{104–107,110}. For example, a 2017 study demonstrated that the expression of ACE enhances the defence capabilities of neutrophils against bacterial infections such as methicillin-resistant staphylococcus, probably by enhancing superoxide production¹¹¹. Whether renin in lymphocytes is simply a marker of a special subtype of B lymphocytes or has a role unrelated to angiotensin generation remains to be determined. The fact that these primitive B renin cells retain phagocytic properties suggests that they participate in innate immune responses. Further work is required to determine whether renin in B lymphocytes has a role independent of its traditional role in the regulation of blood pressure and fluid– electrolyte homeostasis. However, the possibility that a leukocyte RAS acts as a first line of defence against infections and other foreign antigens is an exciting prospect and an area for future exploration.

Changes in renin cell fate and disease

The RAS is a highly evolutionary conserved system^{24,25,112,113} that has retained its main features throughout evolution, enabling it to maintain volume and pressure homeostasis under pathophysiologic conditions. The efficiency of renin-expressing cells to counteract a threat to volume and pressure homeostasis can, under certain conditions, be detrimental. Mice, rats and humans with spontaneous or experimental mutations of any of the RAS genes can develop a spectrum of renal abnormalities including renal medullary underdevelopment, hydronephrosis, an inability to concentrate urine, polyuria, polydipsia, renal failure and anaemia^{114–122}. In addition, animals (including humans) with deletion of any component of the RAS develop characteristic renal arterial and arteriolar abnormalities that precede all other morphological and functional alterations^{1,5,60,114–125}. The arterioles under these circumstances are fewer and shorter than those of control animals, denoting a defect in vascular branching and elongation, and they display a characteristic concentric arteriolar hypertrophy (FIG. 8). Similar vascular abnormalities have also been found in animals treated with RAS inhibitors in early life and in adult hypertensive rats treated with the RAS blockers aliskiren and valsartan^{120,126}, and several lines of evidence suggest that the primary site for the initiation of these abnormalities is the kidney vasculature. First, deletion of *REN* solely in the vasculature replicates the morphological and physiological abnormalities observed in global renin-knockout mice, whereas deletion of *REN* in the tubular compartment does not cause any vascular alterations¹²⁷. Furthermore, deletion of *REN* in the vasculature nearly eliminated plasma renin, indicating that vascular renin is the primary source of circulating renin and that the complex phenotype described above can be achieved by the vascular alterations induced by renin depletion in the vasculature¹²⁷.

Interestingly, ablation of renin-expressing cells with diphtheria toxin does not replicate the concentric vascular hypertrophy of *REN* deletion, suggesting that the renin cells themselves are responsible for the vascular pathology¹²⁸. To explore this hypothesis, we studied renin-null mice, which have the same phenotype as all the other models of RAS ablation and

undetectable levels of angiotensin and renin, making it unlikely that the phenotype is caused by the enzyme or the angiotensin peptides themselves. Using genetic fate tracing and fluorescent reporting of renin promoter activity, we found that the cells that would normally express renin persist in the renin-knockout mice and that these cells maintain the molecular memory of the renin phenotype, increase in number and are broadly distributed along the kidney vasculature (by contrast, renin-expressing cells are restricted to the a few juxtaglomerular cells in wild-type mice)¹¹⁵. Furthermore, these cells encircle the renal vessels and insert themselves in an apparently random fashion within the arteriolar walls among concentric layers of seemingly hyperplastic smooth muscle cells¹¹⁵ (FIG. 8). These findings suggest that renin cells contribute directly to the vessel pathology either by physical interaction and/or through the production of factors that induce the growth of smooth muscle cells. The identification of such factors might uncover potential therapeutic targets to prevent potential vascular complications that could occur during the treatment of hypertension. Although the mechanisms underlying this seemingly nonhomeostatic behaviour of renin cells are not understood, we hypothesize that although the evolutionary conserved ability of renin-expressing cells to sense and respond to sustained threats — such as hypotension and dehydration — by recruiting new renin-producing cells serves the organism well during early development, it can cause adverse outcomes when the desired homeostasis is not achieved. For instance, in mice with deletion of *REN*, the renin-null cells are constantly stimulated by chronic hypotension and decreased volume. As they cannot produce renin, we suspect that the cells continue to attempt to restore homeostasis by activating a variety of genes that are part of the genetic programme of the renin phenotype, including expression of *AKR1B7*, *miR-330* and a variety of angiogenic and growth factors^{39,115}. This futile, chronic attempt to restore homeostasis enables the renin-null cells to maintain a fetal-like state, resulting in the observed concentric vascular hypertrophy. However, this hypothesis requires formal testing.

Other mutations that affect the phenotype of renin-expressing cells also markedly affect renin cell fate and kidney pathology. For example, conditional deletion of connexin 40 (*CX40*; also known as *GJA5*) in renin-expressing cells results in the displacement of juxtaglomerular renin-expressing cells from the juxtaglomerular apparatus to areas surrounding the glomeruli⁷². As a result, the renin-expressing cells are unable to appropriately sense perfusion pressure and are relatively insensitive to ANGII. As a consequence, the *CX40*-knockout mice develop severe hyper-reninaemia and malignant hypertension^{72,129}.

Conditional homozygous deletion of the histone acetyl transferases *Cbp* and *p300* in mice results in an absence of renin-expressing cells and leads to end-stage renal disease characterized by small kidneys possessing an irregular, granular and hard surface with cortical depressions that correspond histologically to bands of fibrosis replacing blood vessels. In addition, the mutant kidneys display cortical and medullary cysts³⁰. The few renin-expressing cells present (less than 1–2% of numbers of wild-type mice) are thin and elongated, resembling fibroblasts³⁰. This study clearly demonstrates that these acetyl transferases are required for the maintenance of renin cells and the structural integrity of the kidney. The observed findings can be in part explained by the lack of renin cells but may also be due to the loss of CBP and/or p300 in cells that expressed renin early in development

because *Cbp* and *p300* were deleted in all cells that expressed renin throughout development (such as renal arterioles, mesangial cells and tubular cells)³⁰. Finally, deletion of the gene for the microRNA-processing enzyme Dicer leads to a lack of crucial microRNAs and an absence of renin-expressing cells, resulting in the replacement of renal arterioles by bands of interstitial fibrosis resembling the ‘striped’ pattern of fibrosis typical of ciclosporin or tacrolimus toxicity⁷⁴. In between the fibrotic bands of *Dicer*-knockout mice are zones of fairly well-preserved parenchyma. The larger intrarenal arteries and arterioles are thickened by perivascular fibroplasia and not by an increase in the number of smooth muscle cells, suggesting that renin-expressing cells have either died or have not differentiated into smooth muscle cells. Careful fate tracing studies combined with markers of cell death are necessary to address these possibilities⁷⁴. In addition, the lack of renin-expressing cells in this model is associated with markedly decreased levels of plasma renin compared with those of wild-type animals and the development of hypotension. The combination of abnormal vessel architecture with hypotension leads to hypoperfusion and localized renal ischaemia, which further aggravates the fibrotic response⁷⁴. These examples highlight the fundamental role of renin-expressing cells and their descendants in the development and maintenance of the structural and functional integrity of the kidney and in cardiovascular homeostasis and illustrate the consequences of their dysfunction.

Conclusions

Renin cell precursors appear early in the developing embryo and differentiate into multiple cell types in different tissues and organs. The descendants of early renin-expressing cells constitute a diverse group of cells with proposed roles in processes such as vascular morphogenesis during development and tissue repair. Available data suggest that these cells maintain a degree of plasticity and are able to switch phenotypes to control homeostatic processes such as blood pressure and volume balance as well as contribute to other defence processes involving cells of the haematopoietic and innate immune systems. Renin-expressing cells also have an intricate lineage and a functional relationship with EPO-producing cells and thus also have roles in tissue perfusion and in oxygen delivery to tissues.

Further work is needed to unravel the mechanisms that regulate renin cell identity, the plasticity of renin-expressing cells and the functional diversity of these cells within different tissues. Such knowledge has the potential to facilitate the design of molecular–epigenetic approaches to target renin-expressing cells and the systems with which they interact to treat and/or prevent complications associated with the dysregulation of systems that are regulated by renin.

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Glossary

Juxtaglomerular cells

A specialized group of renin-producing, myo-epithelioid, granulated cells located at the tip of the afferent arterioles at the entrance to the glomeruli

Juxtaglomerular apparatus

The functional sensory and responding unit of the renin– angiotensin system

it is composed of the afferent and efferent arterioles

the macula densa and the extraglomerular mesangium

Plasticity

The ability of cells to switch phenotypes

Metanephros

The definitive kidney of adult mammals

Fetal zone

A large, eosinophilic steroidogenic group of cells of the fetal adrenal gland, which is believed to involute after birth

Mural cells

Cells located within the wall(s) of the renal arterioles, including smooth muscle cells and renin-expressing cells such as juxtaglomerular cells. In larger arteries, adventitial cells such as fibroblasts and perivascular pericytes are sometimes considered mural cells. Although part of the arterial wall, endothelial cells are not usually considered mural cells

Stromal compartment

One of the three main compartments of the developing kidney; it contains FOXD1⁺ progenitors of vascular smooth muscle cells, renin-expressing cells, mesangial cells and pericytes as well as SCL⁺ progenitors of endothelial cells of arteries and arterioles, glomeruli and interstitial capillaries

Vasculogenesis

De novo, local differentiation and assembly of blood vessels from resident progenitor cells that are usually derived from multiple clones

Angiogenesis

The formation of new blood vessels, usually by sprouting of new branches from pre-existing vessels. This process usually involves the proliferation and/or elongation of cells from single clones. In the case of arterioles, it is followed by the recruitment of perivascular smooth muscle cells

Fractal

A shape or structure made of smaller parts or units that repeat themselves and resemble the whole

Developmental memory

The ability of cells to expressly re-acquire a phenotype previously expressed during development

Metaplastic transformation

Pathological transformation of one cell type into another not related by lineage

Hyperplasia

Increase in cell number, usually due to increased cell proliferation

Neogenesis

De novo expression of a gene (for example, renin) in a cell that has not previously expressed the gene

Direct transdifferentiation

Transformation of one cell into another without reprogramming into induced pluripotent stem cells

Erythrocytosis

Increase in red cell mass

Leukaemic blast cells

Immature forms of white blood cells that fail to differentiate normally and proliferate in an uncontrolled manner, leading to tissue infiltration and, if untreated, death

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Key points

- Renin-expressing cells are evolutionarily conserved and have retained features to contribute to the defence against threats to survival such as bleeding, dehydration, hypotension and/or hypoxia
- In the embryo, renin-expressing cells populate diverse tissues where they might have a role in tissue morphogenesis and growth; in the developing kidney, they are progenitors for arteriolar and mesangial cells and are crucial for arteriolar branching morphogenesis
- In adults, cells derived from progenitors that previously expressed renin retain their developmental memory and can regenerate injured glomeruli or re-express renin to achieve blood pressure and fluid–electrolyte homeostasis
- Renin-expressing cells are linked to other fundamental homeostatic systems, such as the haematopoietic and circulating leukocyte renin–angiotensin systems, through which they might contribute to bone marrow development and the local control of inflammation or infections
- Renin-expressing cells intersect with erythropoietin-producing cells and are therefore at the crossroads of two key life-sustaining systems involved in the control of fluid volume, perfusion pressure and oxygen delivery to tissues

Fig. 1. Distribution and origin of renin-expressing cells in renal and extrarenal sites

a | Renin-expressing cells appear during embryonic development in renal and extrarenal tissues and organs. In the adult, renin-expressing cells in the kidney vasculature are considered the ‘classical’ sites of renin production. These cells descend from forkhead box protein D1 (FOXD1)-expressing progenitors, which give rise to the renin-producing juxtaglomerular cells as well as a subset of mesangial cells, smooth muscle cells and interstitial pericytes. FOXD1 descendants can re-express renin under conditions of physiological or pathological stress. In addition, some renal tubular cells, which descend from homeobox protein Hox-B7 (HOXB7)-expressing (that is, cells of the collecting duct) or homeobox protein SIX2 (SIX2)-expressing progenitors (that is, cells of the proximal tubule cells and Bowman capsule), can express renin during early development and in response to physiological challenges such as sodium depletion. Extrarenal cells derived from a variety of haematopoietic and nonhaematopoietic progenitor cells can also express renin during early development and in response to physiological challenges. For example, the iliac arteries and B lymphocytes can express renin in response to inhibition of the renin–angiotensin system, and adrenal cells can express renin in response to aldosterone synthase (*ALDOS*; also known as *CYP11B2*) deletion or bilateral nephrectomy concomitant with bilateral submandibular gland removal in the adult. Other extrarenal cells, such as Leydig cells, maintain renin expression in adult life. Cells and tissues that express renin in the adult are highlighted in pink. **b** | The various functions of renin cells. Renin-expressing cells are diverse and can have many roles, including in tissue morphogenesis, glomerular regeneration, control of blood pressure and extracellular fluid volume, haematopoiesis and immune responses, red blood cell mass and oxygen delivery.

Fig. 2. Progenitor compartments and nephrovascular development

At embryonic day 11.5, three progenitor compartments can be discerned in the developing mammalian kidney: the ureteric bud characterized by the expression of homeobox protein Hox-B7 (HOXB7); the cap mesenchyme characterized by the expression of homeobox protein SIX2 (SIX2) and Cbp/p300-interacting transactivator 1 (CITED1); and the stromal compartment, which contains forkhead box protein D1 (FOXD1)-expressing cells. Ureteric HOXB7 precursors give rise to the collecting ducts. Cap mesenchyme progenitors give rise to epithelial cells of the proximal and distal tubule, the loop of Henle, Bowman capsule and podocytes. FOXD1⁺ stromal cells are the progenitors for the mural cells of the kidney arterioles, including renin-expressing juxtaglomerular cells, smooth muscle cells (SMCs), mesangial cells and pericytes (not shown). Descendants from stem cell protein (SCL)-expressing endothelial progenitors are not depicted.

Fig. 3. Localization of renin-expressing cells throughout branching morphogenesis of the renal arterial tree

As the arterioles are formed, development of new arteriolar branches is preceded by the appearance of a few renin progenitor cells at the point of branching (part **a**). This event is followed by bulging (part **b**) and elongation (part **c**) of the newly formed branches.

Throughout the maturation of the arterioles, renin-expressing cells cover most of the trajectory of the blood vessels. As maturation is completed, renin precursors differentiate into smooth muscle cells, and renin-expressing cells become restricted to the juxtaglomerular area (part **d**). FOXD1, forkhead box protein D1.

Fig. 4. The Notch/RBP-J signalling pathway controls the fate of stromal and renin cell precursors

Forkhead box protein D1 (FOXD1)-expressing stromal cells are progenitors for renin precursor cells (RPCs), which in turn differentiate into renin-expressing juxtaglomerular cells, smooth muscle cells (SMCs) and a group of mesangial cells. Deletion of *RBP-J* in FOXD1 progenitors leads to striking morphological abnormalities characterized by few and thin blood vessels and an absence of renin-producing cells and mesangial cells. The lack of mesangial cells leads to the development of aneurysms in glomeruli. By contrast, deletion of *RBP-J* in RPCs leads to a change in their fate, as they are no longer able to synthesize renin and properly express smooth muscle genes. Despite the low blood pressure of these mice, the mutant cells are unable to reactivate renin expression. In addition, they do not reactivate renin expression in response to a challenge such as sodium depletion combined with angiotensin-converting enzyme inhibition. E, embryonic day; P, postnatal day; RBP-J, recombining binding protein suppressor of hairless.

Fig. 5. Major mechanisms controlling renin synthesis and release

A decrease in perfusion pressure activates the renal baroreceptor, stimulating renin synthesis and release. A decrease in sodium chloride (NaCl) concentration at the macula densa stimulates renin synthesis and release. Activation of β -adrenergic receptors (β -ARs) present in juxtaglomerular cells induces renin synthesis and release via the cAMP pathway (inset). Generation of cAMP leads to activation of protein kinase A (PKA) and phosphorylation of CREB (cAMP-responsive element-binding protein), a transcription factor that binds CRE (cAMP-responsive element) and activates renin transcription. Angiotensin II inhibits renin synthesis and release (through a negative feedback loop) via activation of the type-1 angiotensin II receptor (AT1R; also known as AGTR1) and by increasing blood pressure. AC, adenylyl cyclase; CBP, CREB-binding protein; $G_s\alpha$, stimulatory G protein subunit α .

Fig. 6. Mechanisms to increase the number of renin-expressing cells

a | In adult unstressed mammals, granulated renin-producing cells are confined mostly to the juxtaglomerular area. **b** | Other cells derived from renin precursor cells — a subset of smooth muscle cells (SMCs), pericytes and mesangial cells — retain the memory to re-express renin when challenged by a physiological stressor, such as hypotension, dehydration or sodium depletion — a phenomenon referred to as developmental memory. **c** | In addition, renin-expressing cells can be generated de novo from non-renin-lineage-derived cells, either by a process of transdifferentiation whereby an existing non-renin cell (SMC or other precursor) is induced to express renin (neogenesis) or by transformation (or differentiation)

of a mesenchymal stem-like cell into a renin-producing cell, potentially through the actions of prostaglandin E₂ on the prostanoid EP4 receptors.

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Fig. 7. Interaction between renin-expressing cells and the erythropoietin–oxygen delivery system

During hypoxia or bleeding, renin synthesis and release are stimulated, leading to the generation of angiotensin II (ANGII) from angiotensinogen (AGT) and angiotensin I (ANGI). ANGI is converted to ANGII by the enzyme ACE. ANGII stimulates Na reabsorption and O₂ consumption in the renal tubules. These effects decrease the local interstitial O₂ concentration, which stimulates the synthesis and release of erythropoietin (EPO) by pericytes, leading to an increase in red blood cell mass, which consequently feeds back to inhibit further EPO production. ANGII, acting on angiotensin receptors in arteriolar smooth muscle cells, induces vasoconstriction, which is potentiated by the altered rheological properties of the blood (such as increased haematocrit level). The increase in blood pressure (BP) consequently suppresses renin release. ACE, angiotensin-converting enzyme.

Fig. 8. Vascular alterations upon ablation of the reninangiotensin system

Experimental or spontaneous mutations in genes of the renin–angiotensin system (such as genes that encode angiotensinogen, renin and angiotensin-converting enzyme, combined deletion of genes encoding angiotensin receptors 1A and 1B and deletion of aldosterone synthase (*ALDOS*; also known as *CYP11B2*)) leads to arteriolar abnormalities. This paraffin section from a renin-knockout mouse kidney immunostained for α -smooth muscle actin demonstrates short and thickened afferent arterioles (aa). The concentric vascular hypertrophy of an interlobular artery (IA) is caused by abnormal smooth muscle cells. Periglomerular (arrows) and interstitial (arrowheads) fibroses are also evident. G, glomerulus.