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Beyond the Paradigm: Novel Functions of Renin-Producing Cells

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Contents

Abstract The juxtaglomerular renin-producing cells (RPC) of the kidney are referred to as the major source of circulating renin. Renin is the limiting factor in renin-angiotensin system (RAS), which represents a proteolytic cascade in blood plasma that plays a central role in the regulation of blood pressure. Further cells disseminated in the entire organism express renin at a low level as part of tissue RASs, which are thought to locally modulate the effects of systemic RAS. In recent years, it became increasingly clear that the renal RPC are involved in developmental, physiological, and pathophysiological processes outside RAS. Based on recent experimental evidence, a novel concept emerges postulating that next to their traditional role, the RPC have non-canonical RAS-independent progenitor and renoprotective functions. Moreover, the RPC are part of a widespread renin lineage population, which may act as a global stem cell pool coordinating homeostatic, stress, and regenerative responses throughout the organism. This review focuses on

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the RAS-unrelated functions of RPC – a dynamic research area that increasingly attracts attention.

Keywords Juxtaglomerular cells · Progenitor cells · Regeneration · Renin lineage · Tissue injury

Abbreviations

AA	Afferent arteriole
ACE	Angiotensin-converting enzyme
Akr1b7	Aldo-keto reductase family 1 member B7
Ang	Angiotensin
ArcA	Arcuate artery
AT1	Angiotensin II type 1 receptors
AT2	Angiotensin II type 2 receptors
BrdU	Bromdesoxyuridin
cAMP	3′,5′-Cyclic adenosine monophosphate
Cre	Cre-recombinase
DAMPs	Damage-associated molecular patterns
DNA	Deoxyribonucleic acid
EP	Prostaglandin EP receptor
EPO	Erythropoietin
FoxD1	Forkhead box D1
G	Glomerulus
GFR	Glomerular filtration rate
Gs	G-protein stimulatory subunit
GTPases	Guanosine-5′-triphosphate hydrolases
IA	Interlobular artery
IP	Prostacyclin I2 receptor
JG	Juxtaglomerular
JGA	JG apparatus
loxP	Locus of X-over P1
MC	Mesangial cell
NB	Nota bene
NF-kappa B	Nuclear factor “kappa-light-chain-enhancer” of activated B-cells
PE	Parietal epithelial
PT	Proximal tubule
RAS	Renin-angiotensin system
Rb	Retinoblastoma protein
RBP-J	Recombination signal binding protein for immunoglobulin kappa J region
RLC	Renin lineage cells
RNA	Ribonucleic acid
RPC	Renin-producing cells

SISC	Stress-inducible stem cells
STAT	Signal transducers and activators of transcription
tet	Tetracycline
TGF	Transforming growth factor
Thy1	Thymocyte antigen 1
VEGF	Vascular endothelial growth factor
VSMC	Vascular smooth muscle cells
WT1	Wilms' tumor suppressor 1

1 Background: The Classical View on Renal Renin-Producing Cells (RPC) Within Renin-Angiotensin System (RAS)

Circulating renin-angiotensin system (RAS) is a major endocrine factor that governs arterial blood pressure acting both in a short-term scale on vascular tone and in a long-term scale on salt, water, and volume homeostasis. Within RAS, the proteases renin and angiotensin-converting enzyme (ACE) sequentially cleave the plasma protein angiotensinogen to angiotensin (Ang) I and then to Ang II. Ang II is the main effector hormone of the system. Acting primarily through Ang II type 1 (AT1) receptors, it induces strong vasoconstriction and maintains sodium and water balance by regulating the production of aldosterone and antidiuretic hormone, respectively. The multifaceted activity of Ang II results in complex cross talk between its different modes of action. Particularly in the kidney, the functional integrity between Ang II effects on afferent/efferent arteriole tone and tubular reabsorption is decisive for the maintenance of glomerular (as well as renal) hemodynamics and water/electrolyte excretion. In fact, RAS is more complicated because it also includes AT2 receptor, prorenin, and its receptor, as well as a protective arm with ACE2, Ang 1–7, and Mas receptor. These further members are responsible for the fine-tuning of RAS under physiological conditions. They acquire a substantial role in patients with cardiovascular diseases in particular when the AT1-mediated Ang II effects of RAS are pharmacologically inhibited. The detailed description of RAS is beyond the scope of this review. Recent reviews summarizing the state of the art on the intricate RAS aspects in health and disease are available elsewhere (Ames et al. 2019; Arendse et al. 2019; Fournier et al. 2012; Santos et al. 2018; Sparks et al. 2014).

The renin-producing cells (RPC) of the adult mammalian kidney are located in the wall of the afferent arterioles next to the glomerular vascular poles. Therefore, the RPC are also dubbed juxtaglomerular (JG) cells. The JG cells are very few – they amount to only 4–8 cells per afferent arteriole. Renin is the rate-limiting factor of circulating systemic RAS since it primarily determines the rate of generated Ang II and thus the overall biological activity of the system. The reason for the key regulatory status of renin in RAS is the tight control of renin synthesis and secretion by systemic and local factors including perfusion pressure, renal sympathetic nerve

activity, macula densa mechanism, and autocrine cues (nitric oxide, prostanoids, and adenosine). The function of renal RPC in steering RAS activity under physiological and pathophysiological conditions has been characterized very well and elucidated in excellent reviews (Castrop et al. 2010; Damkjaer et al. 2013; Friis et al. 2013; Schweda and Kurtz 2011; Sparks et al. 2014).

2 RPC Beyond RAS

For about 10 years, we have being interested whether the renal RPC might be more than a mere source of renin. Initially, there were two lines of evidence justifying this hypothesis. First, the number of RPC in the afferent arterioles of the adult kidney is not constant but changes in response to homeostatic fluctuations in salt intake, intravascular volume, arterial tone, or adrenergic input. Therein, the RPC do not seem to proliferate. Instead, the renin gene is switched on upstream in the afferent arterioles in some vascular smooth muscle cells (VSMC) thus changing their phenotype from contractile to secretory (Cantin et al. 1977; Dominick et al. 1990). This process is reversible and known as recruitment or metaplastic transformation (Gomez et al. 1988, 1990). The latter term, however, is confusing because it implies pathology when in fact it represents a physiological process. The phenotype plasticity of the RPC in adult life is particularly interesting with regard to the localization of these cells within the JG apparatus (JGA), which includes macula densa and the vascular glomerular pole with the adherent parts of the afferent and efferent arterioles. JGA essentially coordinates renal perfusion, glomerular filtration rate (GFR), and tubular reabsorption into integrative mechanistic responses to provide optimal kidney function. While modulation of RAS activity is part of these responses, it was worth arguing that the phenotypic flexibility of the RPC is of further functional and structural importance for the kidney. Second, the prevalence of RPC in the renal vasculature during kidney development (nephrogenesis) is higher than in adult life (Gomez et al. 1986; Sauter et al. 2008). In addition, knockout of renin in mice leads to kidney malformations and perinatal death (Takahashi et al. 2005; Yanai et al. 2000). Importantly, an identical phenotype has been reported in human fetuses with inactivating mutations in the renin gene (Michaud et al. 2011; Zivna et al. 2009). These observations provided a crucial hint that the RPC should be important for the normal development of the kidney. Based on these findings, a role of RPC as a progenitor cell pool during nephrogenesis was originally proposed. However, experimental evidence in rats and frogs suggested a fundamental role of RAS activity in terms of Ang II effects on kidney morphogenesis and vascular development (Tufro-McReddie et al. 1995). In line with these initial findings, studies in mice and humans demonstrated that the very same detrimental renal phenotype is observed when RAS is inactivated by genetic mutations not only in renin gene but also in its further key component genes, namely, angiotensinogen, ACE, and AT1 (Gribouval et al. 2005, 2012; Gubler and Antignac 2010; Hibino et al. 2015; Hilgers et al. 1997; Kim et al. 1995; Krege et al. 1995; Oliverio et al. 1998; Takahashi et al. 2005; Yanai et al.

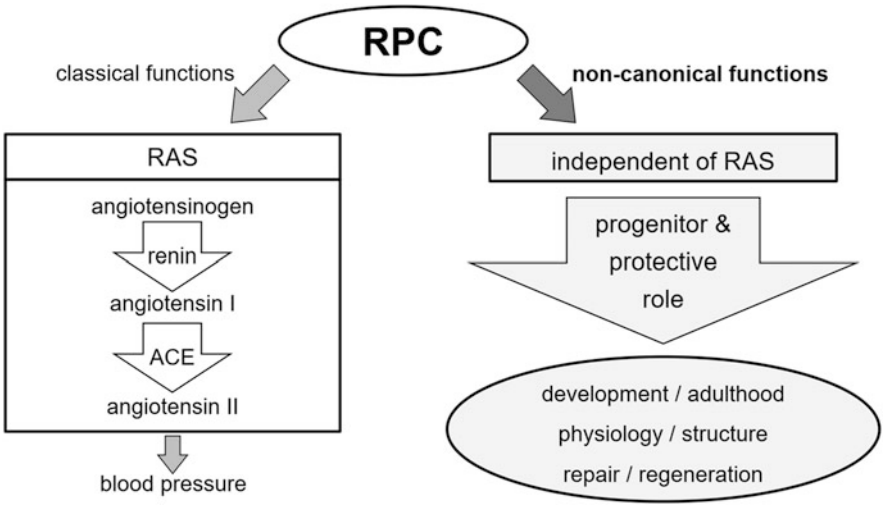

Fig. 1 Novel concept on the dual role of the renin-producing cells (RPC) in kidney highlighting their new RAS-independent functions. *RAS* renin-angiotensin system, *ACE* angiotensin-converting enzyme

2000). Moreover, antihypertensive treatment with RAS inhibitors (ACE inhibitors, AT1 blockers, etc.) is counter-indicated during pregnancy because they cause fetal malformations (Broughton Pipkin et al. 1982; Daikha-Dahmane et al. 2006; Friberg et al. 1994; Grove et al. 1995; Knott et al. 1989; Landing et al. 1994; McCausland et al. 1997; Polifka 2012). RAS is believed to be important in embryonic life for not only maintaining blood pressure and organ perfusion but also because Ang II exerts growth factor-like effects in the developing kidney (Chen et al. 2004; Iosipiv and Schroeder 2003; Madsen et al. 2010; McCausland et al. 1997; Niimura et al. 1995; Tufro-McReddie et al. 1995). Altogether, these findings indicated that active RAS is necessary for normal ontogenesis and nephrogenesis, in particular, thus questioning the role of RPC themselves as progenitors.

Starting from these initial observations, experimental evidence accumulated to favor a concept where RPC do have RAS independent functions (Fig. 1). These non-canonical RAS functions will be discussed in more detail below. Notwithstanding, modern transgenic animal models provided decisive evidence that independently from RAS, the RPC do serve as a progenitor niche in embryonic and adult kidney.

2.1 Progenitor Cell Pool

2.1.1 Nephrogenesis

The original observations that the RPC population is spread throughout the growing renal arterial tree during nephrogenesis before shrinking to the glomerular proximity of the adult kidney came out more than 30 years ago (Gomez et al. 1986; Robillard and Nakamura 1988). This distribution has been demonstrated in multiple studies with mice, rats, pigs, and humans (Celio et al. 1985; Egerer et al. 1984; Gomez et al. 1991; Graham et al. 1992; Molteni et al. 1974). The high interspecies similarity of renal RPC ontogenesis legitimated the widespread use of transgenic animals, mostly mice, as experimental models with high translational capacity and potential clinical relevance. RPC appear in the fetal kidney around embryonic day 16 in mice (gestational week 6 in humans) shortly after the onset of renal vascular development (Celio et al. 1985; Hickmann et al. 2017; Sauter et al. 2008). The renin production is first detected in arcuate arteries and moves next to interlobular arteries and then to the afferent arterioles, i.e., proximal to distal in the growing vascular tree (Fig. 2a). The classic RPC position close to the glomeruli within the wall of terminal afferent arterioles is patterned at the end of nephrogenesis around postpartal day 10 in rodents and gestational week 35 in humans (Graham et al. 1992; Sauter et al. 2008; Sequeira Lopez and Gomez 2011). The RPC in the kidney vessels originate from a subset of cells in the stroma of the metanephric mesenchyme that expresses transcription factor FoxD1 (Pierrou et al. 1994; Lin et al. 2014). In general, the FoxD1 stromal progenitors give rise to intramural and interstitial cells (Hatini et al. 1996; Humphreys et al. 2010; Sequeira Lopez and Gomez 2011). Next to the RPC, renal VSMC, pericytes, and fibroblast-like cells are also of FoxD1 lineage. Therein, cell fate tracing experiments revealed interesting relations (Fig. 2b).

The RPC appear to be exclusively of FoxD1 descent (Gomez and Sequeira-Lopez 2018; Sequeira-Lopez et al. 2015a, b). Within the FoxD1 lineage, the RPC serve as a more differentiated precursor pool giving rise to the JG cells as well as to subpopulations of VSMC and pericytes (Sequeira Lopez et al. 2004). Pericytes are mural cells that stabilize the microvascular tree (Birbrair et al. 2015). In the kidney, mesangial cells of the glomerular capillary tuft and peritubular interstitial cells are regarded as specialized pericyte populations (Stefanska et al. 2013). Thus, in the adult mammalian kidney, a considerable part of the vasculature originates from fetal RPC progenitors. Consistent with the function of RPC as a progenitor pool during kidney development, interference with their intracellular regulatory networks such as Gs-alpha/cAMP, Notch signaling, or micro-RNA leads to adverse renal phenotype (Castellanos Rivera et al. 2011, 2015; Chen et al. 2010a, 2007; Gomez et al. 2009; Medrano et al. 2012; Neubauer et al. 2009; Sequeira-Lopez et al. 2010). As a rule, intervening in these cellular signaling pathways derails the renin production in RPC. Therefore, it remains difficult to completely separate RAS-specific and RAS-independent aspects of RPC in nephrogenesis. Importantly, two lines of recent experimental data shed light on this issue. First, renin cell ablation and renin

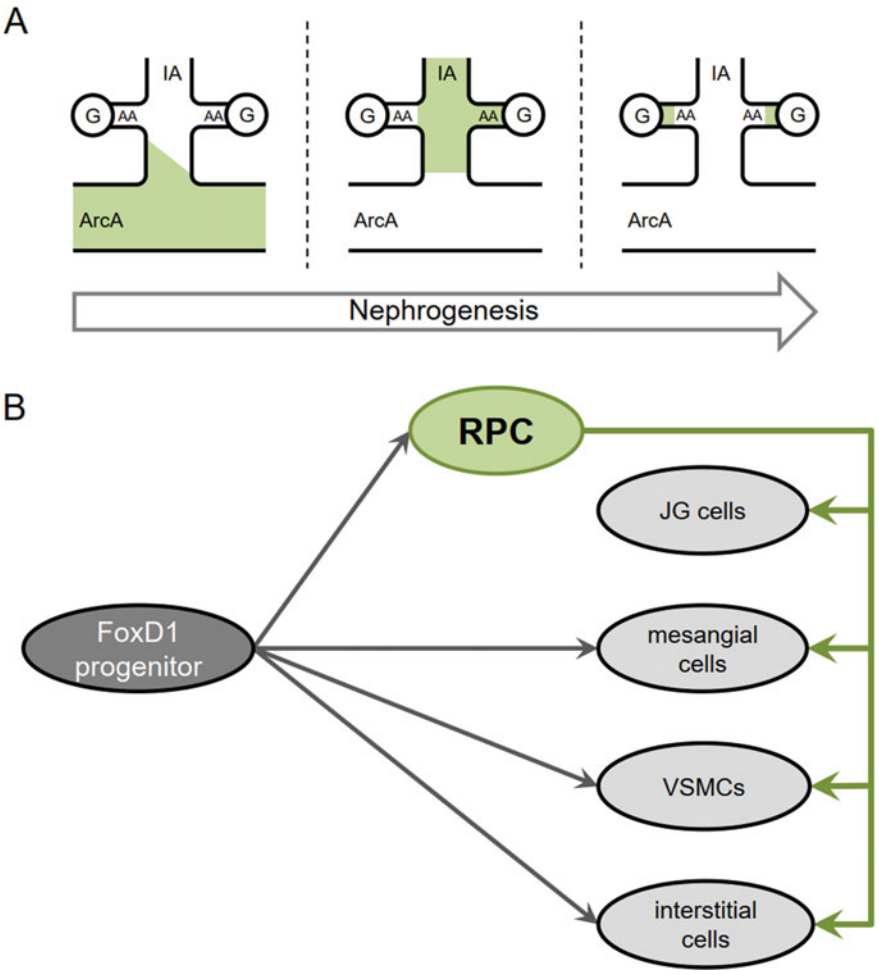

Fig. 2 Renin-producing cells (RPC) in kidney development. (**a**) Localization of RPC (green) in the renal vascular tree at different developmental stages of the maturing kidney. (**b**) RPC as a progenitor niche in nephrogenesis. *AA* afferent arteriole, *IA* interlobular artery, *ArcA* arcuate artery, *G* glomerulus, *JG* juxtaglomerular, *VSMCs* vascular smooth muscle cells

deficiency (renin gene "knockout") during ontogenesis result in different kidney phenotypes (Oka et al. 2017; Pentz et al. 2004; Sequeira Lopez and Gomez 2011; Takahashi et al. 2005). The most striking difference has been observed in the renal arterioles, which in "classical" renin knockout mice are with narrowed lumen due to hyperplasia of mural cells. Interestingly, these cells represent RPC descendants depleted of renin (Oka et al. 2017). On the other hand, the renal arterioles in mice with embryonic ablation of RPC have a thin vascular wall and perivascular fibrosis (Pentz et al. 2004). Second, activating molecular hypoxic signaling by conditional deletion of von Hippel-Lindau protein in RPC converts them into renin-negative

fibroblast-like erythropoietin (EPO)-producing cells without leading to any further major kidney phenotype (Kurt et al. 2013, 2015). EPO is the master hormone regulating erythropoiesis. In adult mammals, it is produced almost exclusively by interstitial cells in the renal cortex (Bachmann et al. 1993; Kurtz 2017, 2019; Maxwell et al. 1997). The surprising finding that RPC could transform into EPO-expressing cells implicates that during nephrogenesis, at least part of the EPO-producing peritubular pericytes may derive from RPC. This exciting possibility awaits definitive experimental confirmation. Importantly, activating hypoxic molecular pathways in the entire FoxD1 lineage cell pool resulted in renal malformations, indicating that intact oxygen signaling in early embryonic life (before the emergence of renal RPC) is essential for the normal development of the stromal compartment of the adult kidney (Gerl et al. 2017).

Altogether, these findings demonstrated a role of RPC as a progenitor pool during ontogenesis irrespective of renin and RAS activity. At the same time, fine-tuning of the complex functions of RPC is indispensable for proper nephrogenesis.

2.1.2 Adult Kidney

The role of RPC as a progenitor niche during fetal life inspired us to address the possibility if these cells have a similar function in the adult kidney. To this end, we used reversible injury models such as intravenous infusion of anti-mesangial cell serum or renal artery perfusion with concanavalin A/anti-concanavalin A antibody to target primarily the glomeruli in the kidney (Hohenstein et al. 2008; Sradnick et al. 2016; Yo et al. 2003). We concentrated our studies on the regenerative phase after the initial acute damage. This approach was based on the general paradigm that developmental cellular mechanisms, which are active during embryogenesis, may be reenacted to regenerate damaged organs in adulthood. Since RPC serve as progenitors for glomerular cells during nephrogenesis (e.g., mesangial cells; see Sect. 2.1.1) and since glomerulopathies are a primary cause for end-stage renal disease (Jha et al. 2013), we have been focusing on glomerular injury models. We also developed a novel transgenic mouse model by combining Cre-loxP recombination with tet-on system (Schonig et al. 2002; Urlinger et al. 2000) to pulse-label and fate-trace RPC in adulthood (Kessel et al. 2019; Lachmann et al. 2017; Ruhnke et al. 2018; Starke et al. 2015; Steglich et al. 2019).

We first found that during the regenerative phase after initial damage induced by anti-mesangial cell serum, the RPC migrate away from their classical JG position into the diseased glomerulus (Starke et al. 2015). Thereby, the migrating cells differentiate in a way that they lose the renin expression and acquire alpha-8-integrin as well as platelet-derived growth factor receptor-beta proteins which are specific for mesangial cells in the glomerulus. Hence, our hypothesis received experimental confirmation because RPC transdifferentiation in the mature kidney recapitulated nephrogenesis, where mesangial cells originate from RPC (Gomez and Sequeira-Lopez 2018; Sequeira Lopez et al. 2004). However, in adult life, this is a regenerative process observed only after organ damage with cell loss and not under

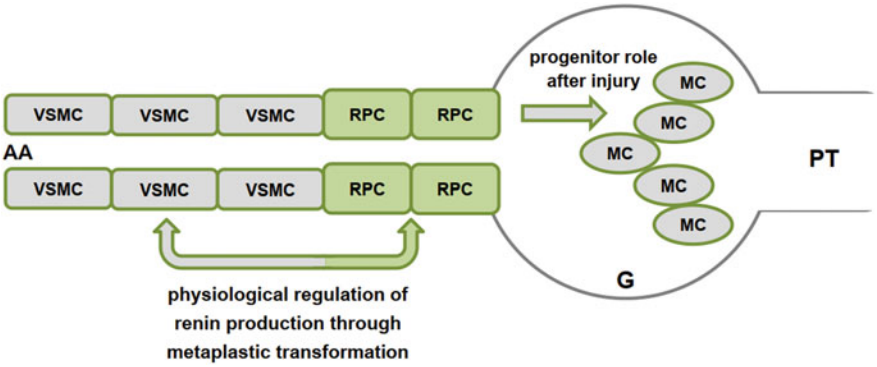

Fig. 3 Plasticity (transdifferentiation) of the renin-producing cells (RPC) in adult kidney recapitulates embryonic patterns. RPC serve as progenitors, which repopulate the glomerulus to replace damaged mesangial cells after injury. RPC could also reversibly switch between secretory and contractile phenotype to regulate renin production under physiological conditions through metaplastic transformation. See also Sects. 2, 2.1.1, and 2.2 and Figs. 2 and 4. *AA* afferent arteriole, *G* glomerulus, *VSMC* vascular smooth muscle cell, *MC* mesangial cell, *PT* proximal tubule

physiological conditions. Throughout development and adulthood, the RPC progenitors maintain cell-specific plasticity, i.e., they transdifferentiate to the very same cell types (Fig. 3). Moreover, RPC descendants did not regenerate the endothelium after depletion of glomerular endothelial cells in reversible endothelial cell injury model induced by renal artery perfusion with concanavalin A/anti-concanavalin A antibody (Ruhnke et al. 2018). Instead, RPC transdifferentiated to exclusively replace glomerular mesangial cells, which seemed to be damaged secondary to the endothelial injury.

Other investigators used an alternative transgenic mouse model for inducible labeling and tracing of RPC in a model of focal segmental glomerulosclerosis (Kaverina et al. 2017b; Lichtnekert et al. 2016; Pippin et al. 2015). They found that RPC repopulate the glomerular Bowman's capsule and differentiate not only to mesangial cells but also to podocytes and parietal epithelial (PE) cells. The reasons for the partial discrepancy compared to our results lay most probably on the different animal or injury models used. For instance, the experimental setups we used do not lead to podocyte depletion (Ruhnke et al. 2018). In any case, it is somewhat counterintuitive that RPC could replace damaged podocytes or PE cells because these are not of FoxD1 origin and thus do not belong to the RPC stromal mesenchyme descendants in the adult kidney (see Sect. 3). Therefore, it is plausible to conclude that after severe glomerular injury the progenitor potential of RPC is utilized beyond the developmentally based transdifferentiation programs of cell type-specific regeneration. Thus, the RPC seem to universally protect damaged tissue as a part of integrative stress response of the organism. Anyway, more experimental support is needed to utterly validate this hypothesis.

The communication modes between RPC and (damaged) intraglomerular cells in the mature kidney are still poorly understood. With this regard, it is unlikely that

soluble messenger molecules are transported with blood flow because the RPC are upstream to the glomerulus. Cell-cell contacts are important for the physiological signaling within the JGA, and therefore they may be involved in regenerative signaling (Just et al. 2009; Kurtz 2015; Wagner et al. 2007). Moreover, the RPC are featured by a specific gap junction protein expression signature where connexin 40 is central for their function and morphology (Kurtz et al. 2009; Wagner and Kurtz 2013). Hence, future studies on the role of cell-cell contacts in transmitting signals from damaged glomeruli to the precursor RPC niche in the afferent arterioles are an attractive perspective. However, the advancements in this strategic area of interest are hampered by a deficit of appropriate experimental models. For instance, efforts to identify mesangial-specific gene(s) fail until now, thus making the generation of transgenic animals with selectively targeted mesangial cells impossible.

Immune cells could also be considered as paramount players mediating cues from injured and regenerating glomeruli to RPC. According to the modern concept of necroinflammation, necrotic organ damage inevitably goes together with an inflammatory component (Linkermann 2019; Sarhan et al. 2018). Conversely, inflammation and release of damage-associated molecular patterns (DAMPs) do not only augment tissue damage but also initiate regenerative reactions (Sarhan et al. 2018). These processes are mediated by resident cells of innate immunity like macrophages, dendritic cells, and natural killer cells that orchestrate local and systemic mechanisms with adaptive relevance in host-pathogen interactions, metabolic responses to tissue injury and degeneration, or allogeneic transplantation. Importantly, we and others have demonstrated that the RPC are equipped with the molecular machinery (including tumor necrosis factor receptors, functional NF-kappa B and STAT signaling, etc.) necessary for acquisition and transduction of innate immunity signals like inflammatory cytokines (Baumann et al. 2000; Desch et al. 2012; Liu et al. 2006; Petrovic et al. 1997; Todorov et al. 2002, 2005, 2004). Therefore, we favor the immune-mediated processes as the most feasible mechanism(s) responsible for signal delivery from damaged glomeruli to RPC and vice versa. There is already indirect evidence in support of such an assumption. Thus, both necroinflammation and RPC progenitor function in adulthood are specific for pathophysiological conditions (Linkermann 2019; Ruhnke et al. 2018; Starke et al. 2015).

At present, little is known about how RPC set up to differentiate and migrate upon glomerular damage. First data from us demonstrated that when renin is switched off by interfering with Gs-alpha/cAMP signaling, the RPC descendants produce increased amounts of tissue remodeling factors (Steglich et al. 2019). The latter could loosen cells and potentiate their migration (see also Sect. 2.3). With this regard, proteins involved in the control of cellular mechanics like small GTPases are particularly interesting targets for future studies, since cytoskeleton rearrangement generally accompanies cell motility and differentiation. The transcription factor Wilms' tumor suppressor 1 (WT1), which belongs to this group of proteins and is expressed in RPC, has already been reported to affect their transformation and glomerular migration after podocyte depletion (Kaverina et al. 2017a).

Collectively, although it is now established that the RPC operate as a progenitor cell niche in the adult mammalian kidney, we are still at the onset of exciting findings

that should elaborate the understanding of underlying molecular mechanisms and pathophysiological relevance. Therein large-scale "omics" analyses of the global transcriptional/translational landscape of RPC would be of exceptional importance (Martinez et al. 2018; Steglich et al. 2019; Wang et al. 2018).

2.2 Neogenesis and Recruitment

The discovery of a progenitor function of RPC inspired studies on their maintenance as a stable population in adulthood. This issue is also critical with regard to the classical role of RPC in RAS – if upon glomerular injury all JG cells differentiate to renin-negative descendants, RAS would be switched off, thus disturbing the general control of circulation and overall homeostasis. Moreover, (self)renewal is an archetypal feature of stem cell niches (Seaberg and van der Kooy 2003). Therefore, it is somewhat surprising that there is no conclusive data demonstrating proliferation of RPC. Early pulse labeling studies with DNA intercalating agents in the rat anti-Thy1 model indicated that repopulation of the glomerulus during repair after mesangial injury involves migration and proliferation of precursors from the JGA (Hugo et al. 1996, 1997). Recent findings did not show prominent RPC proliferation in an equivalent mouse model (Starke et al. 2015). This is consistent with other studies (Cantin et al. 1977; R. Ariel Gomez, personal communication). In contrast, proliferating RPC have been detected after continuous loading with the DNA intercalating agent bromdesoxyuridin (BrdU) for lineage tracing of dividing cells for up to 27 days (Lichtnekert et al. 2016; Owen et al. 1994). Altogether, these findings inferred that mechanisms beyond proliferation are necessary to maintain the RPC precursor niche, particularly after injury when the JG cells transdifferentiate to replace damaged glomerular cells. Progenitor cell niches (such as the RPC) could also be filled up by differentiating pluripotent stem cells through a process termed neogenesis or de novo differentiation. For RPC (and renin lineage cells in general; see Sect. 3), neogenesis is the process where a cell that is not related to the renin lineage (i.e., never expressed renin before and does not originate from cells that express/ed renin) starts to express renin for a very first time (Hickmann et al. 2017). We were lucky to make use of a versatile transgenic mouse model for neogenesis tracing (Muzumdar et al. 2007; Xiao et al. 2013), which was modified for RPC targeting. During nephrogenesis, RPC emerge almost exclusively via neogenesis (Hickmann et al. 2017). Although proliferation should also play a role in the establishment of the RPC population in the developing kidney, de novo differentiation seems to be the superior mechanism. In adulthood, the RPC neogenesis is featured by three hallmarks: it is intrarenal, lifelong, and regulated (Hickmann et al. 2017). Thus, the kidney appears to be able to effectively preserve and renew a local progenitor cell population. Moreover, the process of RPC neogenesis is counteracted by rate-matched apoptotic cell death, which explains why the adult kidney is not overfilled with RPC (Hickmann et al. 2017). Even more important is the fact that RPC neogenesis is stress-inducible. During injury when RPC repopulate damaged

glomeruli, de novo differentiation is upregulated, leading to a moderate increase in RPC number (Hickmann et al. 2017). This mechanism safeguards not only the RPC precursor pool, which is primed to replace the depleted glomerular cells, but also the RAS activity. This is an important aspect demonstrating that the RPC act as a progenitor niche without impeding their classical role within RAS. The origin of the de novo differentiated RPC in the adult kidney remains open. We experimentally excluded the option that the renal RPC are bone marrow-derived (Hickmann et al. 2017). FoxD1-positive precursors are the source for RPC during development (see Sect. 2.1.1), but FoxD1 is not expressed in the mature kidney (Humphreys et al. 2010). Preliminary observations from us suggest a pericyte origin for new RPC after nephrogenesis is finished, but more studies are needed to identify the adult precursor renal niche for RPC.

Increased de novo differentiation of RPC has also been observed in a physiological model of decreased blood pressure (Hickmann et al. 2017). Arterial hypotension is the main stimulus for renin production, and the renin production is scaled up and down by changing the number of RPC, rather than the renin expression rate in the single cell (Castrop et al. 2010; Hackenthal et al. 1990; Rasch et al. 1998). The adjustment of RPC number to the functional status of the organism is a versatile process termed recruitment or metaplastic transformation (see Sect. 2). Recruitment is one of the early described physiological manifestations of RPC plasticity in the adult mammalian kidney (Cantin et al. 1977). It represents a reversible phenotypic switch between VSMC and RPC in the wall of the afferent arterioles upstream to their JG parts. Lineage tracing revealed that the switching VSMC in the afferent arterioles originate from RPC during nephrogenesis meaning that the recruitment is a recapitulation of a developmental process (Gomez et al. 2014; Kurt and Kurtz 2015; Martini and Danser 2017; Sequeira Lopez et al. 2004) in adulthood (see Sect. 2.1.1). It should be emphasized that recruitment is not to be mixed up with neogenesis although both are hallmarks of RPC plasticity. Recruitment (metaplastic transformation) is a reversible phenotype change of a cell within the developmental RPC pool (referred also in Figs. 2 and 3), while neogenesis (de novo differentiation) is the differentiation of a cell to join the renin lineage (Fig. 4a; see the definition of neogenesis above in this section). In addition, neogenesis is involved primarily in RPC renewal and progenitor function after injury, whereas recruitment is responsible for the physiological control of renin production and RAS activity (Fig. 4b; see also Fig. 3).

Thus, the RPC are not only featured by plasticity but also represent a dynamic population predestined to be involved in complex physiological and pathophysiological processes.

Antihypertensive drugs and particularly RAS inhibitors boost the renin production and the RPC count (due to negative feedback within RAS linking blood pressure to renin expression) demonstrating that recruitment and neogenesis could be targeted by therapeutic strategies (Azizi and Menard 2004; Hickmann et al. 2017; Mooser et al. 1990; Nussberger et al. 2007; Pugh et al. 2019). Although an increased number of RPC correlates with the renoprotective effect of the RAS inhibitors, it is still

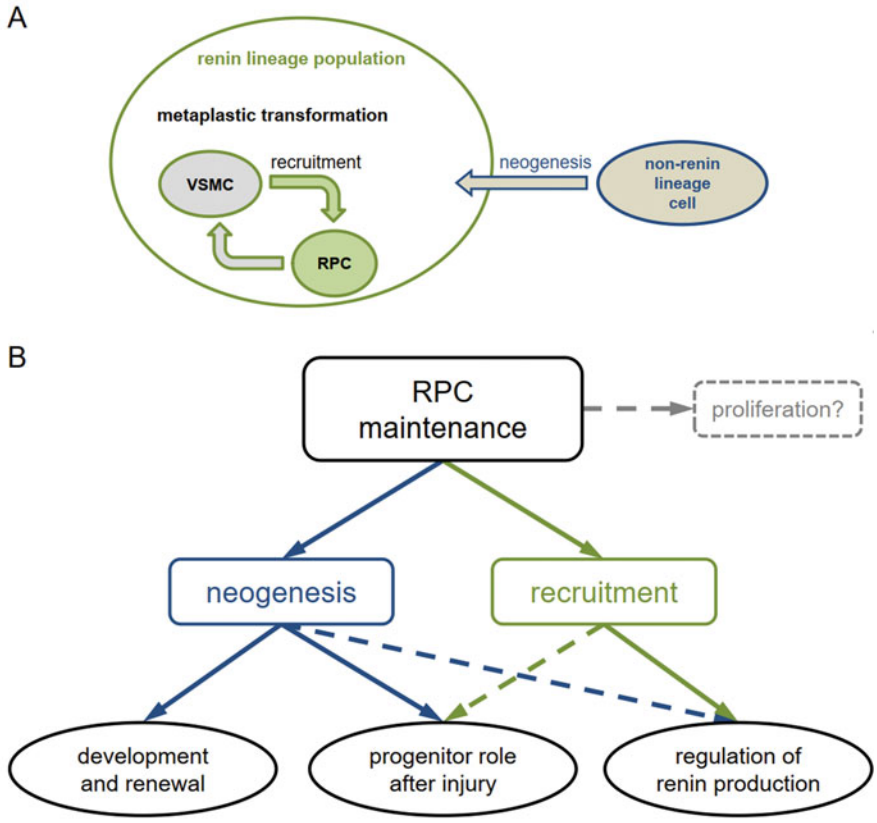

Fig. 4 Recruitment and neogenesis of renin-producing cells (RPC). (**a**) Schematic presentation of the difference between recruitment and neogenesis. Metaplastic transformation is a phenotype switch within the developmental RPC pool (see also Fig. 2) where recruitment specifically refers to the transformation of VSMC into RPC. In neogenesis, an unrelated cell enters the renin lineage population by starting to express renin for the first time (see also Sect. 3). (**b**) Role of recruitment and neogenesis in the maintenance of the RPC population. The role of proliferation therein is not well understood. Dashed arrows represent secondary role. *VSMC* vascular smooth muscle cell

controversial whether this increase might be beneficial (NB! only when RAS activity is inhibited in terms of AT1-dependent Ang II effects) or not (Moniwa et al. 2013).

2.3 Protection of Renal Microvascular Endothelium

Lately, our studies revealed that RPC are quite surprisingly involved in the maintenance of renal capillary endothelium in adulthood. This novel function of RPC has been discovered when characterizing an inducible transgenic model with compromised Gs-alpha/cAMP signaling pathway (Lachmann et al. 2017).

Gs-alpha is the stimulatory subunit of membrane receptor coupled trimeric G-proteins (Spiegel et al. 1992; Weinstein et al. 2001). It catalyzes the generation of cAMP upon ligand binding to the associated receptor. The RPC are equipped with Gs-alpha coupled IP/EP2/EP4 and beta-adrenergic receptors mediating effects of prostanoids and catecholamines, respectively (Boivin et al. 2001; Churchill et al. 1983; Facemire et al. 2011; Friis et al. 2005; Jensen et al. 1996; Karger et al. 2018; Kim et al. 2007; Schweda et al. 2004). Blood pressure fluctuations seem to modulate renal prostanoid production and sympathetic nerve activity to regulate renin production by adjusting the RPC number (Chen et al. 2010b; Kim et al. 2012). Therefore, Gs-alpha/cAMP signaling is central for renin synthesis and secretion, thus essentially determining the RPC phenotype (see also Sect. 2.1.1). It was predictable that the induction of Gs-alpha knockout in RPC of adult mice would result in renin deficiency and arterial hypotension (Kessel et al. 2019; Lachmann et al. 2017). However, these changes were transient because the drop in blood pressure served as a stimulus to recruit RPC in upstream parts of the afferent arterioles (see Sect. 2.2) that were not affected by the pulse induction of the Gs-alpha knockout. Although normal renin production and blood pressure persisted after these initial fluctuations, the JG-specific Gs-alpha-deficient mice developed chronic kidney disease. The adverse renal phenotype most unexpectedly included microvascular endothelial damage featured by morphological and systemic signs of thrombotic microangiopathy (Benz and Amann 2010; Lachmann et al. 2017). Remarkably, kidney injury developed on the background of normalized renin production, indicating that RPC exhibit protective effects on renal microvascular endothelium-independent on their role in the control of RAS activity (Lachmann et al. 2017). The mode of action of RPC on endothelial cells is multifaceted, and the implicated interactions are just beginning to be unraveled. One mechanism involves the production of angiogenic factors by RPC, which has been displayed in several studies (Brunskill et al. 2011; Haltia et al. 1996; Lachmann et al. 2017; Sequeira Lopez and Gomez 2011). Within the RPC-derived proangiogenic cues, vascular endothelial growth factor (VEGF) appears to be particularly relevant for two reasons. First, both pharmacological inhibition and genetically induced intrarenal deficiency of VEGF result in thrombotic microangiopathy (Eremina et al. 2008; Sison et al. 2010). Second, VEGF is a cAMP-regulated gene and its expression in RPC is induced by cAMP (Bradbury et al. 2005; Han et al. 2013; Lachmann et al. 2017). Another factor contributing to the proangiogenic capacity of RPC appears to be their secretory phenotype per se. This conclusion is also based on findings in adult RPC-specific Gs-alpha-deficient mice, where the RPC have been found to persist after Gs-alpha knockout as renin-negative cells (Steglich et al. 2019). In the persisting RPC progeny, a pool of 16 genes involved in tissue remodeling with vascular damage and fibrosis including collagens and TGF-beta were upregulated. Simultaneously, genes conferring the identity of RPC such as renin itself, connexin 40, and aldo-keto reductase family 1 member B7 (Akr1b7) was downregulated. Ablation of RPC resulted in renin deficiency but failed to produce any sign of endothelial injury (Steglich et al. 2019). This observation additionally confirmed that Gs-alpha-negative RPC descendants are necessary for the development of endothelial dysfunction.

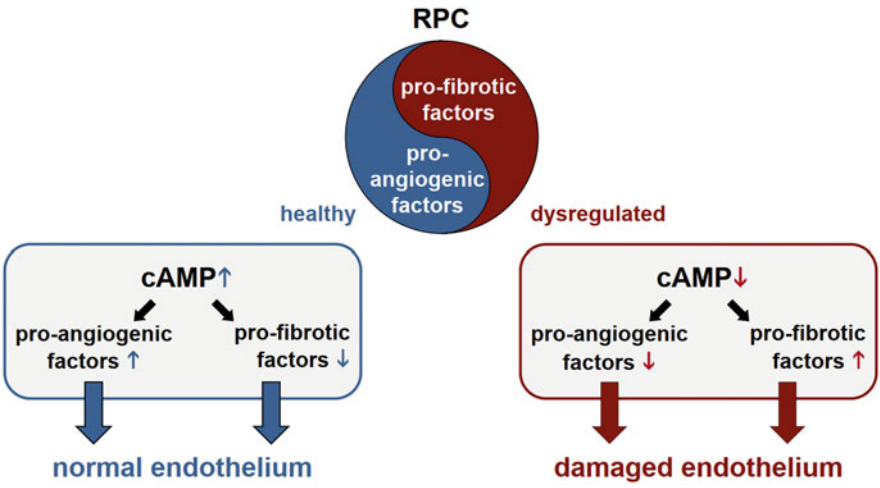

Fig. 5 Current view on the non-canonical effects of renin-producing cells (RPC) on renal microvascular endothelium

In total, the inactivation of Gs-alpha/cAMP signaling seems to switch the RPC phenotype from "protective/secretory" to "damaging/profibrotic" (Fig. 5).

The discovery of a protective role of RPC on renal microvasculature elicits some very exciting questions to be addressed in the future. As discussed above in this section, RPC recruitment is a cAMP-regulated process. Therefore, it would be interesting to know whether the recruitable VSMC in the afferent arterioles may exert profibrotic remodeling effects when not switched to the renin-producing phenotype. It is now established that renal VSMC are of heterogeneous embryonic origin (see Sect. 2.1.1) implying that RPC-derived and non-RPC-derived VSMC may have different functional characteristics. Vice versa, a decrease of RPC number when renin production is suppressed, for instance, in some forms of arterial hypertension, could be an independent risk factor for renal damage. Extrapolating these considerations would suggest that the renoprotective effects of pharmacological RAS inhibitors rely on cAMP-dependent RPC recruitment on top of the Ang II antagonism. Therefore, discoveries of further mechanisms involved in the complex interactions between RPC and kidney microvasculature with potential pathophysiological and therapeutic significance are anticipated.

3 Renin Lineage Cells

Studies in adult mice, rats, and humans unequivocally demonstrated that many organs and specialized tissues express renin mRNA albeit to a much lesser level than the JG cells. The non-JG renin-expressing cells are part of local or tissue-specific RASs (Paul et al. 2006). However, the JG cells appear to be the sole source

for plasma renin because circulating renin disappears after bilateral nephrectomy (Fordis et al. 1983; Hannon et al. 1969; Katz et al. 1997). The generation of renin from its inactive precursor prorenin upon binding to the prorenin receptor does not essentially contribute to the plasma renin activity (Nguyen et al. 2014, 2002; Rosendahl et al. 2014).

Systemic and local RASs functionally integrate into concerted Ang II-mediated effects in a way that the local RASs modulate the action of systemic RAS (Paul et al. 2006). Accordingly, fate-tracing experiments demonstrated that a marked number of cells in kidneys, spleen, bone marrow, and endocrine pancreas of the adult organism could be attributed to the renin lineage (Belyea et al. 2014; Desch et al. 2011; Glenn et al. 2014; Hickmann et al. 2017; Sequeira Lopez et al. 2004). These findings prompted the definition of a renin lineage cell (RLC) population which comprises all cells collectively featured by the expression of renin gene and/or the presence of a renin-expressing cell in their ancestry (Hickmann et al. 2017). The existence of local RAS infers that RLC build a huge population spread throughout the whole body. Such a conclusion appears to diverge from the paradigm that the JG cells are the sole RPC niche in adulthood. Indeed, there is still some controversy on the systemic availability of renin from source(s) other than the JG cells. The current view is a kind of reasonable compromise postulating that in certain diseases such as diabetes mellitus, high-grade obesity, or some subsets of arterial hypertension, renin from non-JG origin would be of pathophysiological relevance. The major issue provoking conflicting interpretations is that with very few exceptions such as pituitary, adrenal glands, or testes (Lee et al. 2005; Naruse et al. 1985), renin protein is detectable exclusively in JG cells of the kidney. The JG cells are the only cell type in the adult organism equipped with molecular machinery to store renin in secretory vesicles, which greatly facilitates their identification as renin-positive cells (Hackenthal et al. 1990; Lacasse et al. 1985; Mendez 2014; Taugner et al. 1984, 1985). In all other renin-expressing cell types, the translated (pro)renin protein is constitutively sequestered to the extracellular compartment. Thus, the lack of secretory granules together with the much lower renin mRNA expression provides a reasonable explanation for why renin is hardly observed in non-JG cells.

What about RAS independent functions for RLC? As already discussed in Sect. 2.1.1, the progenitor RPC in the kidney, which should be regarded as a subpopulation within the RLC pool, give rise not only to JG cells but also to further mural cells in the mature kidney. However, lineage-tracing experiments reproducibly demonstrated that cells in the Bowman's capsule (PE cells), proximal tubules, and collecting ducts of the adult kidney are also mapped to the renin lineage (Hickmann et al. 2017; Sequeira-Lopez et al. 2004, 2015b). Altogether, the renal RLC represent around 10% of the renal cell mass in adult mice, and it is feasible to extrapolate this data to humans. Similar to RPC, the RLC are also maintained by neogenesis balanced by apoptosis, and thus they represent a dynamic population persisting throughout adult life (Hickmann et al. 2017). Therefore, RLC appear to be fundamental for the morphological architecture of the adult mammalian kidney. On the other hand, the renal RLC are not a homogeneous population with regard to their embryonic origin. RPC and their descendants originate from FoxD1-expressing cells

in the stromal compartment of the metanephric mesenchyme (see Fig. 2b and Sect. 2.1), PE cells and proximal tubules from the core layer of the metanephric mesenchyme (known as cap mesenchyme), and collecting ducts from the ureteric bud (Humphreys et al. 2010; Kobayashi et al. 2008; Kress et al. 1990; Nelson et al. 1998; Srinivas et al. 1999). The most probable scenario for the development of FoxD1-unrelated renal RLC is that the renin gene is switched on in their transcriptional programs at some time point of embryonic differentiation. The functional importance of this event remains elusive. Tubular renin is dispensable during nephrogenesis (Sequeira-Lopez et al. 2015b). The role of collecting duct as a source of renin in diabetes mellitus and hypertensive disease is disputed (Gonzalez et al. 2011; Liu et al. 2011; Prieto-Carrasquero et al. 2004, 2005, 2009; Ramkumar et al. 2014; Song et al. 2016; Tang et al. 2019).

Taking into account that local RAS are ubiquitous, extrarenal RLC are still extremely underrepresented in current research. Such status-quo is quite amazing because the few available studies on non-kidney RLC yielded very exciting results. Brain RLC seem to protect from arterial hypertension. The mechanistic explanation is that in brain RLC a specific renin isoform is transcribed from an alternative start codon producing a truncated protein, which remains intracellularly and controls neurotransmitter release (Shinohara et al. 2016). Unfortunately, there are no studies focusing on a putative role of brain RLC after injury in the central nervous system.

RLC are detectable in the bone marrow, peripheral blood, and spleen (Belyea et al. 2014), where they are also maintained by neogenesis (Hickmann et al. 2017). The majority of the immune system RLC are B-lymphocytes. Defects in the developmental transcriptional program induced by RLC-specific knockout of the Notch pathway transcriptional effector RBP-J (recombination signal binding protein for immunoglobulin kappa J region) or p53 and retinoblastoma protein (Rb) result in B-cell leukemia or pancreatic neuroendocrine carcinoma, respectively (Belyea et al. 2014; Glenn et al. 2014). These findings imply that the embryonic differentiation of extrarenal RLC is under tight control to ensure proper organogenesis. At present, further roles for RLC in adulthood are not known.

4 Future Perspectives

This review tells a story where after entering the textbooks in the context of RAS, nowadays the renal RPC revive as a hot topic in research for their novel RAS-independent functions. Progenitor and protective features are the main aspects delineating the new non-canonical profile of RPC (see also Fig. 1). While already expanding the paradigm, the novel insights on RPC summarized above provide also an inspiration for future work. The questions to be addressed could be grouped into three prospective experimental pipelines:

1. Deciphering the molecular “motors” driving the complex protective activity of renal RPC in health and in response to tissue injury

2. Characterization of the RPC niche as a dynamic population with regard to origin, refilling and cell death
3. Unravelling the role of RLC beyond RAS

The last group includes several independent intriguing aspects. One is the role of renin in RLC – is it simply an eponymous marker or it has some non-conventional function(s)? Since renin is a protease, we hypothesize that it might be involved in the remodeling of neighboring tissue by cleavage of extracellular matrix proteins, which is a fundamental process in organ growth and regeneration. Support for RAS-unrelated protease activity of renin provided the recent observation that it activates the complement cascade by triggering C3 proteolysis (Bekassy et al. 2018). Another aspect is the idea that RLC represent stress-inducible stem cells (SISC). SISC have been recently defined as a subpopulation of progenitor cells that are particularly prone to stress-related signals (Bornstein et al. 2019). SISC are featured by coordinated signaling pathways and transcriptional signature, which enable them to be an efficient integrative part of general adaptive stress responses in the entire organism. Accordingly, in distress situations, SISC function would be dysregulated leading to maladaptive reactions and disease. It has been postulated that SISC are ubiquitous and should be present in virtually any organ and specialized tissue. Nestin and Notch1 serve as general markers of SISC populations. RLC fulfill all these criteria thus perfectly fitting into the definition for SISC (Hanner et al. 2008) (see also this section above). Stress signals influencing RLC and particularly renal RPC include acute drop in arterial blood pressure (e.g., due to hemorrhage), chronic salt depletion, extreme dehydration, hyperactivation of the sympathetic nervous system by environmental natural and social factors, etc. Therefore, it is feasible to assume that RLC build at least part of the SISC niche and that the renin lineage might be one further universal SISC marker. Being an attractive unifying concept, the presence of interrelated organ- and tissue-specific RLC (including RPC) with coordinated stress-regulated functions during development and adulthood awaits empirical support. Since transgenic animal models applicable in experiments addressing the issues formulated above already exist, a further expansion of our knowledge on renal RPC and RLC is pending.

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