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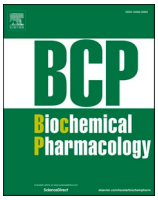

Review

The contribution of the AT1 receptor to erythropoiesis

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ABSTRACT

The renin-angiotensin system (RAS) comprises a broad set of functional peptides and receptors that play a role in cardiovascular homeostasis and contribute to cardiovascular pathologies. Angiotensin II (Ang II) is the most potent peptide hormone produced by the RAS due to its high abundance and its strong and pleiotropic impact on the cardiovascular system. Formation of Ang II takes place in the bloodstream and additionally in tissues in the so-called local RAS. Of the two Ang II receptors (AT1 and AT2) that Ang II binds to, AT1 is the most expressed throughout the mammalian body. AT1 expression is not restricted to cells of the cardiovascular system but in fact AT1 protein is found in nearly all organs, hence, Ang II takes part in several modulatory physiological processes one of which is erythropoiesis. In this review, we present multiple evidence supporting that Ang II modulates physiological and pathological erythropoiesis processes trough the AT1 receptor. Cumulative evidence indicates that Ang II by three distinct mechanisms influences erythropoiesis: 1) stimulation of renal erythropoietin synthesis; 2) direct action on bone marrow precursor cells; and 3) modulation of sympathetic nerve activity to the bone marrow. The text highlights clinical and preclinical evidence focusing on mechanistic studies using rodent models.

1. Introduction

Angiotensin II (Ang II) is the most active peptide hormone of the renin-angiotensin system (RAS). Classically Ang II was discovered to be produced in the circulation but later it became evident that Ang II is additionally locally synthesized in tissues. Angiotensinogen is the only precursor protein for Ang II and all other angiotensin peptides of the RAS [1] (Fig. 1). Liver angiotensinogen is secreted into the bloodstream and cleaved by renin which is primarily expressed and released in the circulation by renal juxtaglomerular cells (Fig. 1). The reaction produces the inactive peptide Ang I that is further cleaved by angiotensin converting enzyme (ACE), mainly in the pulmonary circulation. ACE is a transmembrane protein strongly expressed by the endothelium of the lung vasculature but also in endothelium of other vascular beds (Fig. 1). The RAS components mentioned above, including shedded ACE, are imported from the circulation to locally form angiotensin peptides in tissues. Additionally, RAS components are also expressed in those tissues, including the hematopoietic system, potentially contributing to the local production of the peptides [2–6]. The import of RAS proteins from the circulation takes place in all peripheral organs. The brain is an exception because the blood–brain-barrier limits the traffic of RAS proteins and peptides such as Ang II. Ang II has well described modulatory roles in the brain acting on its receptors expressed at neuronal populations involved in vasopressin release, sympathetic nerve activity and salt-and-water appetite. Part of these physiological responses are triggered by peripheral Ang II action on neurons positioned at circumventricular areas where the blood–brain-barrier is permeable. Local formation of angiotensins in the brain has been a controversial topic,

Abbreviations: ACE, Angiotensin converting enzyme; AcSDKP, N-acetyl-Ser-Asp-Lys-Pro; Agt, Angiotensinogen; Ang I, Angiotensin I; Ang II, Angiotensin II; AT1, Angiotensin II type 1 receptor; AT2, Angiotensin II type 2 receptor; BFU-E, Burst-forming unit erythroid; CFU-E, Colony-forming unit erythroid; Epo, Erythropoietin; EpoR, Erythropoietin receptor; FoxD1, Forkhead Box D1; HIF-2α, Hypoxia inducible factor 2-alpha; HSCs, hematopoietic stem cells; IML, Intermediolateral cell column; MAPK, mitogen-activated protein kinase; NE, Norepinephrine; NTS, Nucleus tractus solitarii; OVLT, Organum vasculosum of the lamina terminalis; PVN, Paraventricular nucleus of the hypothalamus; RAS, Renin angiotensin system; RBCs, Red blood cells; RVLM, Rostroventrolateral medulla; SFO, Subfornical organ; SNA, Sympathetic nerve activity; β2, Beta-2 adrenergic receptor.

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because the brain produces low amounts renin [7]. Nevertheless, some preclinical models support the existence of a functional brain RAS [8,9]. Finally, during insults such as hypertension circulating Ang II may access brain areas otherwise only available to brain-borne Ang II [10,11].

Most of the responses to homeostatic and environmental changes are adjusted by the sympathetic nervous system. Sympathetic nerves innervate virtually all organs of the body. Neurotransmitters released by these peripheral neurons control cellular responses at targeted tissues. The most abundant and effector sympathetic neurotransmitter is norepinephrine, additionally neuropeptide Y and ATP are co-released at sympathetic terminals [12–14]. At an organizational level, the sympathetic nervous system is composed of presympathetic neurons mainly originating from two brain areas, the paraventricular nucleus of the hypothalamus (PVN) and the rostroventrolateral medulla (RVLM), located in the hypothalamus and brainstem, respectively. Importantly, there are several brain nuclei projecting and modulating the activity of the two areas mentioned including the nucleus tractus solitarii (NTS), the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT). The PVN and RVLM neurons project to spinal sympathetic preganglionic neurons at the intermediolateral cell column (IML) which synapses in peripheral sympathetic ganglia releasing mostly acetylcholine. Acetylcholine stimulates nicotinic receptors on postganglionic neurons that are the neurons effectively innervating peripheral organs [14–16]. Importantly, the central effects of Ang II on the sympathetic control are complemented by direct modulation of neurons of the spinal cord, sympathetic ganglia, and those innervating peripheral organs. For instance prejunctional neurons express AT1 receptors and Ang II facilitates norepinephrine containing vesicles release via membrane depolarization [17–20].

Ang II binds to two major angiotensin receptor types termed angiotensin receptor type 1 (AT1) and 2 (AT2). AT1 and AT2 receptors are G-protein coupled receptors, coupling primarily to Gq/11 and Gi, respectively. Most of the physiological effects of Ang II are mediated via the Ang II/AT1 axis because AT1 expression is abundant in adult mammals. AT2 receptor signaling often exerts antagonistic effects of those elicited by Ang II binding to the AT1 receptor [4]. In addition, to the G-protein signal, the Ang II/AT1 axis is known to recruit several G-protein independent pathways including MAPK, JAK/STAT and β-arrestin dependent signaling [21]. The AT1 receptor is widely distributed across the body and is critical for cardiovascular homeostasis and hydromineral balance control. Various independent studies from the past decades clearly showed that the Ang II/AT1 axis is involved in the pathogenesis of several cardiovascular diseases rendering AT1 blockers one of the most successful drug therapies for cardiovascular and renal diseases. Many additional physiological and/or pathological processes are under Ang II influence because Ang II receptors, especially AT1, are expressed at least in some subset of cells of almost all tissues [22]. Using genetically modified rodents and pharmacological approaches targeting RAS components many additional roles of Ang II were revealed including in kidney development [23–25], adipocyte metabolism [26,27], insulin signaling [28,29], inflammation [30–32], fibrosis [33,34], bone mass regulation [35,36] and erythropoiesis the subject of this review [8,37–39].

This review covers aspects evidencing that Ang II is a modulator of erythropoiesis by activation of the AT1 receptor. We bring together clinical and preclinical studies demonstrating the dependence of erythropoiesis on the Ang II/AT1 axis giving a particular focus on mechanistic data derived from rodents.

2. Erythropoiesis

Erythrocytes, also known as red blood cells (RBCs) actively take part in the respiratory gas exchange. In mammalians, oxygen is transported from the lungs to other organs and carbon dioxide from organs to the lungs bound to hemoglobin molecules within enucleated RBCs. Erythropoiesis defines the production of RBCs the most abundant cell type in the blood accounting for ~ 99% of the circulating cellular mass which correspond to ~ 45% of the blood, the remaining is plasma. Throughout life the RBC count is kept well balanced due to highly controlled erythropoietic mechanisms that may sharply boost erythropoiesis *e.g* during homeostatic threats such as bleeding [40,41].

There are two phases in mammalian erythropoiesis termed primitive and definitive. Both primitive and definitive erythropoiesis originate from the yolk sac. Primitive erythropoiesis is exclusively embryonic and is substituted by definitive erythropoiesis during fetal life, which persists across adult life. RBC production during the fetal definitive erythropoiesis phase takes place in the liver and spleen and as the animal grows erythropoiesis is transferred to the bone marrow. Certain pathological conditions or insults like anemia may shift erythropoiesis back to the spleen and liver in adulthood. [42–44].

Bone marrow adult mammalian erythropoiesis begins with hematopoietic cell lineage-commitment of pluripotent myeloid progenitor cells, these cells differentiate into erythroid progenitors, precursors, and finally into RBCs. The last step takes part already in the circulation. Each process of cellular differentiation is tightly governed by changes in gene expression patterns that are tuned by the action of several cytokines including erythropoietin (Epo), iron, and hypoxia among others [43,45]. Progenitor cells (BFU-E, burst-forming unit erythroid and CFU-E, colony-forming unit erythroid) are classified based on the properties of these cell types in producing erythroid cells in culture. Erythroid precursors form and develop in erythroblast islands surrounding a central macrophage. This macrophage plays a fundamental role during the cellular differentiation steps (erythrocyte maturation), and at the final step it phagocytes the extruded nucleus during enucleated RBC

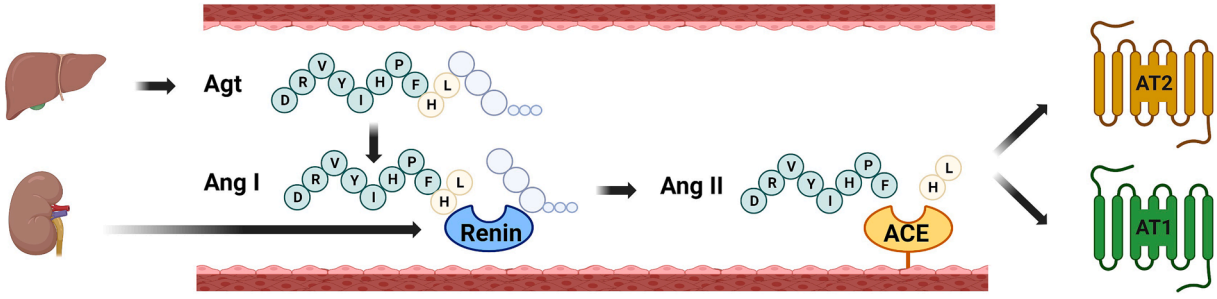

Fig. 1. Classical renin angiotensin sytem (RAS). The precursor protein angiotensinogen (Agt) is secreted in the circulation by hepatocytes. Renin, released from the kidneys into the bloodstream, cleaves Agt into the inactive peptide angiotensin I (Ang I). Lung endothelial cells express the transmembrane angiotensin converting enzyme (ACE) that cuts Ang I further into the active peptide hormone angiotensin II (Ang II). In addition, Ang II is produced locally in tissues by local expression and/or import of circulatory RAS components. Angiotensin type 1 (AT1) receptor is the major Ang II receptor expressed across the body including erythropoiesis relevant cells like cells of the bone marrow, erythropoietin producing cells and neurons controlling sympathetic activity. In addition, Ang II binds to angiotensin type 2 (AT2) receptors. This illustration was created with BioRender.com.

formation [43].

Epo is a major factor required for physiological baseline erythropoiesis (Fig. 3). The production of Epo takes place primarily in renal cortical fibroblasts, and the major stimulus controlling Epo expression is the reduction of oxygen levels in the kidney. During hypoxia, HIF-2α (hypoxia inducible factor 2-alpha) which is otherwise constitutively degraded by proteasomal targeting accumulates in this specialized population of fibroblasts and is translocated to the nucleus. As consequence HIF-2α upregulates Epo mRNA synthesis that will in turn increase bone marrow erythropoiesis [46,47]. Epo binds to its receptor expressed by erythroid progenitors. The binding of EPO prevents apoptosis, consequently proliferation and differentiation are stimulated resulting in higher numbers of functional RBCs being released into the blood stream (Fig. 3). Moreover, the genetic deletion of Epo or Epo receptor in mice are incompatible with life, *in utero* death occurs highlighting the essential role of this element for RBC production [48,49].

3. Clinical evidence for Ang II involvement in erythropoiesis

Homozygous deletional mutations in the angiotensinogen, renin, ACE and AT1 genes cause a common pathology known as autosomal-recessive renal tubular dysgenesis (OMIM #267430). Most of the patients born with the disease die in the perinatal period due to renal failure and respiratory complications driven by lung hypoplasia [50,51]. There has been reports describing patients who survived with the help of medical intervention. Survived patients most commonly present with mutations that allow a certain residual activity of the RAS characterized by very low levels of Ang II produced. Some examples in which a residual activity of the RAS is expected are driven by three types of point mutations: 1) Mutations in the sequence coding the renin signal peptide that do not allow renin release. 2) Mutations in the angiotensin converting enzyme leading to rapid solubilization instead of cell membrane anchoring. 3) Mutations in the angiotensinogen gene that decrease the renin affinity [51–54]. Nevertheless, these patients are severely hypotensive and anemia has been described as well [55–57]. The clinical presentation of this devastating disease demonstrates that Ang II via AT1 receptor is essential for blood pressure control and additionally strongly suggests that the axis controls erythropoiesis. Importantly, anemia is often observed in renal failure patients due to reduced Epo production and iron deficiency [58–61]. Both phenotypes were previously observed in case reports of patients with extremely suppressed Ang II synthesis, and Epo/iron administration are successfully used to manage the anemia [62]. Therefore, the anemia observed during autosomal-recessive renal tubular dysgenesis is probably not solely due to Ang II deficiency but also a product of renal failure.

A relatively common form of secondary hypertension is caused by renal artery stenosis. The reduced renal blood flow activates the RAS due to an exaggerated renin production driven by hypoxia. This pathological Ang II overproduction has been associated with gain of erythropoiesis [63–65]. A caveat is that the increased hematocrit cannot be attributed exclusively to Ang II once Epo is also upregulated during renal hypoxia [66–69]. Interestingly, the intravenous administration of Ang II for few hours increases plasma Epo levels even at subpressor doses. The Ang II effects are abolished by the coadministration of the AT1 antagonist losartan suggesting that the AT1 receptor, exclusively, mediates this process [70,71]. A similar renal hypoxia-driven erythrocytosis is observed in circa 15% of patients usually in the first year after renal transplant. Interestingly plasma Epo levels seem to be in the normal range in the affected patients but other erythropoietic factors such as Ang II, androgens and insulin-like growth factor 1 seem to cause the pathology. Interestingly, patients who develop erythrocytosis post-transplant have more AT1 receptor expression in their erythroid precursors [72]. The fact the hematocrit levels return to normal levels when treating these particular patients with AT1 or ACE blockers strongly indicates that Ang II controls erythropoiesis [73–77].

Another pathological RAS activation is found in chronic obstructive pulmonary disease. Some patients develop erythrocytosis during this condition. One study compared patients that had an increased hematocrit with patients with a normal hematocrit. Interestingly, Epo levels were not different between the groups but plasma renin activity was increased in the group that had an increased hematocrit [78]. Moreover plasma renin activity but not Epo correlated with the hematocrit suggesting that Ang II may control erythropoiesis beyond Epo production [78]. In this particular condition the hematocrit is lowered by treating the patients with AT1 blockers [79,80].

Collectively the data demonstrates that an increased formation of Ang II correlates with an increased hematocrit. However, one should critically interpret those findings once the effects of Ang II on erythropoiesis might be biased by mechanisms of pressure natriuresis that ultimately influence the plasma volume. Normally the kidneys balance blood pressure by controlling the extracellular fluid volume. Hence prolonged high levels of Ang II are expected to cause hypertension and upregulate the hematocrit due to plasma volume depletion.

3.1. RAS blockers and erythropoiesis

There are three major classes of RAS blockers used clinically. ACE, renin and AT1 blockers, the two first moderate the Ang II production and the last one limits Ang II binding to its major receptor (Fig. 1). ACE inhibitors and AT1 blockers are widely used clinically due to less side effects compared to direct renin inhibitors. These drugs constitute the first line of pharmacological therapy to lower blood pressure during hypertension and are also successfully used in other cardiovascular and renal diseases. Captopril was the first RAS blocker approved for clinical use in the early 1980s, eventually AT1 antagonist and direct renin inhibitors were introduced [4,81,82].

Clinical studies demonstrated early that the use of antihypertensive medication targeting the RAS is associated with anemia development and resolution after treatment discontinuation [83–85]. Other hematological disorders like hemolytic anemia, agranulocytosis, neutropenia, pancytopenia were also described in same patients [86–88]. Patients that are particularly susceptible to develop anemia during ACE blocker treatment are patients suffering from different renal and heart conditions [89–92]. RAS inhibition on these patients is effective in delaying their disease progression because their RAS is normally activated. The fact that these populations are particularly susceptible to anemia development could be explained by a higher dependence on Ang II for erythropoiesis maintenance. Anemia and other hematological alterations caused by ACE inhibition are also observed in patients treated with renin inhibitors and AT1 antagonists, and cardiac and renal disease patients receiving these medications are especially susceptible [92–96]. Altogether, there is abundant clinical evidence supporting that RAS inhibition disturbs erythropoiesis at least in some patients.

4. Erythropoiesis in rodent models

Genetic deletion of RAS proteins in rodents does not induce tubular dysgenesis as in humans, this demonstrates a differential role of the RAS for renal development across species. RAS-deficient mice (devoid of Ang II production or both AT1 receptors) are born with a morphologically intact kidney, however as early as two weeks after birth morphological changes start to become evident. Consistently observed changes are thickening of interlobular arteries and hydronephrosis due to excessive renin cell recruitment and urine elimination impairment, respectively [97,98]. The period these alterations start to develop coincides with a high mortality phase of these mice, after this critical period they usually reach adult life [99]. In adulthood, glomerular filtration rate is impaired but albuminuria is minimal, increased fibrosis and infiltration of immune cells is also observed in the kidneys of these mice [25,99–101].

Early studies discovered that ACE-deficient mice are anemic and because ACE cleaves N-acetyl-Ser-Asp-Lys-Pro (AcSDKP), a peptide that inhibits erythropoiesis, AcSDKP was believed to be the culprit [37].

Later, the N-terminal portion of ACE was specifically deleted in mice leading to accumulation of AcSDKP but preserving Ang II formation [102,103]. These mice had normal hematocrit despite elevated accumulation of AcSDKP similar to conventional ACE-KO mice lacking plasma Ang II [103]. Nowadays, it is known that the genetic deletion of the Ang II/AT1 axis leads to anemia independently of ACE activity. Mice with genetic deletion of angiotensinogen, renin and ACE are similarly anemic, as are mice lacking both angiotensin type 1 receptors, AT1a and AT1b. The selective deletion of either AT1a or AT1b has no major influence on the hematocrit of mice [38,104,105]. Similarly, AT2-deficient mice have an apparently normal erythropoiesis [106]. Considering that Ang II is a major vasoconstrictor agent, anemia could be secondary to a compensatory plasma volume increase. At least one study using ACE knockout mice controlled for the serum volume and could demonstrate true anemia [37]. The anemia phenotype is rescued in RAS-deficient mice by constant infusion of exogenous Ang II using minipumps. A study with angiotensinogen knockout mice could consolidate that Ang II/AT1 is relevant for erythropoiesis. In this study, the anemic phenotype of angiotensinogen deficient animals could be restored by Ang II administration but not when the same dose of Ang II was co-administered with the AT1 specific antagonist losartan [38].

There were studies demonstrating gain of erythropoiesis associated to increased Ang II levels [39,107] or by AT1a receptor mutation-induced gain of function [108]. Other reports showed a tendency to increased hematocrit or no alteration [37,109–111]. The discrepancies among studies are probably driven by differences in the Ang II levels reached in each study. Collectively the data suggests that in rodents as in humans the Ang II binding to AT1 receptor upregulates erythropoiesis.

5. Impact of the Ang II/AT1 axis on erythropoiesis control

There are many studies defending the existence of an intracellular (intracrine) RAS where Ang II is generated and may even bind to intracellular receptors to regulate cellular functions [112–116]. One argument in favor is that there are two isoforms of renin expressed, one that remains intracellular and another one being secreted. The intracellular isoform is expressed in organs as the brain, heart and adrenals at much lower levels when compared to the classical secreted renin produced by juxtaglomerular cells [117]. It is important to highlight that the interaction between cytoplasmic renin and secreted angiotensinogen is unlikely to happen and to result in the intracellular production of angiotensins [7]. Mouse models with specific targeted deletion of the secreted or the cytoplasmic renin isoform were generated but only mice lacking the secreted isoform were anemic [118,119]. Collectively the data indicate that the extracellularly produced Ang II takes part in erythropoiesis control.

Abundant clinical as well as preclinical evidence demonstrated an association of erythropoiesis with the RAS especially with the Ang II/AT1 axis as discussed above. In more recent years, researchers mainly employing *in vivo* and *ex vivo* preclinical experimental setups pointed out the following three major mechanisms by which Ang II influences erythropoiesis. First, Ang II stimulates Epo secretion. Second, Ang II itself promotes survival of erythroid progenitors. Third, brain Ang II modulates erythropoiesis by bone marrow sympathetic nerve activity control (Fig. 3).

5.1. Ang II and Epo secretion

Epo is mainly synthesized by a specific subset of renal fibroblasts expressing PDGFR-β located at the corticomedullary junction [46]. Epo production can be significantly upregulated because there is great amount of interstitial cells that might start producing Epo in conditions where erythropoiesis has to be upscaled [120,121]. More recently it was shown that some interstitial fibroblasts of the kidney express renin mRNA, these cells are also PDGFR-β positive. Interestingly, both Epo and renin mRNAs may be found in some of these cells, especially during anemic and hypotensive conditions [122,123] (Fig. 2). It remains largely unknown if a direct modulation exists, such as an Ang II autocrine signaling (Fig. 2). During kidney development renin producing cells give rise to several other renal cell types including vascular smooth muscle and Epo producing cells [124] (Fig. 2). Therefore, the remaining adult renin positive and Epo producing cell populations share a similar genetic configuration. Classical juxtaglomerular renin producing cells readily stop producing renin and transform themselves in Epo positive cells, if HIF-2α accumulates in these cells [123,125].

In vivo administration or transgenic expression of Ang II increases the circulating levels of Epo in a dose dependent manner in humans and rodents which stimulates erythropoiesis (Fig. 3). These alterations are prevented by AT1 blocker co-administration showing that the AT1 receptor modulates the response [39,70,71,126–128]. In agreement the administration of ACE blockers and AT1 antagonists cause a decrease in renal and plasma Epo as well as in RBC counts [129–132]. Hence, it is plausible that Ang II directly stimulates Epo production/release, especially because the expression of AT1 receptors by renal PDGFR-β positive fibroblasts is acknowledged [133,134] (Fig. 2). A major confounding factor indirectly implicated in the Epo response to Ang II is the reno-cortical blood flow that is known to be modulated by Ang II. By modulating the vascular tone in the kidney, Ang II influences tissue oxygen levels which is major determinant of Epo expression [129,135,136]. In line with this observation, HIF-2α is upregulated along with Epo upon Ang II infusion in mice [126]. Finally, it is worth mentioning that a similar correlation of Epo release is described for renal sympathetic nerve activity. Similar to Ang II, high renal sympathetic nerve activity or norepinephrine infusion reduce reno-cortical blood flow and increase Epo production as a consequence of tissue hypoxia [69,137,138].

One study has detected increased Epo secretion in mouse kidney slices and in human 786-O cells incubated with Ang II. In this study, it was concluded that Ang II induced Egr-1 nuclear translocation that is dependent on the activation of the Ras/ ERK1/2 MAPK pathway by the AT1 receptor [139]. Other studies used HepG2 and Hep3B cells and could not find evidence that Ang II increases Epo expression [39,140]. More recently a study deleted the AT1a receptor in cells originated from Forkhead Box D1 (FoxD1) lineage in AT1b deficient mice [133]. FoxD1-positive early progenitors give rise to several renal cell types including Epo, renin and smooth muscle cells [124,141]. Mice lacking AT1 receptors in these cells had normal hematocrits and circulating levels of Epo, and additionally blood pressure, renal morphology, and renin expression were not affected [133]. Perhaps future studies aiming to delete AT1 receptors using the promoter of a fibroblast specific marker like PDGFR-β would be interesting to study the *in vivo* effects of Ang II injection without the blood flow bias of smooth muscle AT1 deletion produced by the FoxD1 loss-of-function strategy.

Plasma levels of Epo in mice globally lacking ACE or angiotensinogen, which exhibit anemia and renal hypoxia, are elevated. If the Epo response would be stronger in the presence of Ang II to fully recover the anemia is unknown. However, submitting angiotensinogen knockout to bleeding increases blood Epo similarly to controls demonstrating that Ang II is not necessary to increase Epo at least during bleeding [37,38]. Altogether, the lack of Ang II or AT1 receptor in Epo producing cells has no major influence on Epo production, but Ang II seems to control Epo production if it causes renal hypoxia.

5.2. Ang II stimulation of erythroid cells

The bone marrow expresses all relevant components to locally produce Ang II as well as AT1 and AT2 receptors [142–146]. Furthermore, Ang II could be detected in cell media of *in vitro* cultured rat bone marrow [145]. *In vivo* additional circulating angiotensinogen and renin probably increases local bone marrow Ang II generation. Finally, circulating Ang II is expected to penetrate the bone marrow stroma as it does elsewhere except the brain and may therefore modulate

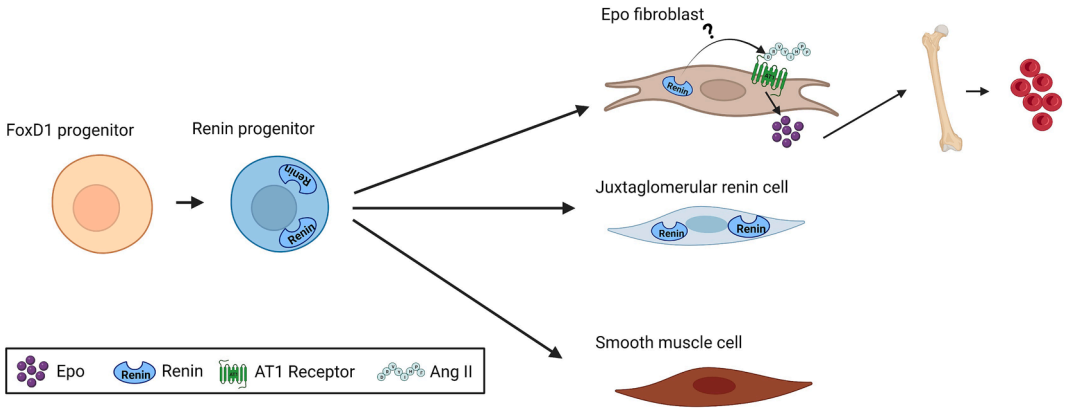

Fig. 2. Origin and fate of renal renin progenitors and their contribution to erythropoietin production. Renal renin progenitors originate from the Forkhead Box D1 (FoxD1) lineage. Renin progenitors further differentiate to juxtaglomerular renin-producing cells, vascular smooth muscle cells, and erythropoietin (Epo)-producing fibroblasts. Epo producing fibroblasts express the AT1 receptor. The binding of angiotensin II (Ang II) to these cells triggers the release and production of the major bone marrow erythropoiesis-stimulating cytokine Epo. Some of the Epo-producing fibroblasts also express renin, but whether an autocrine mechanism governs local Ang II formation and Epo release is largely unknown. This illustration was created with BioRender.com.

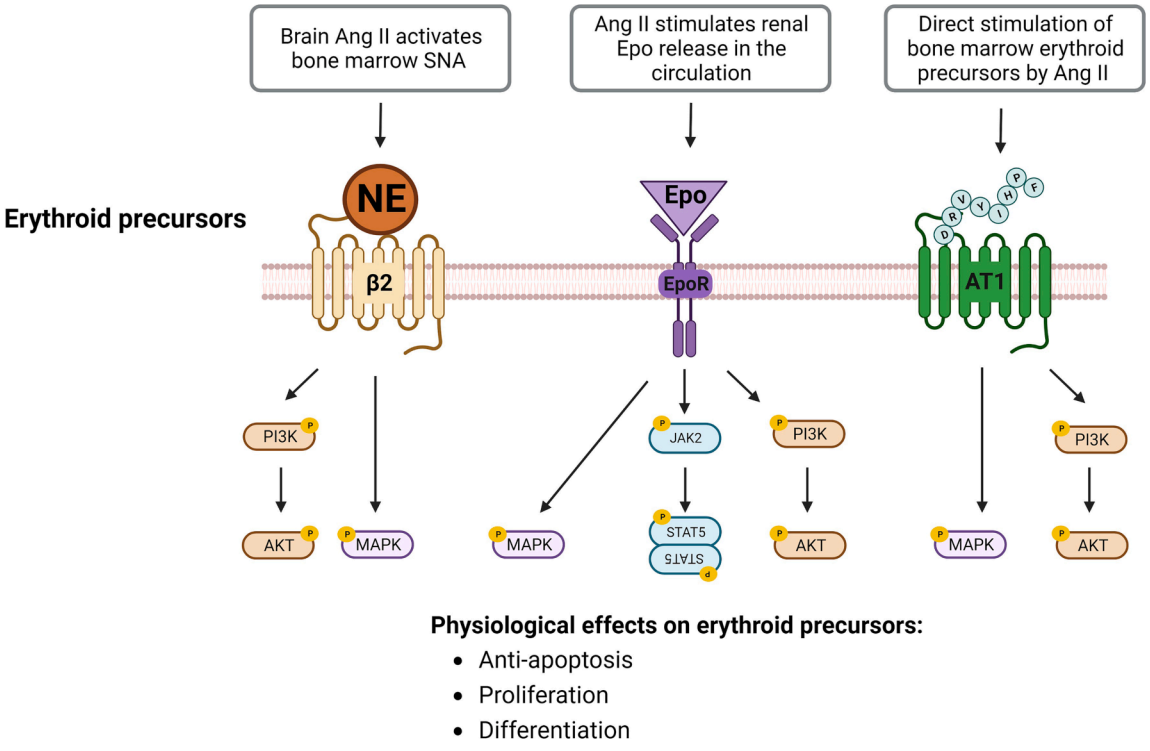

Fig. 3. Direct and indirect mechanisms of cell signaling triggered by the angiotensin II (Ang II) type 1 receptor (AT1) on erythroid precursors. Ang II activates brain circuits controlling sympathetic nerve activity (SNA). Activated bone marrow innervating sympathetic nerves release the effector neurotransmitter norepinephrine (NE). NE activates β2 adrenergic receptors on erythroid precursors that recruit the PI3K/AKT and MAPK pathways. Ang II facilitates the production and release of erythropoietin (Epo) from specialized renal fibroblasts. Epo binding to Epo receptor (EpoR) activates downstream signaling including JAK2/STAT5, PI3K/AKT, and MAPK. Erythroid precursors express the AT1 receptors, and locally produced or circulating Ang II activates these AT1 receptors which signal through the PI3K/AKT and MAPK pathways that facilitate erythropoiesis. This illustration was created with BioRender.com.

erythropoiesis [2,3,147].

Ang II receptors are expressed by hematopoietic stem cells (HSCs) defined as $CD34^+$ [142,148–150]. *In vivo* administration of Ang II increases the number of HSCs in bone marrow and spleen of mice and greatly increases myelopoiesis [151]. Furthermore, Ang II facilitates erythroid colony formation from mouse bone marrow and human cord blood isolated $CD34^+$ HSCs. Importantly, this effect is largely suppressed by the AT1 antagonist losartan, and apparently is dependent on culture supplemented with serum [142,152]. *In vitro* incubation of common myeloid progenitors (precursor of erythrocytes) with Ang II facilitates proliferation [153] (Fig. 3). Similarly, BFU-E colonies form efficiently if $CD34^+$ HSC cells are treated with Ang II in culture media containing Epo [142,150]. The need for serum or Epo being present for Ang II induced survival of erythroid progenitors strongly suggests that Ang II potentiates the Epo signal. Epo survival mechanisms are known to be triggered by recruiting the JAK/STAT pathway (Fig. 3). More precisely, JAK2/STAT5 are activated by the erythropoietin receptor resulting in expression of anti-apoptotic proteins, like Bcl-xL [49,154]. Moreover, Epo receptor activation activates PI3K-AKT and MAPK pathways contributing to survival and proliferation, respectively [49,154] (Fig. 3).

All these pathways are well known to be activated by the AT1 receptor in smooth muscle cells [21,155]. Possible erythroid progenitors are activated in a similar manner but confirmatory studies should be performed.

Chronic hemodialysis patients often receive Epo to correct anemia but RAS inhibitors decrease the beneficial effects of Epo. Indeed, ACE inhibitors and especially AT1 antagonists reduce the amount of BFU-E colonies of healthy and chronic hemodialysis patients [156]. Chronic upregulation of Ang II in mice by transgenic expression of renin and Agt leads to erythrocytosis [39]. Exposing these animals to irradiation and transplanting them with bone marrow from either wildtype or AT1a-deficient mice does not lower their hematocrit [39]. It is important to state that AT1a-KO mice are not anemic because the AT1b seems to compensate for the AT1a loss in erythropoiesis control. Altogether, Ang II seems to potentiate the Epo signaling on erythroid cells and the strength of the stimulus is probably different under disease conditions and it seems to be more complex in *in vivo* conditions [38].

5.3. Brain Ang II sympathetic activity and erythropoiesis

Hematopoietic organs, bone marrow and spleen, are innervated by sympathetic neurons such as other peripheral organs [12,157,158]. Sympathetic nerves enter the bone via the nutrient foramen and sympathetic terminals are found in close proximity with the bone marrow niche serving as a key keeper of HSC health [159,160]. A well characterized role of the adrenergic nerves is the modulation of the HSC niche. Sympathetic nerves mobilize HSC from the bone marrow into the circulation in a circadian fashion that relies on the circadian pattern of sympathetic activity [161]. The mobilization of HSC is key to replace tissues resident immune cells, and during immune modulatory responses to injury [162,163]. Following injury sympathetic activity is activated and the excessive recruitment of HSC to injury sites depletes bone marrow erythroid progenitors causing prolonged anemia but additionally induces extramedullary erythropoiesis and myelopoiesis in the spleen [164,165]. More recently it was shown that the sympathetic system causes this HSC shift to the spleen because β-adrenergic agonists mimick the phenotype *in vivo* [166]. The knowledge that the sympathetic system controls erythropoiesis is supported by clinical evidence from patients with autonomic failure (impaired sympathetic outflow) that develop anemia [167,168]. In agreement sympathectomized rats develop anemia [169] and cisplatin treated mice develop anemia due to loss of adrenergic nerves [170].

There have been previous studies using preclinical models describing increased sympathetic nerve activity to bone marrow and spleen induced by brain or peripheral Ang II infusions [12,171,172]. Chronic administration of Ang II or by transgenic RAS protein expression in the brain reduces the peripheral RAS activity and increases sympathetic nerve activity. Interestingly, this brain-specific increase in Ang II also increases erythropoiesis [8,173,174] (Fig. 3). We have recently demonstrated in a transgenic mouse model with increased brain Ang II and erythropoiesis that these effects are mediated by the sympathetic nervous system, because the ablation of the peripheral sympathetic system eliminates the effects of brain Ang II on RBC production [8]. In agreement transgenic rats with depleted brain Ang II levels have a reduced hematocrit demonstrating that the endogenous brain RAS is relevant for the homeostatic control of erythropoiesis [175]. Finally, transgenic mice expressing human ACE2 in the brain and periphery, a major enzyme degrading Ang II, have a lower hematocrit [176].

During essential hypertension the peripheral RAS is normally found suppressed, however the brain RAS seems to be hyperactive because patients often present increased levels of vasopressin in their blood [177–179]. Preclinical research demonstrated that during hypertension the blood–brain-barrier becomes permeable for Ang II, therefore circulating Ang II or intrinsically produced Ang II in the brain overactivates existing neuronal brain Ang II receptors. During human essential hypertension, which is commonly accompanied by increased sympathetic nerve activity, an increased hematocrit is often observe and both increased sympathetic activity and the alteration in the hematocrit precede hypertension. Therefore, the increased hematocrit in hypertension is not solely explained by compensatory mechanisms of pressure natriuresis but rather by other mechanism such as increased sympathetic activity [180–184]. Owing to the ability of Ang II to drive sympathetic activity it is reasonable to postulate that part of the phenotype might be attributed to increased activity of the brain RAS. The features of increased hematocrit during essential hypertension are also observed in the preclinical rat and mouse models of hypertension, spontaneously hypertensive rat and Schlager hypertensive mouse. Both models of sympathetically mediated hypertension with a contribution of an activated brain RAS also have increased bone marrow sympathetic nerve activity and hematocrit levels [185–188].

In vitro studies showed that norepinephrine stimulates erythropoiesis by increasing CFU-E and BFU-E growth via β2-adrenergic signaling by a mechanism apparently operating synergistic to Epo [167,189–192] (Fig. 3). Studies indicated that cAMP recapitulates the effects on erythroid proliferation triggered by the β2-adrenergic agonist isoproterenol [191,193]. β2-adrenergic receptors are known to facilitated cAMP production by activating adenylyl cyclase via the Gs pathway [194]. This effect is also observed in erythroid progenitors and interactions with other pathways such as the MAPK recruited by the Epo signal may lead to cell proliferation [191,195] (Fig. 3). A possible additional contribution of β2-adrenergic receptor activation on erythroid cells is the PI3K-AKT anti-apoptotic signal triggered by recruiting Gi proteins [194,196] (Fig. 3). Importantly, it seems that norepinephrine has a dose dependent effect on erythropoiesis because too high norepinephrine concentration inhibits growth of erythroid progenitors [71,190]. Finally, α1-adrenergic receptor activation is associated to erythropoiesis suppression [197]. Not only HSC but also progenitors and other cells in the bone marrow express adrenergic receptors [162,185]. Therefore, the modulatory role of the sympathetic nervous system on erythropoiesis is rather complex involving direct modulatory actions on progenitor cells or indirect via modulating the release of factors such as cytokines by other cells of the niche.

Because of the highly complex interaction between the sympathetic system with other factors regulating erythropoiesis in physiological and pathological conditions, the role of norepinephrine is not precisely defined and most likely differs depending on homeostatic conditions [167]. Which neurons control bone marrow activation is another puzzling question to be answered. There have been at least two studies in this direction. One deleted AT1a receptors in vasopressinergic neurons and the other in the paraventricular nucleus of the hypothalamus, both could not demonstrate changes in the hematocrit of mice [198,199].

6. Final considerations and future directions

The RAS evolved in mammalians with a major function in restoring homeostasis when threatened. An upregulation of the RAS is usually a response to reduced renal perfusion. To restore homeostasis Ang II has a well-recognized role in upregulating blood volume by fostering fluid intake and reducing renal salt and water losses. It is reasonable that during the course of evolution the effector peptide Ang II not only evolved to increase blood volume but also the circulating RBC mass in order to improve tissue oxygenation. Evidence supporting the role played by the Ang II/AT1 in RBC production was already laid down in the past decades. However, it remains experimentally challenging to dissect the precise mechanisms utilized by Ang II to influence erythropoiesis.

As mentioned in this review at least three major mechanisms whereby Ang II can influence RBC production were defined. 1) stimulation of renal erythropoietin synthesis; 2) direct action on bone marrow precursor cells; and 3) modulation of sympathetic nerve activity to the bone marrow (Fig. 3). Erythropoiesis regulation involves several organ systems. Thus, *in vitro* experiments are useful to dissect molecular mechanisms but they are not useful to quantify the *in vivo* contribution

of these mechanisms. Regarding the contribution of Ang II to erythropoiesis a major confounding factor is the broad expression of its receptors across different tissues. Ang II certainly modulates erythropoiesis but it also causes physiological disturbances that influence measurement of parameters *e.g.* plasma volume. In addition, the impact of Ang II on RBC production seems to vary significantly between health and disease states. Altogether, the contribution of each mechanism as well as synergistic interactions between them are challenging to be established in *in vivo* experimental settings.

There are available tools to better dissect mechanisms of erythropoiesis control using *in vivo* models. To understand if Ang II controls Epo secretion, specific fibroblast promoters in combination with Cre-LoxP may be used to manipulate Ang II receptor expression in renal fibroblasts. Regarding the role of Ang II on erythroid progenitors again selective genetic tools might be used to manipulate Ang II receptors during specific differentiation stages. In addition, the depletion and replenishment of HSCs with different receptor knockouts as well as rescue of anemic knockout with wildtype HSCs have not yet been performed. There are still many open questions regarding how brain Ang II increases erythropoiesis via sympathetic activity, already developed techniques such as opto-and chemo-genetics might be helpful to provide important insights. Finally, OMICS tools are essential to gain insights in the cellular and molecular bases of the regulatory mechanisms but also to understand possible compensatory mechanisms driven by Ang II/AT1 signal manipulation. ACE inhibitors and AT1 blockers are widely used clinically. Therefore, understanding how Ang II controls physiological and pathological erythropoiesis will be helpful to use these drugs with more safety in patient care.

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During the preparation of this work the authors have not used AI-assisted technologies.

CRediT authorship contribution statement

André F. Rodrigues: Conceptualization, Investigation, Visualization, Writing – original draft. **Michael Bader:** Conceptualization, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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