An Insight on Multicentric Signaling of Angiotensin II in Cardiovascular system: A Recent Update

Kanika Verma¹, Malvika Pant¹, Sarvesh Paliwal¹, Jaya Dwivedi² and Swapnil Sharma¹*†

¹Department of Pharmacy, Banasthali Vidyapith, Banasthali, India, ²Department of Chemistry, Banasthali Vidyapith, Banasthali, India

The multifaceted nature of the renin-angiotensin system (RAS) makes it versatile due to its involvement in pathogenesis of the cardiovascular disease. Angiotensin II (Ang II), a multifaceted member of RAS family is known to have various potential effects. The knowledge of this peptide has immensely ameliorated after meticulous research for decades. Several studies have evidenced angiotensin I receptor (AT₁ R) to mediate the majority Ang II-regulated functions in the system. Functional crosstalk between AT₁ R mediated signal transduction cascades and other signaling pathways has been recognized. The review will provide an up-to-date information and recent discoveries involved in Ang II receptor signal transduction and their functional significance in the cardiovascular system for potential translation in therapeutics. Moreover, the review also focuses on the role of stem cell-based therapies in the cardiovascular system.

Keywords: angiotensin II, stem cell, biomarkers, hypertrophic markers, cardiac gene regulation, signaling

INTRODUCTION

In the last decades, researchers have successfully unraveled key functions and mediators of the renin-angiotensin system (RAS). Ubiquitously available RAS plays numerous physiological roles including regulation of blood pressure, fluid volume, vascular wall integrity, cell growth, cardiac output, and vascular tone in the body (Forrester et al., 2018). RAS is also involved in maintaining cardiovascular homeostasis, a network of intracellular signaling pathways, and various processes through endocrine, paracrine, and autocrine mechanisms (Bussard and Buss, 2018). Regardless of complexities associated with its movement from the local system occurring virtually in each organ to the hormonal system existing in circulation, the active end product is still Angiotensin II (Ang II) (Colafella and Danser, 2017).

Historically, in 1898, renin was discovered as a pressor compound within the extracts of the renal cortex of rabbits by Robert Tigerstedt. Their work was renewed in 1934, when Henry Goldblatt demonstrated induction of chronic hypertension by constriction of renal arteries in a dog with silver clamps. In continuation to this, Page and Helmer and Braun-Menéndez et al., discovered angiotensin as another compound from renal secretion bearing quick pressor response. These studies focused on the involvement of Ang II in physiological and pathophysiological functions. Besides, RAS inhibiting agents have shown promising benefits in the management of end-organ damage, ischemia, atherosclerosis, and cardiovascular-related disease (Nehme, 2019). A timeline of key historical findings associated with the study and discovery of Ang II associated with RAS is shown in Table 1 (Burton et al., 1985; Gibbons, 1998; Basso and Terragno, 2001; Andrea et al., 2006; Atlas, 2007; Skrbic and Igić, 2009; Benigni et al., 2010).
In view of traditional applications, investigators are making a consistent effort to explore the associated pharmacological effects of Ang II. Unfortunately, it is hoped that the next 100 years of research into RAS will uncover hitherto unimaginable therapeutic opportunities (Ferrario, 2006). The review will provide recent findings on Ang II receptor signal transduction and its functional significance in the cardiovascular system. In addition to this, the review also focuses on the applications of stem cell-based therapies in the cardiovascular system. The majority of pathophysiological conditions including hypertension and cardiac remodeling of Ang II are mediated by AT1R, which makes specific signaling pathways much clearer. In light of these facts the purpose of the present review is to provide newer insights in future research with an instinct that it will help emerging novel strategies to establish Ang II as a promising therapeutic candidate in translational research in the near future.

**METHOD: EXCLUSION AND INCLUSION CRITERIA**

The articles, written in English, published from 1985 to 2020, were exploited for gathering all relevant information of Ang II related articles from search databases namely, Science Direct, Medline/PubMed, Google Scholar, and other sources. Various databases were used to identify peer-reviewed papers dealing with the review theme of angiotensin-induced cardiovascular issues. A pilot review of literature assisted in identifying search terms that were used to categorize articles through a standardized and systematic process. The strings/words used for search purposes were as follows: “angiotensin”, “induced”, “receptor”, “signaling”, “disease”, “mediators”, “animal model”, “biomarkers”, “hypertrophic markers”, “cardiac genes”, “stem cells and others”.

**ANGIOTENSIN II RECEPTORS AND SIGNALING PATHWAYS**

RAS involves different peptides with opposing biological effects. To sum up, the pro-inflammatory, pro-proliferative, and vasoconstrictive molecules are Ang II, AT1R, and angiotensin-converting enzyme (ACE). Contrarily, AT2R, ACE2, Ang (1–7), MrgD and MasR, exerts cardio-protective effects. In brief, angiotensinogen produced from the liver is converted into Ang I and Ang II via renin, esterase-2, cathepsin G, kallikrein, chymase, and angiotensin-converting enzyme. Ubiquitous actions of Ang II can be attributed to activation of several signal transduction pathways modulated by receptors including AT1R and AT2R to initiate RAS or further get cleaved into peptides namely, Ang IV, Ang (1–7), and alamandine, which express their effects via AT4R, MasR and MrgD, respectively (Adamcova et al., 2021; Matsubara, 1998). Interestingly, administration of Ang (1–7) was evidenced to provide a protective effect during chronic infusion of Ang II in rats (Grobe et al., 2007). However, the pharmacology of AT1R and AT4R has not been categorized fully and hence they are not definitively classified under mammalian Ang receptors (Figure 1) (Touyz and Berry, 2002). Based on several investigations, AT1R

| Discoverer (Year)                        | Development in RAS                                                                 |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| Richard Bright (1836)                   | Related hypertrophy to an increased resistance to blood flow in the small vessels due to the altered condition of the blood |
| George Johnson (1868)                   | The pathology behind left ventricular hypertrophy                                 |
| F.A. Mahomed (1872)                    | Described high blood pressure using a primitive sphygmograph                      |
| Riva Rocc (1896)                        | Linked left ventricular hypertrophy to hypertension due to nephritis              |
| Tigerstedt and his assistant Bergman (1898) | Presence of high blood pressure in patients without renal disease               |
| Korotkoff (1905)                        | Introduced first indirect sphygmanometer to measure arterial pressure in humans   |
| Goldblatt et al. (1934)                 | Analyzed and discovered the presence of a pressor compound in the renal tissue ‘Renin’ |
| Irvine. H. Page heading Indianapolis group (1940) | Explained association between renal disease and cardiac hypertrophy           |
| Edward Braun Menendez heading Argentine group (1940) | Defined the cardiac sounds                                                        |
| Argentine group (1943)                  | Related hypertrophy to an increased resistance to blood flow in the small vessels due to the altered condition of the blood |
| Skegg’s et al. (1956)                   | Proposed the existence of a humoral mechanism                                     |
| Braun Menéndez (1958)                   | Discovered renin as an inactive enzyme, activated by plasma protein compound renin activator and they named it angiotensin |

**TABLE 1 | Glimpse of the historical development of RAS.**

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and AT2 R have been evidenced to be associated with the majority of Ang II mediated signaling pathways (Kawai et al., 2017). AT1 R is clearly different from AT2 R in signalling mechanisms, tissue-specific expressions, and molecular weight. AT2 R may also counter-regulate functions mediated via AT1 R. However, the signaling mechanisms of AT2 R are still speculative compared with those of AT1 R. Moreover, most of the classic cardiovascular effects of Ang II are conveyed by AT1 R, including, vasoconstriction, hyperplasia, sodium retention, vascular cell hypertrophy, myocardial fibrosis, arterial wall thickening, aggravation of inflammatory responses, and stimulation of ROS.

AT1 R is a G protein-coupled receptor and is widely expressed in the heart, endothelium, smooth muscle, kidney (mainly in glomerulosa cells), brain, adipose tissue and adrenal glands (Li et al., 2012). AT1 R encourages intracellular pathways via activation of subunits of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, several protein kinases, transactivation of growth factor receptor, or direct interaction with AT1 R interacting proteins like Guanine nucleotide exchange factor (GEF)-like protein (GLP), AT1 R associated protein (AT1 R AP), phospholipase C (PLC γ1) and Janus activated kinase (JAK 2) (Figure 2). In addition, it also turns on several downstream signals, like mitogen-activated protein kinase/extracellular signal-regulated kinases (MAPK/ERK), Ras/Rho, and translocation of MAPK in the nucleus (Ahmadian et al., 2015). AT1 R of mouse and rat exists as Ang II type I subtype A receptor (AT1A R) and Ang II type I subtype B receptor (AT1B R), which have similar activation, ligand binding properties, and identical amino acid sequences, but differ in tissue transcriptional and distributive regulation. AT1A R is widely expressed and regulate blood pressure. Thus, it is anticipated to be the closest homolog to the human AT1 R (Touyz and Berry, 2002).

**FIGURE 1 |** Schematic representation of Ang II peptides and receptors in RAS signalling pathway AT1 R, Angiotensin II Type 1 Receptor; AT2 R, Angiotensin II Type 2 Receptor; ANG II, angiotensin II; Ang-(1–7), Angiotensin-(1–7); Ang-(1–8), Angiotensin-(1–8); ACE2, Angiotensin-converting Enzyme 2; Mas R, Mitochondrial assembly protein Receptor.

**G-Protein, Protein Kinases, Nicotinamide Adenine Dinucleotide Phosphate , and Growth Factor-Mediated Signaling**

Ang II activation of AT1 R promotes variously convoluted, convergent, and diverse signaling pathways. However, research has established specific components essential for Ang II dependent signaling pathways. In brief, AT1 R binds with heteromeric G-protein (Gq11, G12, and G13) and allows activation of secondary messengers such as Rho GEFs, PLCβ, inositol 1,4,5-trisphosphate (IP3), diacyl glycerol (DAG), and
reactive oxygen species (ROS). This further regulates downstream effectors like phospholipases. The response may differ depending on effector tissue, such as in vascular smooth muscle cells (VSMCs) contraction is regulated through G12/13 Rho/Rho kinase-mediated myosin light chain phosphatase (MLCP) inhibition or Gq/11 Ca2+ sensitive myosin light chain kinase (MLCK) activation. Similarly, Src family kinase also regulates vascular contraction through MLCP inhibition and Rho kinase/RhoA signaling. Ang II mediated AT1R potentiates various serine/threonine kinases such as PKC, Akt, and mitogen-activated protein kinase (MAPK) family kinases and other intracellular protein kinases like, non-receptor and receptor tyrosine kinases (Figure 2 and Table 2).

Ang II stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidases to produce ROS causing renal deterioration, cardiac hypertrophy, and VSMC migration. In

**FIGURE 2 |** Ang II signaling via AT1R mediated pathways. Ang II, Angiotensin II; Ca++, Calcium; CaMKII, Ca2+/calmodulin-dependent protein kinase II; NFAT, Nuclear factor of activated T-cells; HDAC, Histone deacetylases; PLC, phospholipase C; IP3, Inositol triphosphate; DAG, Diacyl glycerol; pPKC, Protein kinase; CaMKII, Calcium/calmodulin-dependent protein kinase II; NFAT, Nuclear factor of activated T-cells; MLCK, Myosin light chain kinase; MAPK, Mitogen activated protein kinase; PAI, Plasminogen activator inhibitor; NFKB, Nuclear factor-kB; MMP, Matrix metalloproteinase; TIMP, Tissue inhibitor metalloproteinase; VCAM, Vascular cell adhesion molecule; PVN, Paraventricular nucleus; ECM, Extracellular matrix; HDAC, Histone deacetylase; GTP, GDP, Nucleotides; Akt, Protein kinase B; cGMP, Guanosine 3’,5’ cyclic monophosphate; ROS, Reactive oxygen species; Grb2, Growth factor receptor bound protein 2; TGF, Tissue growth factor; PLC, phospholipase C; mTOR, mammalian target of rapamycin; GSK, Glycogen synthase kinase; TNF, tumor necrosis factor; Sirt: Sirtuin; MMP, Matrix metalloprotease; ERK, extracellular-signal-regulated kinase; WNK, lysine deficient protein kinase 1; SPAK, SPS1-related proline/alanine-rich serine/threonine kinase.
### TABLE 2 | Identified protein kinases in ANG II signaling in cardiovascular system.

| S. No. | Kinase | Associated physiology | References |
|--------|--------|------------------------|------------|
|        | **Ser/Thr kinase** | | |
| 1. | ERK | Stimulate NADPH oxidase and ROS generation causing hypertrophy, hyperplasia, and migration of VSMCs | Moraes et al. (2017) Chen et al. (2020) Ge et al. (2021) Xu et al. (2021) Chen et al. (2020) |
| 2. | JNK | Cardiac hypertrophy | Xu et al. (2021) |
| 3. | P38 | Cardiac hypertrophy | Xu et al. (2021) |
| 4. | MAPK | Cardiac hypertrophy, hyperplasia and migration of VSMCs | Chen et al. (2020) Ge et al. (2021) |
| 5. | GRK | Regulate function of GPCR | Rukavina Mikusic et al. (2020) Murga et al. (2019) Brinks and Eckhart (2010) Brinks and Eckhart (2010) Bai et al. (2021) Liu et al. (2016) |
| 6. | ROCK | Fibrosis and involved in TGF-β1-induced atrial remodeling | Zhou et al. (2021) Bai et al. (2021); Liu et al. (2016) |
| 7. | PAK1 | Attenuation of cardiac fibrosis and hypertrophy | Ge et al. (2021) Wang et al. (2017) Li et al. (2010) Xu et al. (2021) Gao et al. (2021) |
| 8. | Raf | Phosphorylates and activates the MAPK kinase, MEK-1, which, in turn, phosphorylates and activates MAPK. | Ge et al. (2021) Wang et al. (2017) Li et al. (2010) Xu et al. (2021) Gao et al. (2021) |
| 9. | MLCK | Regulating cardiac muscle contraction and hypertrophy | Wang et al. (2017) Li et al. (2010) Xu et al. (2021) Gao et al. (2021) |
| 10. | CaMKII | Regulates Erk1/2 and Akt-dependent signaling in VSMC | Xu et al. (2021) Gao et al. (2021) |
| 11. | IkK | Triggers myofibroblast survival | Xu et al. (2021) Gao et al. (2021) |
| 12. | PI3K | Stimulate NADPH oxidase and ROS generation causing hypertrophy, hyperplasia and migration of VSMCs | Zhong et al. (2021) Cheng et al. (2021) Gao et al. (2021) |
| 13. | P70S6K | Stimulate NADPH oxidase and ROS generation causing hypertrophy, hyperplasia and migration of VSMCs | Gao et al. (2021) Gao et al. (2021) Kim et al. (2012) Kim et al. (2012) |
| 14. | Akt | Stimulate NADPH oxidase and ROS generation causing hypertrophy, hyperplasia and migration of VSMCs | Gao et al. (2021) Gao et al. (2021) Kim et al. (2012) Kim et al. (2012) |
| 15. | mTOR | Cell proliferation, motility and protein synthesis | Fang et al. (2020) Lins et al. (2021) Chen et al. (2020) |
| 16. | PERK | Inhibition of protein synthesis | Fang et al. (2020) Lins et al. (2021) Chen et al. (2020) |
| 17. | AMPK | Preventive in AAA, endothelial dysfunction | González-Núñez et al. (2015) |
| 18. | ALK1/2/4 | Central regulation of hypertension, cardiac fibrosis, cardiac hypertrophy | Kasuya et al. (2021) Yuan et al. (2016) Simoes et al. (2020) Shao et al. (2021) Shao et al. (2021) Brown et al. (2021) Brown et al. (2021) |
| 19. | MNK | Attenuation of cardiac fibrosis and hypertrophy | Kasuya et al. (2021) Yuan et al. (2016) Simoes et al. (2020) Shao et al. (2021) Shao et al. (2021) Brown et al. (2021) Brown et al. (2021) |
| 20. | WNK | Hypertension and vascular contraction | Kasuya et al. (2021) Yuan et al. (2016) Simoes et al. (2020) Shao et al. (2021) Shao et al. (2021) Brown et al. (2021) Brown et al. (2021) |
| 21. | SPAK | Hypertension and vascular contraction | Kasuya et al. (2021) Yuan et al. (2016) Simoes et al. (2020) Shao et al. (2021) Shao et al. (2021) Brown et al. (2021) Brown et al. (2021) |
| 22. | MKK4 | Atrial fibrosis via kinase activation | Fang et al. (2020) Li et al. (2017) |
| 23. | TRPM7 | Implicated in cardiac fibrosis | Zhong et al. (2018) Usui et al. (2012) Ock et al. (2021) Weber et al. (2004); An et al. (2020) Wang J. et al. (2020) Wang J. et al. (2020) Dai et al. (2019) |
| 24. | DAPK | Vascular constriction via kinase activation | Zhong et al. (2018) Usui et al. (2012) Ock et al. (2021) Weber et al. (2004); An et al. (2020) Wang J. et al. (2020) Wang J. et al. (2020) Dai et al. (2019) |
| 25. | SGK1 | Cardiac remodeling | Zhong et al. (2018) Usui et al. (2012) Ock et al. (2021) Weber et al. (2004); An et al. (2020) Wang J. et al. (2020) Wang J. et al. (2020) Dai et al. (2019) |
| 26. | PKD1 | Cardiac hypertrophy and fibrosis | Weber et al. (2004); An et al. (2020) Wang J. et al. (2020) Wang J. et al. (2020) Dai et al. (2019) |
| 27. | PKC | Stimulate NADPH oxidase and ROS generation causing hypertrophy, hyperplasia and migration of VSMCs | Wang J. et al. (2020) Wang J. et al. (2020) Dai et al. (2019) |
| 28. | PKA | Cardiac hypertrophy | Wang J. et al. (2020) Wang J. et al. (2020) Dai et al. (2019) |

### Tyrosine kinase

| S. No. | Kinase | Associated physiology | References |
|--------|--------|------------------------|------------|
| 1. | Axl | Inhibitor of innate immunity | Berk and Corson, (1997) Batchu et al. (2016) Callera et al. (2016) Luo et al. (2020) Touyz et al. (2002) Berk and Corson, (1997) Holopainen et al. (2015) Mitchell-Jordan et al. (2008) Berk and Corson, (1997) Berk and Corson, (1997) |
| 2. | Src | Hypertension and hypertrophy | Berk and Corson, (1997) Holopainen et al. (2015) Mitchell-Jordan et al. (2008) Berk and Corson, (1997) Berk and Corson, (1997) |
| 3. | BMX | Cardiac hypertrophy via endothelial activation | Berk and Corson, (1997) Holopainen et al. (2015) Mitchell-Jordan et al. (2008) Berk and Corson, (1997) Berk and Corson, (1997) |
| 4. | sFLT-1 | Anti-angiogenic | Berk and Corson, (1997) Berk and Corson, (1997) |
| 5. | FAK | Enhance protein synthesis | Berk and Corson, (1997) Berk and Corson, (1997) |
| 6. | PYK2 | Allows growth-promoting signal by Ang II in VSMC | Berk and Corson, (1997) Berk and Corson, (1997) |
| 7. | JAK | Mediates Ang II triggered gene transcription | Berk and Corson, (1997) Berk and Corson, (1997) |

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general, Ang II increases the production of ROS via activation of the catalytic subunit of NADPH, the Nox family proteins. The catalytic subunits of NADPH include dual oxidase (Duox1 and Duox2) and the Nox family (Nox1-5). Subsequent stimulation of Nox family proteins increases its interactions with associated specific regulatory subunits p67 phox, p47 phox, p22 phox, and Nox1 (Kawai et al., 2017). Ang II stimulated Nox4 generation in vascular cells and renal tissues via AT1 R is a source of oxidative stress, expression mice (Aoyagi et al., 2019). Moreover, it stimulates the hypertension and organ failure. Ang II upregulates JNK and Nox4 in established dynamic phenomenon for AT1 R dependent regulate cell hypertrophy in VSMCs. Investigations have Griendling, 2014). It can act as a growth factor that can of various downstream targets like MAPK (Vukelic and Griendling, (2014) EGFR, followed by subsequent activation of Akt/p70S6, mechanistic target of rapamycin (mTOR), and Ras/ERK signaling resulting in cardiac hypertrophy and fibrosis (Eguchi et al., 1999; Eguchi et al., 2001; Ohtsu et al., 2006). Ang II stimulates selective mTOR2-dependent phosphorylation of SGK1 but not Akt (Gleason et al., 2019). The transactivation is mediated by secondary messengers like ROS, PKC, Src kinase, and metalloproteinase-dependent release of EGFR ligands such heparin-binding EGF, TGF- α, and EGF. Peng et al., 2016 evidenced that c-Src dependent EGFR transactivation in ERK/ Akt pathway may play a crucial role in Ang II induced cardiac remodeling in H9c2 cells (Peng et al., 2016). AT1 R mediated A Disintegrin And Metalloproteinase 17 (ADAM17) dependent EGFR activation results in VSMC migration and hypertrophy via PI3K/Akt/mTOR/p70S6K pathway and Ras/ERK pathway. Ang II mediated ADAM17 requires ROS and p38 MAPK phosphorylation. Zhang Y. et al. (2019) demonstrated that Ang II promotes Mer tyrosine kinase shedding via AT1 R/ROS/ p38 MAPK/ADAM17 pathway in macrophages of ApoE−/− mice (Zhang Y. et al., 2019). Furthermore, BMX (bone marrow kinase), a non-receptor tyrosine kinase has been identified as an upstream signalling molecule for Ang II-mediated EGFR activation. Thus, systemic inhibition of EGFR or ADAM17 decreases Ang II-induced cell migration and aortic aneurysm.

Ang II-dependent connective tissue growth factors (CTGF) and transforming growth factor-β (TGF-β) are initial pro-fibrotic mediators involved in cardiac fibrosis (Wong et al., 2018; van Beusekom and Zimmering, 2019). The expression of CTGF and TGF-β are interlinked. Ang II increases mRNA expression of TGF-β and NF-κB, an important mediator of the hypertrophic growth of the heart, in H9c2 cells (Prathapan et al., 2013). Further, myocardial CTGF expression after Ang II exposure is likely dependent on latent activation of TGF-β via canonical Smad-pathway in NIH/3T3 fibroblasts (Wong et al., 2018). Overexpression of fibroblast growth factor 23 (FGF23) augmented cardiac fibrosis and hypertension in Ang II administered mice via PPARα/PLCy-1/FGF23 signaling (Liu et al., 2020). Contrarily, FGF21 enhances cardiac function and reduces Ang II induced cardiac hypertrophy through in silent information regulator 1 (SIRT1)/ inflammatory and mitogenic properties. Similar to Ang II-mediated IGF-IR, TGF-β, and PDGFR in cardiovascular pathophysiology is still limited.

Ang II-induced signaling via AT1 R is correlated with MAPK activation and enhanced phosphorylation of protein tyrosine. This fact highlights that besides vasoconstriction, Ang II also possesses the inflammatory and mitogenic properties. Similar to AT1 R, the existence of AT2 R is also opting for increased attraction due to its opposite effect than the former. AT2 R also belong to the GPCR family and stimulates the SH2 domain-containing phosphatase (SHP-1) and MAPK phosphatase 1 (MKP-1) resulting in attenuation of tyrosine phosphorylation. In addition, AT1 R accelerates vasorelaxation through PKA-dependent eNOS phosphorylation.
### TABLE 3 | Studies of effect of angiotensin II in in-vivo and in-vitro studies.

| Model | Dose, Route, Duration of Ang II | Result | Limitations | Ref. |
|-------|---------------------------------|--------|-------------|------|
| Sprague-Dawley rats and cardiomyocytes | 20 µM, 2 h | Short-term treatment with Ang II attenuates the transversal YM in isolated adult rat cardiomyocytes acting via an AT1 R | High sample indentation in direct contact mode or lack of selectivity or that makes it difficult to assess the sample–probe interaction | Swiatłowska et al. (2020) |
| C57BL/6J mice & Primary cardiomyocytes from C57BL/6J mice | 2.5 mg/kg/day, s.c., 2 weeks. 100 nM, 24 h | Administration of Ang II increases the expression of miR-154-5p and cardiac remodeling concurrently. miR-154-5p interacts with 3′ UTR and inhibits arylsulfatase B to trigger cardiomyocyte apoptosis and hypertrophy associated with oxidative stress | The hypothesis of miR-154-5p promoting hypertrophy needs further testing in the near future | Wang Q. et al. (2019) |
| HEK293T, HEK293-AT1R, and HEK293T-SIN1/−/− cells | 200 nM | SGK1 activation occurs at a distinct subcellular compartment from that of Akt | The use of SIN1 and SGK1 overexpression since overexpression of these proteins might influence their subcellular localization. | Geason et al. (2019) |
| ApoE/−/− mice | 750 µg/kg/day, s. c. | Ang II increases the expression of EMMPRIN in atherosclerotic plaque Ang II and TGF-β1 are efficient cardiomyogenic inducers of human AF-MSCs; They initiate protein expression, alterations at the gene and epigenetic levels in stem cells leading towards cardiomyocyte-like phenotype formation. | Further research is required to elucidate the details of the mechanism involved | Zhang Y. et al. (2019) |
| Amniotic fluid mesenchymal stem cells | 0.1 and 1 µM | Ang II and TGF-β1 show a similar result to TGF-β1 if the AT1 R was expressed more in CRFK cells | | Gasiuniene et al. (2019) |
| Male silent information regulator 1 (SIRT1) flox/flox and cardiomyocyte-specific inducible SIRT1 knockout mice (SIRT1−/−) | 1.1 mg/kg/day for 4 weeks | FGF21 improves cardiac function and alleviates Ang II-induced cardiac hypertrophy in a SIRT1-dependent manner | Presence of a small number of animals in a group | Li et al. (2019) |
| CRFK cells (feline kidney epithelial cell line) | - | Ang II shows a similar result to TGF-β1 if the AT1 R was expressed more in CRFK cells | The experiment could have involved other cell types. | van Beusekom and Zimmering, (2019) |
| C57BL/6J mice | 1.5 µg/min/kg, s.c., 4 weeks | Soluble receptors for advanced glycation end-products were evidenced to attenuate Ang II-induced LV hypertrophy using a 9.4T pre-clinical magnetic resonance imaging instrument | Since they didn't perform electrocardiography, they were unable to confirm the superiority of MFR in assessing cardiac remodeling | Gao Q. et al. (2020) |
| Thromboxane A2 (TP) knockout (Tp−/−) mice | 1,000 ng/kg/min, s.c., 28 days | TP receptors may contribute to cardiac hypertrophy but not, proteinuria and are responsible for the pathogenesis of Ang II induced hypertension and hypertrophy | As thromboxane production was not analyzed in Cox1−/− mice, they were unable to assure the reduction caused by TXA2 | Heo et al. (2019) |
| Sprague-Dawley rats | 200 ng/kg/min, micro-infusion | Ghrelin inhibited Ang II-induced cardiac fibrosis in a PPAR-dependent manner | The study was performed on young male rats which restricts the extrapolation of results for females and older cohorts. Also, the age and sex-mediated effects of ghrelin need to be explored. | Zhong et al. (2018) |
| Rat tubular epithelial cell line NRK52E | 1 mM for 0−24 h | Inhibition of HMGB1 and gene silencing of TLR4 decreases Ang II-mediated inflammation in the kidney The existence of HMGB1-TLR4 signaling is a development of hypertensive renal injury | Future in-vivo studies will be required for elucidating the role of TLR4 signaling in Ang II-induced renal injury on the AT1 R. Knock out model | Nair et al. (2015) |
| Mouse Neuro-2a cells | - | Involvement of HMGB1 in the PVN for development of Ang II-induced hypertension | Further research depicting the involvement of Mas will be necessary | Nair and Philips, (2015) |

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activation and paracrine signaling through bradykinin/cGMP/NO production. Considering AT2 R, some AT2 R interacting proteins have shown physiological roles in the suppression of tumors, inflammation, ROS production and hypertrophy.

G-Protein Independent Signaling via β-arrêstine

Ang II stimulated AT1 R can activate various signaling cascades such as G-protein independent and G-protein dependent signaling. Unlike G-protein dependent signaling, the G-protein independent signal transduction cascade includes G-protein and β-arrêstine (Forrester et al., 2018). Isoforms of β-arrêstine i.e., β-arrêstine 1 and 2 are recruited to AT1 R and stabilize them with high-affinity conformations (Sanni et al., 2010). Mechanistically, β-arrêstine were described as a protein that uncouples GPCR from G-protein for mediating receptor internalization and G-protein independent signaling. β-arrêstine mediated signaling includes activation of p38 and Akt/MAPK, JNK, ERK1/2, and Src tyrosine kinases. A study involving human embryonic kidney (HEK)-293 cells biased agonist Sar1, Ile6-ANG II (SII) or a mutant AT1 R-DRY/AAY suggested various active conformation of AT1 R. The SII or mutant AT1 R induced G protein independent, but β-arrêstine 2-dependent ERK activation (Wei et al., 2003).

AT1 Receptor and Gq11G proteins mediate biased signaling (Ferrario et al., 2021). β-arrêstine-biased AT1 R signaling promotes vascular remodeling with the activation of MAPK and Src-based signaling. Interestingly, mechanical activation of AT1 R caused increased affinity toward β-arrêstine biased ligand TRV120055, suggesting stabilization of a biased active receptor conformation (Ma et al., 2021). Apart from its involvement in β-arrêstine-dependent signaling, AT1 R was also reported to be involved in stretch-induced pathways in different cells. Interestingly, GRK2 and PKC, the kinase responsible for β-arrêstine binding of many GPCRs have also been found to be activated up on a stretch in rat ventricular myocytes (Turu et al., 2019). In a study, the vasoconstrictor responses were increased by Gq11 AT1 R biased agonists TRV120055 and TRV20056. Here, Gq11 AT1 R was an essential component of dynamic mechanochemical signaling in VSMC causing myogenic tone (Cui et al., 2020). Alongwith AT1 R, AT2 R is also suggested to be primarily stimulated via G-protein independent signal transduction cascade including β-arrêstine and GPCR kinase.

### ANGIOTENSIN II IN CARDIOVASCULAR SYSTEM

As a vital bioactive peptide of RAS, Ang II is associated with diverse mechanistic insights into understanding how Ang II contributes to multiple cardiovascular physiology and pathophysiology functions. Century-old research on RAS has uncovered Ang II and its involvement in the pathophysiology of cardiovascular diseases. Ang II is involved in the regulation of cell communication, impulse propagation, cardiac contractility, apoptosis, growth, and remodeling (Kawai et al., 2017). Summary of in vivo and in vitro pharmacological investigations are presented in Figure 2 and Table 3. In most of the in-vivo studies, the approach used for induction was a subcutaneous infusion of Ang II.

### Angiotensin II in Hypertension

Hypertension is one of the most critical predisposing factors for the development of cardiovascular disease. Several factors contributing to the pathogenesis of hypertension include salt intake, stress, and Ang II (Kulkarni et al., 1998; Meneton et al., 2005). Ang II as a powerful vasoconstricting agent can induce

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### Table 3 (Continued) Studies of effect of angiotensin II in in-vivo and in-vitro studies.

| Model | Dose, Route, Duration of Ang II | Result | Limitations | Ref. |
|-------|--------------------------------|--------|-------------|------|
| Sprague-Dawley rats | 120 ng/kg/min, s.c., 2 weeks | Activation of brain RAS and PPAR-γ to reduce central inflammation may be used as a strategy in the management of Ang II-induced hypertension | Studies need to be performed to evaluate the relative role of individual types of cell | Yu et al. (2015) |
| Sprague-Dawley rats | 100 ng/kg, i. c. v., before and after a 1 h ICV infusion of inhibitor | Role of brain p44/42 MAPK signaling cascade in the maintenance of renal sympathetic excitation in HF rats. Alteration in brain p44/42 MAPK can increase adverse effects of brain RAS on renal and cardiovascular functions during HF progression. Attenuation in Fra-LI-positive PVN neurons in p44/42 MAPK inhibitors treated rats suffering from HF. | They evaluated the involvement of p44/42 MAPK signaling in the brain containing presympathetic neurons of PVN neurons only and did not evidence the contribution of p44/42 MAPK signaling in other nuclei of brain-like RVLM or other neurons in cardiovascular and autonomic centers, including organum vasculosum of the lamina terminalis, median preoptic nucleus, and the subfornical organ. | Shinozara et al. (2015) |
| Sprague-Dawley rats | 800 ng/kg/min, s.c., 1 week | Association of NO-mediated mechanisms with presence of female sex hormones to be protective against sympathetically mediated Ang II-induced hypertension in female mice | - | Wattanapitayakul et al. (2000) |
aldosterone secretion and thereby retention of salt and water, which regulates blood pressure. In addition to this, Ang II has also been shown to have important oxidative, inflammatory, and immune-mediated actions. Ang II even at doses that do not alter blood pressure, allows the migration of inflammatory cells and induces the expression of inflammatory markers in the aorta of normotensive mice (Lima et al., 2019).

Nair et al. in 2015 found toll-like receptor 4 (TLR4), high-mobility group box 1 (HMGB1), and proinflammatory cytokines mediated immune response contributed to Ang II-induced hypertension in rat tubular epithelial cell line NRK52E (Nair et al., 2015). In support of this concept, they designed another study to determine the involvement of HMGB1 signaling in Ang II-induced hypertension in the para ventricular nucleus (PVN). The interaction between the inflammatory cytokine protein, HMGB1, and TLR4, resulted in the up-regulation of NF-κB which in turn resulted in hypertension in Neuro-2a cells of mice treated with Ang II (Nair and Philips, 2015). These findings were consistent with reports by Li et al. (2016) and Yu et al., 2015 that showed Ang II increases hypertension and hypothalamic infiltration via TLR4/MyD88/NF-κB signaling pathway and peroxisome proliferator-activated receptor-γ (PPAR-γ) in the PVN in hypertensive rats (Yu et al., 2015; Li et al., 2016).

In addition to, TLR4 and PPAR-γ, Ang II is known to induce ROS via activation of NADPH oxidase mediated Nox-1 and p22phox in Ang II-induced DNA damage in-vitro and in-vivo models (Wattanapitayakul et al., 2000; Sarr et al., 2006; Zimmol et al., 2020). Hyperactivation of Nox acts as a major source of ROS production in cardiac tissue, promotes apoptosis and increases oxidative stress via the MAPK pathway (Wen et al., 2019). Ogola et al., 2019 evidenced that pretreatment with G protein-coupled estrogen receptor (GPER) agonist G1 inhibits Ang II-induced ROS, NADPH, Nox4 mRNA expression via cAMP and phosphodiesterase inhibition (Ogola et al., 2019). Moreover, Ang II also induces pressor response and vasoconstriction by reduction of an active form of Ras-related C3 botulinum toxin substrate 1 (Rac1) and Nrf2 nuclear translocation (Pepe et al., 2019). Rac, a small G protein is an essential molecule for the function of NADPH oxidase components along with, phosphorylated Smad 2/3, atrial TGF-β1, and atrial superoxide in Ang II hypertensive rats (Yagi et al., 2010).

Another enzyme source of ROS includes uncoupled nitric oxide synthase (NOS), endoplasmic reticulum oxidase, xanthine oxidase, and mitochondrial oxidase. ROS affects the function of a cell by modifying proteins through post-translation modifications such as phosphorylation and oxidation (carbamylation, glutathionylation, nitrosylation, and sulfenylation). Proteins that are affected include matric metalloproteinases, cytoskeletal structural protein, transcriptional factors, signaling molecules, and ion transporter receptors (Griendling et al., 2016). ROS activate all 3 members of the MAPK family, including JNK, p38MAPK, and ERK1/2, essential for regulating vascular and cardiac cells (Jennings et al., 2010). In a study, catechins were reported to inhibit Ang II-induced VSMC proliferation by inhibiting Ang II activated MAPK and activator protein-1 signaling pathways (Won et al., 2006) (Figure 2). MEK-ERK are phosphorylated in arteries of hypertensive individuals and in a mouse model. Activation of this pathway results in the promotion of human arterial SMC (HASMCs). A known cysteine protease, Cathepsin L/V is interdependent on extracellular matrix accumulation and tissue inflammatory responses, allowing regulation of arterial remodeling. Lu et al., 2020 showed that Z-FF-FMK, a cathepsin inhibitor significantly reduces MEK-ERK phosphorylation (Lu et al., 2020).

Also, Ang II is responsible for causing atherosclerosis through VCAM 1 activation via protease-dependent NF-κB-like transcriptional mechanisms (Tummala et al., 1999). Acute doses of Ang II act primarily on VSMC to reduce blood pressure whereas chronic infusion of Ang II is neutrally mediated (~10 h) (Li et al., 1996). It has been reported that statins reduce the incidence of cardiovascular remodeling. It is well known that apart from cholesterol-lowering, it also provides pleiotropic effects on the cardiovascular system, including antioxidant, anti-inflammatory, and improvement of endothelial function (Yagi et al., 2010). Candesartan, an AT1 R blocker and apocynin, NADPH oxidase inhibitor evidenced reduced pressor effect by ATIR-dependent ROS-SAPK/JNK, ERK1/2, and p38MAPK signaling (Jiang et al., 2019). Likewise, Pitavastatin exerts eNOS based protective action in Ang II-induced cardiovascular remodeling through suppression of (TGF)-β1–Smad 2/3 signaling pathway and oxidative stress (Yagi et al., 2010). Ang II inhibition extensively improved hypertension, hyperfiltration and control renal damage. Inhibition of Ang II enhanced the NF-KB activity which may additionally result in inhibition of its downstream gene expression, particularly NADPH-oxidase.

**Angiotensin II in Cardiac Remodeling**

Cardiac remodeling can be described as a pathologic or physiologic condition that may occur after volume overload or idiopathic dilated cardiomyopathy, inflammatory heart muscle disease, pressure overload, or myocardial infarction (Cohn et al., 2000). Investigations have shown that Ang II promotes excessive accumulation of collagen leading to cardiac dysfunction as well as cardiac remodeling (Du et al., 2019). Several mechanisms have been implicated in the pathogenesis of Ang II-induced cardiac remodeling including dysfunction, hypertrophy, apoptosis and fibrosis. Ang II has been closely related to remodeling, which acts mainly via AT1 R in the animal and human cardiovascular systems. PKCs-EKR1/2-NFκB-NLRP3-IL1β pathway signaling cascades have been shown to promote Ang II-induced cardiomyocyte hypertrophy in H9c2 cells through AT1 R, RAGE, and NADPH oxidase inhibition (Lee et al., 2020). Soluble RAGE (sRAGE) was demonstrated as a decay receptor for RAGE in Ang II-induced cardiomyocyte hypertrophy using in vivo and real-time 9.4T MR imaging (Heo et al., 2019). In addition to RAGE, it has been noted that Toll-like receptor 2 (TLR2)- and TLR4-dependent pathways are stimulated by Ang II in cardiac dysfunction, fibrosis and hypertrophy (Lee et al., 2020). TLR4 is involved in the upregulation of monocyte chemoattractant protein (MCP-1), IL-6, and ROS (Matsuda et al., 2015). Ang II stimulated direct binding of STAT3 with
TLR4 activates STAT3 via IL-6/glycoprotein 130/JAK2 pathway, resulting in altered gene regulation for cardiac remodeling (Han et al., 2018).

Similarly, TGF-β has been proposed to act in a paracrine/autocrine manner between fibroblast and cardiomyocytes to stimulate cardiac remodeling (Leask, 2010).Valsartan, angiotensin receptor blocker, or Stachydrine mediated inhibition of Ang II/AT1 R/TGF-β signaling is a pivotal mechanism of anti-hypertrophic and anti-fibrotic effect (Teekakirikul et al., 2010; Liu et al., 2019; Tashiro et al., 2020). Ang II-induced fibrosis is associated with altered expression of inflammation-related genes such as TGF-β, TNF-α, MCP-1, IL-6, and type 3 collagen (Azushima et al., 2019).

miRNA including miR-154, miR-155, miR-132, miR-21, miR-503, miR-214, miR-19a, and miR-410 are involved in promoting hypertrophy, fibrosis, apoptosis, and inflammation. On the other hand, miR-16, miR-98, miR-30a, miR-133, miR-433 possess cardio-protective effects (Wang Q. et al., 2019; Song et al., 2019; Adamcova et al., 2021). Luciferase assay evidenced that miR-214 acts as a target for Long non-coding RNA (lncRNA) Pscr4 and ameliorated levels of miR-214 oppose the anti-hypertrophic effect of Pscr4 in Ang II treated cardiomyocytes via lncRNA Pscr4-miR-214-mi-5 miRf (Mfn2) axis (Lv et al., 2018). Ang II down-regulated expression of Neuregulin-1 (NRG-1) as a member of the epidermal growth factor family via the circNRF-1-mi1R-19b-3p-mediated post-transcriptional mechanism in mouse aortic smooth muscle cells (MASMCs) (Sun et al., 2019). Interestingly, the antiaging gene klotho modifies Ang II-induced cardiac remodeling via altering the expression of TGF-β and miR-132, a downstream mediator of TGF-β. LY364947, a TGF-β and klotho gene inhibitor, inhibited fibrosis, hypertrophy, expression of fibrotic marker genes (α-SMA, collagen I), pro-hypertrophic genes (atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), β-myosin heavy chain (β-MHC)) and Smad2/3 phosphorylation in cultured cardiomyocytes, fibroblasts and heart tissue (Ding et al., 2019). Zheng et al. evidenced similar results that liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, reduced protein levels of shes are

Despite the growing interest in big data approaches, with the aim of studying the genetics of cardiovascular disease, fishes are becoming an increasingly popular choice to study associated genetic alterations. To clarify the putative actions of Ang II in cardiac remodeling, Anguilla Anguilla was selected. Immunoblotting and immunolocalization results suggested that Ang II downregulates both localization and expression of molecules affecting apoptosis and cell growth such as eNOS, heat shock protein-90, and c-kit (Imbrogno et al., 2010; Imbrogno et al., 2013; Filice et al., 2017). Another recent study demonstrated the effect of Ang II on morpho-functional remodeling in heart of Danio rerio. The findings were paralleled by the upregulation of AT₃, AT₂, and AT₁ receptors. Moreover, a significant change in expression of cytochrome b-245β polypeptide protein, superoxide dismutase I soluble mRNAs, NF-κ-light polypeptide gene enhancer in B cell, and GATA binding protein, indicated cardiac remodeling (Filice et al., 2021).

**Angiotensin II in Stem Cell Therapy in Cardiovascular System**

Recent investigations have endeavored to improve stem cell functionality, provide stem cells as a promising therapeutic candidate for tissue transplantations in the cardiovascular system. Evolving research has evidenced the influence of RAS on stem cell growth, function, and proliferation (Becher et al., 2011). Several studies have demonstrated the role of Ang II in the differentiation of progenitor cell/stem cell (Matsushita et al.,...
The presence of AT₁ R in differentiated, but not in undifferentiated cells, suggests the concept that Ang II can regulate differentiation of stem cells (Huang et al., 2007). In addition to influencing a different kind of stem cells, the RAS effect on cardiovascular-related stem cell transplantation has largely been evaluated regarding the intracellular pathways of Ang II.

Mesenchymal stem cells (MSCs) are of great significance, along with their various autocrine-paracrine effects on the cardiovascular system and immune system (Zhang et al., 2020). Local RAS component Ang II has been reported to be expressed in rat MSCs. Vascular endothelial growth factor (VEGF) has been recognized in an invasion of extracellular matrix, migration, proliferation and survival of MSCs. Pretreatment with Ang II increases mRNA expression of VEGF in MSCs through Akt/ERK1/2 signaling pathway via AT₁ R. Considering this, pre-treatment of MSCs with LY292002, an Akt inhibitor attenuates Ang II-induced expression of VEGF. Notably, the involvement of Ang II increases the expression/production of VEGF in MSC grafts and improves transplantation efficiency (Liu et al., 2014). Thus, an angiogenic function of Ang II stimulates cells in ischemic regions through VEGF-induced endothelial nitric oxide synthase (eNOS). Ang II induces cardiomyogenic differentiation of rat bone marrow MSCs more efficiently than TGF-β1. The autocrine TGF-β/Smad pathway makes the differentiation of adipose tissue-derived MSCs to SMCs. Also, it acts synergistically with VEGF to ameliorate the differentiation of bone marrow-derived MSCs into endothelial cells (Ikhapoh et al., 2015).

Cardiac hypertrophy is a phenotypic response of the heart associated with various disorders. The genetic factor is an important determinant of phenotypic expression in hypertrophy (Marian, 2008). Neuron-derived orphan receptor-1 (NOR-1) transgenesis upregulates key genes involved in cardiac hypertrophy (Myh7, encoding for β-myosin heavy chain (β-MHC)) and fibrosis (Loxl2, encoding for the ECM modifying enzyme, Loxl2) in Ang II-induced cardiomyocytes (Cañes et al., 2020). In another study, Ang II and TGF-β1 upregulated the expression of the structured cardiomyocytes genes such as DES, TNNI2 and MYH6 as well as main cardiac genes-markers like GATA4, TBX5, and NKK2-5. Also, an increased expression of cardiac ion channel genes is evidenced with Ang II and TGF-β1 in human amniotic fluid-derived MSCs (AF-MSCs). Ang II and TGF-β1 treated AF-MSCs showed an increase in connexin43 protein and Nkx2.5 protein in AF-MSCs (Gaščinič et al., 2019). MSC can be an effective route for refining cell-based therapy of angiogenesis, vascular stabilization, and endothelial cell survival (Yang et al., 2019). Besides, TGF-β secretion is associated with the MAPK/ERK pathway; and Ang II in this pathway interferes with TGF-β production.

Bone marrow is one of the major Ang II producing organs and participant in the regulation of immunity and hematopoiesis (Yamashita et al., 2020). Being an inducer of differentiation of MSC, Ang II at doses ranged 0.1 to 10 μM can regulate apoptosis. Ang II could increase mitochondrial ROS through the activation of Nox2. In a study, Ang II at the dose of 1 and 10 μM leads to apoptosis in bone marrow-derived MSCs due to mitochondrial ROS production and mitochondrial DNA leakage mediated via AT₁ R. Treatment with AT₁ R inhibitor, losartan, markedly inhibited the Ang II-induced apoptosis and mitochondrial ROS (Zhang F. et al., 2019). Ang II production by cleaving enzyme chymase is several times higher in bone marrow than in other tissues. In a study, flow cytometry results showed Ang II generated via a chymase-dependent pathway in bone marrow was 280 -fold higher than in the heart. CD68⁺ myeloid progenitor possesses higher chymase expression than CD68⁺ progenitor cell in bone marrow (Yamashita et al., 2020). Another study showed that AT₁a R was widely expressed by human bone marrow CD34⁺, CD38⁺ cells, and lymphocytes (Rodgers et al., 2000). Ang II, but not Ang (1–7), increased adhesion of MNCs or CD34⁺ cells to fibronectin via ACE2/Ang-(1–7)/Mas pathway (Singh et al., 2015). The reported pathway stimulates vasoprotective functions of CD34⁺ cells.

Ang II inhibits colony growth by myeloid progenitors in a dose-dependent manner via AT₁ R (Iokuibaitis et al., 2008). Depletion of myeloid cells reduced vascular expression of AT₁ R, adhesion molecule and vascular accumulation of oxidative stress, endothelial dysfunction, and Nox2⁺ CD45⁺ cells (Molitor et al., 2021). Bone marrow-derived fibroblast precursors express certain chemokine receptors, such as CCR2, CCR5, CCR7, and CXCR4. Treatment of wild-type mice with Ang II (1,500 ng/kg/mouse) caused accumulation of bone marrow-derived fibroblast precursor expressing CD45, CD34, hematopoietic markers, collagen I, and mesenchymal markers. Whereas, the produced effects were abolished in CCR2 deficient mice depicting its role in the pathogenesis of Ang II-induced cardiac fibrosis (Xu et al., 2011). Everolimus, a rapamycin blocker, inhibited Ang II-induced aneurysm in ApoE⁻/⁻ mice through diminished M1 polarization and suppressed the development of bone marrow CCR2 monocytes (Moore et al., 2015). Ishibashi et al. evidenced that, MCP-1 regulates monocyte-mediated inflammation through leukocyte derived CCR2 receptor (C-C chemokine receptor) and its deficiency can reduce the pathogenic effect in Ang II (1.9 mg/kg per day, s. c, 4 weeks) induced atherosclerosis and aneurysm in ApoE⁻/⁻/CCR2⁻/⁻ and ApoE⁻/⁻ CCR2⁻/⁺/⁻ mice (Ishibashi et al., 2004).

Autologous bone marrow MSCs are effective for regression of aneurysms in Ang II-induced ApoE⁻/⁻ mice (Akita et al., 2019). Bone marrow MSCs derived conditioned medium could prevent aneurysm growth through macrophage polarization regulation (Zhou et al., 2019). In addition, precursor fibroblast type III domain-containing protein 5 or irisin, a novel myokine has the potential to improve bone marrow MSC mediated paracrine effect and engraftments in infarcted hearts (Deng et al., 2020). Previous studies have shown that MSC-derived exosomes have distinct properties, including immunomodulation, angiogenesis, and paracrine effect that protect organ functions in animal studies. Additionally, recent investigations have evidenced that adipose-derived MSCs (ADMSCs) derived exosomes also possess a capacity of immunomodulatory, cardioprotective, and anti-inflammatory effects. Interestingly, irbesartan, an AT1 R blocker, was shown to abolish the effects of ADMSC-derived cell sheets in a rat model (Yamamoto et al., 2018). Administration of miR-19a/19b (exo/miR-19a/19b) using bone marrow-derived MSCs to
cardiac HL-1 cells significantly suppressed the apoptosis and fibrosis in infarcted hearts (Wang S. et al., 2020).

Human-induced pluripotent stem cells (iPSCs) possess unique features to differentiate and self-renew into different types of cells in the body (Johansson et al., 2020). They are artificially derived from adult differentiated non-pluripotent somatic cells. In particular, these human cells-based models are anticipated to become an alternative for animal models. iPSCs can express Ang II receptors. As evidenced, Ang II induces the proliferation of PSC and allows their differentiation into MSCs. Treatment of PSC with Tempol, a ROS inhibitor, and Ang II reduces the cell proliferation and DNA synthesis, indicating the involvement of ROS signaling (Ahmadian et al., 2015). The presence and activation of the JAK/STAT pathway play a crucial role in stem cell renewal. It causes p38 phosphorylation and eventually, results in the differentiation of iPSCs in the target cell. A study showed that Ang II could stimulate hypertrophy in human embryonic stem cells (hESC)- and iPSCs derived cardiomyocytes (Földes et al., 2011). However, no significant effect was observed in cell death after treatment of Ang II (200 nM) with hESC- and iPSCs derived cardiomyocytes (Nunes et al., 2017). Immunofluorescent study and RNA seq revealed the involvement of low AT1 R expression in iPSC cardiomyocytes. Long-term Ang II incubation up-regulates AT2 R expression to induce downstream apoptosis signaling in iPSC-derived cardiomyocytes (Gao J. et al., 2020). Whereas, short-term Ang II treatment reduces Young modulus in rat cardiomyocytes via AT1 R. Inhibition using Rho-kinase or TGF-β1 abolished this effect (Swiatlowska et al., 2020).

Erythropoiesis is a tightly regulated process reinforced by systematic hematopoietic progenitor cells and some cohort of multipotent hematopoietic stem cells (HSCs) at its apex. HSCs form the basis of widely practiced therapies, including bone marrow transplantation and stem cell therapies (Jokubaitis et al., 2008). Chronic Ang II infusion imparts important regulatory roles on HSC proliferation, differentiation, and engraftment at the level of bone marrow (Kim et al., 2016). Flow cytometry analysis has revealed the involvement of Ang II in the regulation of hematopoiesis in HSCs and granulocyte/monocyte progenitor cells but, not in megakaryocytes/erythroid progenitors when coculture with stromal S17 cells. (Costa et al., 2021). In addition, protein microsequencing has also reported an increase in Gr-1+/Mac-1+ cells, BB9 protein and decrease expression of Ki67+ in presence of Ang II (Jokubaitis et al., 2008; Costa et al., 2021).

CONCLUSION AND FUTURE PROSPECTS

In the last decades, there has been a noteworthy progression in the number of molecules targeting Ang II signaling pathways. Since the discovery of Ang II, it has been characterized to be involved in various cellular activities such as proliferation, contractility, apoptosis, dysfunctions, remodeling, etc. Dysregulated Ang II signaling is considered to induce various cardiovascular diseases involving hypertension, inflammation, myocardial infarction, atherosclerosis, fibrillation, ventricular dystrophies, etc. While many ARBs are available commercially, the statistics indicate the need to look for novel mechanisms of Ang II causing cardiovascular diseases independently, which would provide a therapeutic target. The involvement of the RAS component in cardiovascular tissue and progenitor cells may regulate development and growth; and thus, allow the preparation of cardiac progenitor cells for clinical transplantation. Being a multi-functional peptide, Ang II stands amidst varied systems integrating multiple cellular signaling events that broadly have counterregulatory or opposing actions. The turmoil in the balance of such processes can lead to diverse pathologies and dysfunctions. Understanding how these processes are integrated with each other in real-time and remain a formidable challenge. Further studies with transgenics or cell-specific knockouts are needed to unravel the role of inflammatory and hypertrophic markers in Ang II-induced remodeling. Another challenge is providing evidence for working with cardiovascular progenitor cells for clinical transplantation. Further, the role of epigenetic/genetic programming impacting the cardiovascular system is an emerging area of study. Many questions still remain as well regarding paracrine, autocrine, and intracrine actions of Ang II and its interaction with receptor-associated proteins. In addition, an approach that integrates elements of metabolomics, proteomics, epigenomics, and genomics is likely to reveal novel, as yet unforeseen facet of Ang II signal transduction. Understanding diverse regulatory signaling mechanisms of Ang II can, therefore, offer better insight into various pathological states which in turn may help in designing ideal drug candidates for their management.

AUTHOR CONTRIBUTIONS

KV: Writing and drafting review MP: Compilation and design SP: Supervise and editing JD: Manuscript Checking SS: Conceptualization and manuscript Checking.

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GLOSSARY

AA Aortic aneurysm
ACE angiotensin-converting enzyme
ApoE apolipoprotein E
AR angiotensin receptor
Ang II Angiotensin II
AT1 R Angiotensin type I receptor
AT1 AP AT1 receptor-associated protein
AT1A R Ang II type I subtype A receptor
AT1B R Ang II type I subtype A receptor
AT2 R Angiotensin type II receptor
AT1 R-(PI3K)/Akt Ang II-mediated AT1 R- phosphoinositide 3-kinase/protein kinase B
CaN calcineurin
CTGF connective tissue growth factor
DAG diacylglycerol
ECM extracellular matrix
EGF Endothelial growth factor
EGFR Endothelial growth factor receptor
ERK extracellular-regulated kinase
GLP-1 Glucagon-like peptide-1
HSC hepatic stellate cells
HMGB1 high-mobility group box 1
ICAM Intercellular Adhesion Molecule
IL interleukin
iNOS inducible nitric oxide synthase
IP3 inositol triphosphate
IRAK-4 Interleukin-1 receptor-associated kinase 4
JAK Janus activated kinase
LVH Left ventricular hypertrophy
miR microRNA
MLCK myosin light chain kinase
MLCP myosin light chain phosphatase
MKP-1 MAPK phosphatase1
MMP mitochondrial membrane potential
MyD88 Myeloid differentiation factor 88
NADPH nicotinamide adenine dinucleotide phosphate
NO nitric oxide
PI3K phosphatidylinositol 3-kinase
PLC γ1 phospholipase C
PLD phospholipase D
PVN para ventricular nucleus
RAS renin angiotensin system
RASMC rat aortic smooth muscle cells
ROS reactive oxygen species
SFK Src family kinases
SIRT1 sirtuin 1
SOD superoxide dismutase
SAPK Ste20/SPS1-related proline/alanine-rich kinase
SRA suprarenal aorta
STAT signal transducer and activators of transcription
TGF-β1 Transforming growth factor-β1
TLR4 Toll-like receptor 4
TRAF-6 TNF receptor-associated factor 6
TRPC6 transient receptor potential cation channel, subfamily C
VCAM vascular cell adhesion molecule
VEGF vascular endothelial growth factor
WNK with-no-lysine