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Chapter 9

Current Research of the Renin-Angiotensin System Effect on Stem Cell Therapy

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Abstract

The renin-angiotensin system (RAS) is a chief regulator of the cardiovascular system and body fluid homeostasis. Stem/progenitor cell therapy has pointed towards a novel tool for medical and therapeutic intervention. In addition to the physiological and pathological role of the RAS and its pharmacological inhibitors, the proliferation, differentiation in stem cells is mediated through various cell-signalling pathways. This book chapter reviews the new role of RAS components, distinct from other common roles by considering its regulating impact on the several signalling pathways involved in different body tissues, as well as in stem cell therapy.

Keywords: stem cell, progenitor cell, renin-angiotensin system, pancreatic stem cells, cardiac stem cells

1. Introduction

The concept that the renin-angiotensin system (RAS) is involved in the regulation of stem (progenitor) cell function is novel. This is beyond the conventional notion of the RAS acting as a potent vasoconstrictor responsible for blood pressure regulation and body fluid homeostasis. The expression of RAS components during human embryonic development has been addressed in the literature. The existence of RAS components in different organs and tissues suggests the presence of local RAS in addition to the circulating common RAS, which has paracrine effects mediating stem (progenitor) cell function. Moreover, recent evidence has shown the expression of major RAS components such as angiotensinogen, renin, angiotensin-converting enzyme (ACE), angiotensin receptors type 1 and 2 and angiotensin-(1–7)

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during growth, proliferation and differentiation of stem cells. Improvement of the stem cell functionality and making them ideal candidates in different kinds of disorders has been a new research field in the last decade. Meanwhile, the effect of RAS on stem cell growth, proliferation and function is an emerging attempt among researchers. Ang II receptor activation increases the proliferation of several progenitor cells, such as mouse bone marrow-derived stem cells and human cord blood cells. Accordingly, manipulation of the RAS may alter and/or have beneficial effects on the efficacy of stem cell therapy.

2. Stem cells

The term stem cell stands for the population of immature precursor cells, which are able to renew themselves and be the source of de novo replacement for many body tissues. Stem cells are classified into two main groups: embryonic stem cells (ESCs) and adult stem cells. ESCs can be obtained from the inner cell mass of the embryonal blastocyst. Although they are easily achieved, some disadvantages restrict their application. Adult stem cells such as mesenchymal and haematopoietic stem cells (HSCs) are obtained from mature tissues. Due to their plasticity, adult stem cells produce cell lineage different from their original organ. Thus, adult stem cells seem to be an appropriate candidate for organ regeneration in different kinds of diseases or lost/damaged organs. **Table 1** represents the main stem cell and their advantages and disadvantages.

Stem cell type	Origin	Advantages	Disadvantages
Embryonic stem cell	Blastocyst stage of an embryo	- High expansion - Pluripotent	- Ethical objection - Risk of rejection - Risk of teratocarcinoma
Adult stem cell	Mature tissue	- Easily obtained - No ethical objection - High compatibility	- Lack of specific identification markers

Table 1. Main stem cell and their advantages and disadvantages.

3. The RAS and ESCs

ESCs are pluripotent cells capable of differentiation into different cells such as cardiomyocytes, and endothelial cells have been considered as a source of regenerative medicine [1]. For instance, ESC-derived endothelial cells have therapeutic effects via the increment of angiogenesis and heart functionality [2]. PI3/Akt-signalling pathway has been shown to be linked with human ESC-derived cardiomyocyte proliferation in vitro [3]. RAS stimulation activates PI3/AKT pathway, while the inhibition of RAS increases Akt phosphorylation [4], which

might influence the proliferation of ESCs. High survival rate after transplantation is another main, noteworthy issue about ESCs [5].

RAS is a novel regulatory candidate, which controls the development of ESCs into different cell types. It has been reported that the expression AT1 receptors were detected in an early stage of human ESCs differentiation. Since the addition of Ang II results in the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 and Jun N-terminal (JNK) 1/2, this peptide is capable of acting as signalling molecules and thus it could regulate differentiation [6]. Moreover, Ang II has been shown to increase glucose uptake in ESCs [7] and induce mitogenic effect, possibly through protein kinase C and mitogen-activated protein kinase (MAPK)-signalling pathways. Interestingly, exposure to a high glucose niche in the presence of Ang II has been shown to produce a synergistic impact on ESC proliferation [8].

4. The RAS and mesenchymal stem cells

Mesenchymal stem cells (MSCs) as multipotent cells are mainly found in bone marrow and adipose tissue and can differentiate into various cell types [9]. Simple isolation, high immune prevalence and angiogenic-inducing properties have made MSCs suitable candidates for stem cell therapy of different kinds of diseases [10]. Besides, these MSCs exert paracrine effects causing the modulation of a large number of cellular responses, such as survival, proliferation, migration and gene expression [11]. Diminishing oxidative stress and suppression of the TGF-β/Smad2-signalling pathway are some of these paracrine effects [12, 13]. In the rat pulmonary hypertension model, MSCs have shown superiority regarding the lowering of blood pressure and ventricular overload; hence, MSC transplantation in chronic lung disease with pulmonary hypertension has pointed towards a new therapeutic option [14]. Concomitant percutaneous trans-luminal renal angioplasty with MSC therapy has been reported to decrease inflammation, fibrinogenesis and vascular remodelling in atherosclerotic renal artery stenosis of swine [15]. Also, MSCs have the ability to recognize inflammation lesions, and Ang II effects the migration and homing of these cells to the site of injury [16]. Dysregulation of the RAS decreases the paracrine therapeutic potential of MSCs [17].

Expression of renin, AT1 and AT2 receptors has been implicated with the regulation of MSCs differentiation to adipocytes, while the differentiated cell produces significant amounts of endogenous RAS [18]. Indeed, endogenous blockade of AT1 receptor inhibited adipogenesis of MSCs [18]. These outcomes are in line with clinical observations that RAS blockade acts as a protective factor against the onset of obesity-induced diabetes mellitus type 2 [19]. Ang II also has been shown to stimulate the synthesis of vascular endothelial growth factor (VEGF) that is an angiogenic agent in MSCs [20]. Additionally, MSCs have been suggested as a promising regenerative medicine for treating ischaemic heart disease and diabetes [21]. Hence, it is probable that Ang II-induced production of VEGF might be a contributing underlying mechanism of the beneficial consequences obtained following MSC transplantation.

5. The RAS and endothelial progenitor cells

The identification of circulating endothelial progenitor cells (EPCs) has introduced the concept of postnatal vasculogenesis. EPCs could originate from haematopoietic stem cells (HSCs) or MSCs [22, 23]. Also, the EPCs existing in the adventitial layer of vessels have the ability to differentiate into adult endothelial cells [24]. Different factors such as ischaemia, vascular damage and even physical exercise result in the recruitment of circulating EPCs and thus neovascularization and restoration of endothelial functionality [25, 26]. In this context, the improvement of myocardial perfusion after EPC transplantation has been observed in clinical trials [27]. Several mechanisms have been suggested regarding EPCs mobilization. For instance, it was observed that ischaemic lesions release angiogenic factors like VEGF and activate MAPK or the RAS-signalling pathways [28], which increase EPCs migration.

Despite the important role of vascular endothelium in cardiovascular disease (CVD), their limited regeneration capacity remains a vital problem. EPCs improve angiogenesis and participate in endothelium recovery subsequent to vascular injuries [29]. Cardiovascular diseases (CVDs) are directly related to both the decline of EPC mobilization and the number of EPCs present in the damaged site. In this context, Ang II stimulates EPCs migration to ischaemic regions and commences vascularization through VEGF-associated endothelial nitric oxide synthase [30]. The activation of NAPH and subsequent ROS (reactive oxygen species) generation constitutes the stimulatory impact of Ang II on EPCs that is required for normal EPC function. However, the long-term activation of NADPH and oxidative stress is concomitant with cell senescence [31]. Moreover, acute high-dose exposure to Ang II has been shown to negatively modulate EPC function in the hind limb ischaemic rat model [32].

6. The vascular RAS and erythropoiesis

RAS has been shown to result in progenitor cell senescence and suppression of differentiation and adherence in bone marrow-derived EPCs in Ang II infusion models. This inhibitory impact could be attenuated by the administration of AT1 receptor antagonists [31]. Previous reports have proved the crucial role of Ang II during erythropoiesis [33]. In studies using transgenic mice expressing human renin and angiotensinogen, a drastic rise in levels of erythropoietin was observed, which is a glycoprotein hormone that controls erythropoiesis. Genetic ablation of AT1 receptor from these mice reduced erythropoietin levels and restored haematocrit levels [34]. Also, ACE blockade has been concomitant with haematocrit decrease in vivo [35]. The idea of ACE and/or Ang II being contributed to erythropoiesis was further confirmed by a recent research in which ACE marked haematopoietic stem cells from human embryonic, fetal and adult haematopoietic tissues [36]. However, the mechanism of Ang II-associated regulation of erythropoiesis is mainly unclear. Most of these effects are observed during early phases of erythropoiesis [37]. As mentioned above, some researchers imply that Ang II acts indirectly via its effect on erythropoietin levels [38], whereas others do not agree with this link [39]. The other possible mechanism is proposed to be the involvement of JAK (Janus kinase)/STAT (signal transducer and activator of transcription) pathway. JAK/STAT pathway is known to be activated by Ang II [40].

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7. Current research on the RAS in pancreatic stem cells

The local RAS is not only involved in the physiology of pancreas, but it also influences the pancreatic stem cell (PSC) functionality. RAS has been shown to be associated with pancreatic islet cell function and proliferation and differentiation of PSCs/progenitor cells during development [41]. Different stem/progenitor cells have been reported to be differentiated into insulin-expressing cells, which make them appropriate candidates for islet cell transplantation. Regarding the potential role of RAS in stem cell differentiation, it is possible that RAS-modulated stem cell could be a new source of pancreatic β-cells. Both exocrine and endocrine pancreas are known to have local RAS components [42]. In exocrine part, AT1 receptor activation turns on signalling pathways such as ROS generation and activation of pro-inflammatory, vasoactive and growth factor receptors [43, 44]. Therefore, Ang II might result in fibrosis and inflammation of exocrine pancreas through the AT1 receptor. Hence, blockade of RAS has been considered a potential therapeutic opportunity for some pancreas disorders.

In the endocrine portion of pancreas, RAS has been shown to be a key regulator of insulin and islet physiology [43]. AT1 receptor stimulation leads to β-cells, decreased islet blood flow and insulin secretion, while AT2 receptor activation results in β-cell proliferation and islet blood flow and insulin secretion enhancement [19]. Moreover, the ACE2/Ang-(1–7)/Mas axis, which has been attracting more research attention recently, is present in several local tissues and mainly acts as a negative modulator of ACE/Ang II/AT1R signalling. Similar to AT2 receptor activation, ACE2 overexpression in the pancreas of type 2 diabetic animals restored glucose homeostasis, as evidenced by diminished blood glucose levels, elevated insulin secretion and β-cell proliferation [45].

PSCs exist in both developing and adult pancreas in three major pancreas sections, that is, ductal endothelium, islet and acinar tissues [46]. Embryo, foetus and adult pancreas as well as bone marrow-derived MSCs are probable sources for PSCs. Transplantation of mouse or human PSCs into diabetic mice has been revealed to reduce their diabetes [46].

A novel well-defined area of research is the developmental control of RAS on cell proliferation in tumours and in tissue regeneration. Both the ACE/AngII/AT1R signalling and the alternative RAS arm (ACE2/Ang-(1–7)/Mas) interact with different growth factors; hence, they might contribute to cell proliferation and angiogenesis in neoplasms, including pancreatic cancers [47–49]. It has been demonstrated that RAS inhibition seems to be a promising therapeutic approach for the mitigation of pathophysiological circumstances of the pancreas including diabetes [50], pancreatitis [43] and pancreatic cancer [51]. Transplantation of human fetal pancreatic progenitor cell has been shown to reverse hyperglycaemia and glucose intolerance in diabetic mice [52]. ROS production has a close relation with RAS activation, and ROS-signalling pathway is associated with stem/progenitor cell proliferation, differentiation and function [53]. So, it is an interesting probability that the elevation of RAS-induced differentiation of pancreatic progenitor cells towards an endocrine lineage might offer a basis for therapy in terms of islet replacement treatments for diabetes.

MSCs have been suggested as an appropriate substitute to islet transplantation for promoting regeneration of endogenous pancreatic progenitor cells to achieve permanent normal blood glucose level in patients with type 1 diabetes [54]. Local RAS in pancreatic islet could regulate PSC differentiation and thus lead to the beneficial outcomes following MSC transplantation. In a study, these kinds of pancreatic progenitor cells have shown to differentiate into insulin-secreting cells.

RAS components like angiotensinogen and renin are expressed after the beginning of pancreatic progenitor cells differentiation, but they are not present in undifferentiated cells. These results indicate that a functional RAS exists in pancreatic progenitor cells and in mature islets that could be modulating cellular differentiation. The mitogenic behaviour related to the Ang II bindings of AT1 receptors has been proposed to regulate reprogramming of pancreatic cells and the differentiation plasticity [55]. However, it is unclear whether AT2 receptor activation reveals counter-regulatory role in this context. Furthermore, it is hypothesized that the ACE2/Ang-(1–7)/Mas axis plays an essential role in pancreatic stem cell differentiation as previous studies have shown the involvement of ACE2 arm in the proliferation and differentiation of other stem cells [56].

8. Current research on the RAS in cardiac stem cells

Regarding the intracellular signalling pathway of Ang II, RAS effect on cardiovascular stem/progenitor cell transplantation has largely been investigated. Among the regenerative medicine-based therapies in the cardiovascular system, induced pluripotent stem cells (iPSCs), which are artificially derived from an adult non-differentiated somatic cell, are a field of research study. In spite of different origin, they resemble ESCs in their growth and gene expression profile [57]. Also, Ang II receptors are expressed in iPSCs, which induce the proliferation and differentiation of pluripotent stem cells to several kinds of stem cells. As mentioned before, Ang II stimulates cell-signalling cascade through ROS production which in turn instigates stem cell proliferation [58]. In a study, the administration of Tempol (ROS generation-blocking agent) in Ang II-treated pluripotent stem cells has attenuated the proliferation of stem cells and DNA synthesis suggesting the role of oxidative-signalling pathway in RAS-associated cell proliferation. The other signalling pathway linked to the differentiation of iPSCs and Ang II is JAK/STAT pathway [59].

Ang II is also able to induce ESCs differentiation. In this context, the effect of AT1 receptor activation on collagen IV protein has been investigated [18]. Collagen IV is an extracellular matrix protein having a role in cell adhesion, growth, migration and differentiation. Collagen IV has been shown to be involved in the differentiation of ESCs to smooth muscle cell.

Up-regulation of several transcription factors such as egr-1, c-fos/c-jun, Stat91, NFk-B, which has a fundamental role in stem cell differentiation, is mediated through PI3/Akt pathway. Ang II is the upstream cascade of PI3/Akt82-84. NFk-B is markedly up-regulated in Ang II-treated cells, proposing that there is NFk-B involvement in ESC differentiation into the smooth muscle cells [60].

The TGF-β/Smad pathway plays a key role in the cellular responses to Ang II. Ang II activates TGF-β secretion in various tissues, such as fibroblasts and smooth muscle cells that induce interstitial fibrosis in the heart and kidney. Besides, TGF-β/Smad pathway is highly engaged to vascular fibrosis and arteriosclerosis [61] and gives rise to the differentiation of MSCs to smooth muscle cell. Furthermore, TGF-β secretion is connected with the MAPK/ERK cascade, and Ang II in this pathway interferes with TGF-β production, thus leading to the differentiation of MSCs to smooth muscle cells [62].

Regarding owning various paracrine effects, MSC transplantation has gained great importance in cardiovascular disease [63]. The supportive effects of vascular VEGF have been recognized in the migration, invasion of extracellular matrix, proliferation, survival of MSCs, and they contribute to MSCs' paracrine effects [64, 65]. In this context, all pathways increasing VEGF would give rise to the function of MSCs. Ang II increases VEGF mRNA and protein expression in MSCs [20], which is associated with Akt-signalling pathway. Pre-treatment of MSCs with the Akt inhibitor (LY292002) has been shown to reduce Ang II-induced VEGF expression. So, local Ang II, as a cytokine, might boost VEGF generation in MSC grafts and upgrade the transplantation effectiveness.

The excess RAS expression is detected in CVDs such as myocardial infarction, hypertension, heart failure and atherosclerosis [66]. On the other hand, RAS inhibition via ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) has been widely examined in cardiovascular disease beyond their effects in lowering the blood pressure [67]. Despite the daily increasing use of regenerative medicine in treating different disorders, the functionality of stem cell transplantation is not sufficient in animal models and clinical trials [68].

Therefore, clarifying the mechanisms that enhance the graft efficacy seems important. Researchers have investigated the effect of RAS inhibition on stem cell therapy of cardiovascular system [69].

The insulin-like growth factor 1-1 secreted from stem cells has a close relationship with the RAS and down-regulates the local RAS through the attenuation of the p53 gene [70]. The IGF-1 has an anti-apoptotic effect on cardiomyocytes in ischaemic heart disease and also enhances differentiation and survival of stem cells after transplantation [71]. In acute MI in cardiomyocytes, ACEIs up-regulate the IGF-1 receptors; thus, the concurrent use of perindopril in bone marrow stem cell transplantation increases the paracrine effects of the IGF-1, which abolishes apoptosis through increased Bcl2 expression and improves cardiac function [72]. Also, pre-treatment of MSCs with ARBs before transplantation increases their trans-differentiation efficacy and also improves the systolic function of the heart [73].

9. Limitations and future directions

Comprehensive elucidation of the complexity of the regulatory network that drives stem cell therapy will require extensive effort and time. The accretion of daily increasing research and obtained ideas will undoubtedly assist the current research field of stem/progenitor cell

therapy. Regenerative progenitor cell therapy has emerged as a possible alternative for pharmacotherapy in different human diseases. A major problem in this field is insufficient efficacy during stem cell transplantation. In order to improve the efficiency of regenerative medicine, researchers examined the impact of the modulation of various cell-signalling pathways, including the RAS. Effects of Ang II in stem cell proliferation and differentiation have been documented in the literature. The presence of the RAS components in progenitor cells and many tissues may regulate growth and development and thus might contribute to the preparation of various progenitor cells for clinical transplantation.

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