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# Lipotoxicity-Related Hematological Disorders in Obesity

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## Abstract

Lipotoxicity can mediate endothelial dysfunction in obesity. Altered endothelial cell phenotype during the pathobiological course of the lipotoxicity may lead to the hemostatic abnormalities, which is a hallmark of several hematological disorders. Impaired hemostasis could also be directly related to the numerous metabolic diseases such as hypertension, diabetes and atherosclerosis. On the other hand, local hematopoietic bone marrow (BM) renin-angiotensin system (RAS) contributes to the development of atherosclerosis via acting on the lipotoxicity processes. Local BM RAS, principally an autocrine/ paracrine/ intracrinehematological system, is located at the crossroads of cellular regulation, molecular interactions and the lipotoxicity-mediated vascular endothelial dysfunction. The positive regulatory role of plasma LDL on AT1 receptor-mediated hematopoietic stem cell (HSC) differentiation and the production of pro-atherogenic monocytes had been described. LDL-regulated HSC function may explain in part hypercholesterolemia-induced inflammation as well as the anti-inflammatory and anti-atherosclerotic effects of AT1 receptor blockers. The role of local adipose tissue RAS is directly related to the pathogenesis of metabolic derangements in obesity. There may be a crosstalk between local BM RAS and local adipose tissue RAS at the genomics and transcriptomics levels. The aim of this chapter is to review hematological alterations propagating the pathological influences of lipotoxicity on the vascular endothelium.

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## Keywords

Hematological disorders • Lipotoxicity • Obesity

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## 1 Introduction

Apart from the circulating renin-angiotensin system (RAS), there is a local RAS in many different organs. It is well known that the local RAS has different paracrine, autocrine, and intracrine effects. Obesity is defined as abnormal body weight with a body mass index (BMI, kg body weight/height (m)<sup>2</sup>) of greater than 30 and is related with increases in all-cause mortality, including death from cardiovascular disease and heart failure. Obesity is considered as a part of the metabolic syndrome and at present, obesity is an epidemic health disaster that is widely seen in the world population. It was shown that lipotoxicity can mediate endothelial dysfunction in obesity (Kim et al. 2012). The obesity pandemic currently affects several hundred million people worldwide, comprising increasing numbers of patients in developing countries such as India and China. In the US, the incidence of childhood obesity and obesity-related hypertension has reached to an alarmingly high level, and preventive measures have been taken to fight this disease. In the nineteenth century Rudolf Virchow defined inflammation as well as injury of endothelial cells in atherosclerotic vascular tissues. Also it was demonstrated that augmented proliferation of vascular smooth muscle cells after mechanical endothelial injury proposing that intact endothelial cells protect against atherosclerosis. Endothelial cells form the inner lining of arterial and venous blood vessels and were afterward found to secrete vasoactive and trophic substances such as prostacyclin endothelium-derived relaxing factor/nitric oxide (NO), angiotensin II as well as endothelin-1. At the present time it is well known that these endothelial substances control vascular growth, vasomotion, platelet function, immunologic and inflammatory responses as well as plasmatic coagulation. Blood pressure, blood flow, fluid volume, hemodynamic status, and electrolyte balance are managed by circulating RAS and therefore there is relationship between the RAS and development of atherosclerosis (Ferrario and Strawn 2006). In experimental studies it was proven that AT1a receptor (AT1R) is associated with atherosclerosis development (Daugherty et al. 2010).

Endothelial and regenerating vascular cells are shown to be effected by RAS (Becher et al. 2011). In a study which was conducted with mice, Ang II–AT1R pathway in the BM is shown to increase atherosclerosis development (Kato et al. 2005). RAS is associated with atherosclerosis because RAS increases endothelial dysfunction, cellular proliferation and programmed inflammation. Hematopoietic cells that contain AT1Rs augment the migration of BM-derived inflammatory cell into the vessel walls (Kato et al. 2005; Sata and Fukuda 2010). Also, chronic hypertension is developed due to the AT1R receptors limited mononuclear cell accumulation in the renal tissue by the modulation of vasoactive cytokines (Crowley et al. 2010). Therefore altered endothelial cell phenotype during the pathobiological course of the lipotoxicity may lead to the hemostatic abnormalities, which is a hallmark of several hematological disorders. The aim of this chapter is to review hematological alterations propagating the pathological influences of lipotoxicity on the vascular endothelium.

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## 2 The Relationship Between Ras, Endothelium and Lipotoxicity

The components of the metabolic syndrome can be affected by the stability of hemostasis. In many studies it was shown that impaired hemostasis could also be directly related to the numerous metabolic diseases such as hypertension, diabetes and atherosclerosis (Aryan et al. 2009; Atalar et al. 2005; Erdem et al. 1999; Guven et al. 2006; Yildiz and Haznedaroglu 2006). On the other hand, local hematopoietic bone marrow (BM) renin-angiotensin system (RAS) (Haznedaroglu and Beyazit 2013) contributes to the development of atherosclerosis via acting on the lipotoxicity processes (Beyazit et al. 2010). Local BM RAS, principally an autocrine/ paracrine/ intracrine hematological system, is located at the crossroads of cellular regulation, molecular interactions and the lipotoxicity-mediated vascular endothelial dysfunction (Beyazit et al. 2010; Haznedaroglu and Beyazit 2010). The major active peptide in RAS is Angiotensin II (Ang II) which is trans-

formed from Angiotensin I (Ang I) by angiotensin converting enzyme (ACE). Ang I is produced from angiotensinogen by Renin (Paul et al. 2006). However Ang II may also be generated by chymase which is an enzyme in the form of serine protease. Although there are other enzymes such as tonin and cathepsins, chymase is the main alternative enzyme for Ang II generation since it has the highest specificity to the substrate. This pathway is not inhibited by ACE inhibition (Urata et al. 1996). Chymase is blamed for RAS related arteriosclerosis since it is widely present in vascular walls (Arakawa and Urata 2000). AT1R and AT2R are receptors that facilitate the effects of Ang II (De Gasparo et al. 2000). AT1R actions results in vasoconstriction and aldosterone secretion. In vessel walls, kidney, heart, and brain RAS is locally stimulated (Ruiz-Ortega et al. 2001). Stimulation of AT1R leads to intracellular free radical production that contributes to tissue injury by increasing mitochondrial dysfunction. Inhibition of Ang II provides protection for neurodegenerative processes and stimulates longevity in experimental models. The development of atherosclerosis is related with RAS activity. Ang II stimulates the endothelial cell apoptosis thus it compromises the structural integrity of the endothelial barrier. Oxidative lipoprotein alteration, smooth muscle cell relocation from the media into the intima, proliferation, and conversion from a contractile to a synthetic phenotype are stimulated by oxidative stress and hyperthrombotic state by inflammatory response in the vessel intimal layer comprising T lymphocytes and macrophages with RAS stimulation. This process eventually leads to shrinkage of the vessel lumen. Although AT1aR expression on vascular cells is the main reason for these effects, AT1aR expression on BM-derived cells contributes to this process by quickening of infiltration of BM-derived inflammatory cells to the vessel wall.

Both angiotensin II and endothelin-1, the major effector peptide of the endothelin family were known as vasoconstrictor peptides and are secreted by endothelial and other vascular cells. At the present time it is also known that these peptides are not only take part in the management of vascular tone, but also have strong growth-stimulating and pro-inflammatory effects in dif-

ferent cell types. Besides RAS stimulation, also endothelin might also contribute to experimental and human hypertension and that inhibition of action or secretion of endothelin preserves functional and structural alterations in kidney and vasculature. Stimulation of G-protein coupled receptors—in response to either angiotensin II or endothelin-1—and the intracellular events downstream of receptor stimulation seems to be vital to maintain these disease progressions. Furthermore, both proteins potentiate each other's actions since angiotensin II induces expression of endothelin-1 in vitro and in vivo and effects of the enzymes involved in endothelin-1 formation.

Endothelium-dependent vasomotion is imperfect in obese humans and animals and it is not much known regarding the mechanisms of this vascular “dysfunction”. It is known that obesity result in stimulation of thromboxane receptor gene expression that is one of the main goals for vasoconstrictor prostanoids. Obesity was related with boosted prostanoid-controlled vasoreactivity that in vascular beds is preserved by endogenous endothelin. These alterations were not related with systemic blood pressure, so this makes us think that obesity per se stimulates vasoconstriction. The role of perivascular adipose tissue for vasomotion is important that reduces vasoconstriction. An adipose-tissue related relaxing factor has been also detected. Local stimulation of vasoactive systems in fat cells raises actions of the sympathetic nervous system in obese patients. The RAS and the ET system stimulate sympathetic system since blockade of ACE, AT1 receptors or ETA receptors affects this stimulation. Thus, obesity-related vasoconstriction could promote hypertension, atherosclerosis, and thrombosis.

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### 3 Metabolic Effects of the Local Bone Marrow RAS

The local BM RAS was first described in 1996 (Haznedaroglu et al. 1996). Since then many studies have been conducted in order to further clarify the role of local BM RAS. Intracellularly produced Ang II in BM stem and progenitor cells

contribute to the hematopoietic niche Ang II relations for autocrine/paracrine effects and to intracellular levels for intracrine effects. The BM microenvironment and blood cell types of the health and disease, the intracrine pathway could be the main mechanism of the effects of angiotensin peptides. Ang II and gene expression of the RAS were found in human mast cells which are considered as the “mobile RAS” controlled by cytokine effects (Hara et al. 2004). Also T and NK cells are also contain RAS elements and they could secrete and transfer AngII to inflammation sites. AngII stimulates the cellular chemotaxis that causes a potential inflammatory amplification system in the vasculature (Jurewicz et al. 2007). It was shown that regulatory T cells can improve Ang II-related cardiac damage (Kvakan et al. 2009).

Human primitive lympho-hematopoietic cells, embryonic, fetal and adult hematopoietic tissues also have ACE activity (Zambidis et al. 2008). Human umbilical cord blood cells are shown to exert Renin, AGT, and ACE mRNAs (Goker et al. 2005; Acar et al. 2007). ACE and other angiotensin elements activity in human hematopoietic stem cells (HSCs) during hematopoietic ontogeny and adulthood (Zambidis et al. 2008), thus local RAS may also have a role in HSC plasticity, and various hematological neoplastic diseases (Haznedaroglu and Beyazit 2010). The extensive pathobiological features of local BM RAS are related with the presence of ACE on leukemic blast cells within leukemic BM (Aksu et al. 2006; Beyazit et al. 2007), on erythroleukemic cells, ACE-expressing macrophages in lymph nodes of Hodgkin lymphoma (Koca et al. 2007), renin action in leukemic blasts (Wulf et al. 1996), Ang II as an autocrine growth factor for AML (Pinto et al. 2004), augmented renin gene action throughout NUP98-HOXA9 boosted blast development (Takeda et al. 2006), increased levels of BB9/ACE (+) AML isoforms, and changed JAK-STAT pathway as a link between RAS and leukemia (Haznedaroglu and Beyazit 2010; Haznedaroglu et al. 2000). JAK-STAT is a critical pathway between the upstream local BM RAS and neoplastic hematopoiesis (Haznedaroglu and Beyazit 2010; Haznedaroglu et al. 2000). In

myeloproliferative diseases imatinib mesylate decreases the abnormally enhanced expressions of the main RAS components (Sayitoglu et al. 2009). The choice between to produce either blood or endothelial cells of the hemangioblast is affected by RAS (Slukvin 2009).

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#### 4 Local Hematopoietic Bone Marrow Renin-Angiotensin System and Atherosclerosis

The cardiac RAS and the hematopoietic BM RAS are closely associated with each other (Haznedaroglu et al. 1996; Haznedaroglu and Ozturk 2003). Myocardial tissue repair by hematopoietic stem cell plasticity could represent an association between local cardiac RAS and hematopoietic RAS (Ozturk et al. 2004). Blood cells predominantly macrophages/monocytes, neutrophils and T-lymphocytes exist in all phases of atherosclerosis. In a previously published study it was proposed that there is a lipid-angiotensin system connection within the BM that is responsible for the predisposition of immune cells to home to coronary arteries and lead to development of atherosclerosis (Strawn et al. 2003; Strawn and Ferrario 2008). This novel hypothesis takes the former lipid hypotheses together and certificates for an immunological stimulation model that arises as early as alterations in the BM that lead to the development of stimulated circulating monocytic phenotypes which leads to atherogenesis. The effects of modified LDL on hematopoietic management within the BM control the homing features of monocytes which is critical for the initiation of atherogenesis. The “bone marrow response-to-lipid” theory combines the idea that pro-atherogenic fetatures of hematopoietic and non-hematopoietic progenitors are managed by the local effects of modified LDL on the expression of local RAS genes (Strawn et al. 2003). LDL-regulated HSC function could clarify in part hypercholesterolemia-related inflammation and also the anti-inflammatory or anti-atherosclerotic properties of angiotensin receptor blockers (Strawn and Ferrario 2008). Relations between modified LDL

and the hematopoietic BM RAS could stimulate some monocytic phenotypes which lead to atherosclerosis (Strawn et al. 2003; Strawn and Ferrario 2008). BM recipient AT1a receptors are shown to be necessary to stimulate Ang II related atherosclerosis in hypercholesteromic mice in which BM transplantation trials were performed (Cassis et al. 2007). AT1a receptors which are expressed on infiltrating cells manage the Ang II-related atherosclerosis. Moreover, AT1a receptors on resident tissue are vital for the Ang II-related atherosclerosis and on aneurysms abdominal aorta. The pro-atherogenic activity of Ang II controlled differentiation/proliferation of monocyte-lineage cells was shown in a study (Kato et al. 2008). In this study investigator produced BM chimeric apoE negative mice repopulated with AT1-deficient (*Agtr1*<sup>-/-</sup>) or wild-type (*Agtr1*<sup>+/+</sup>) BM cells. The atherosclerosis process was considerably decreased in apoE<sup>-/-</sup>/BM-*Agtr1*<sup>-/-</sup> mice compared with apoE<sup>-/-</sup>/BM-*Agtr1*<sup>+/+</sup> mice, along with a reduced numbers of BM granulocyte/macrophage progenitors and peripheral blood monocytes. As a result it can be concluded that Ang II manages the expression of c-Fms in HSCs and monocyte-lineage cells over BM stromal cell originated TNF-alpha to augment M-CSF-stimulated differentiation/proliferation of monocyte-lineage cells and may play role in atherosclerotic activity (Kato et al. 2008). The immunity and isolated lymphocytes are stimulated by Ang II managed autocrine loop. The immuno-stimulator activity of Ang II, particularly shown in T subset, could be harmful when local RAS are mismanaged as in cardiovascular atherosclerotic disease (Coppo et al. 2008). AT1aR in BM cells take role in atherosclerosis development by detecting numerous BM chimeric mice whose BM cells were positive or negative for AT1aR (Sata and Fukuda 2010). It was shown that the number of smooth muscle progenitor cells is increased after Ang II infusion. These smooth muscle progenitor cells were originally peripheral blood cells that transform to  $\alpha$ -smooth muscle actin-positive cells after culture in the presence of PDGF-BB. Destabilization of atherosclerotic plaques is stimulated by these smooth muscle-like cells which exert abundant

matrix metalloproteinase-9 (MMP-9). As a result it can be concluded that in order to prevent atherosclerosis, inhibition of AT1R should be performed in vascular cells as well as in BM (Kato et al. 2005; Sata and Fukuda 2010). To summarize, the hematopoietic BM RAS with local vasculature RAS have effects in the development and advancement of atherosclerosis, thus leading the development of cardiovascular diseases. Pathophysiology of atherosclerotic diseases gained a new perspective by RAS stimulation of cellular proliferation and programmed inflammation and in future this new approach may lead to a new therapeutic strategy. In a study it was reported that there is no change in atherosclerotic process in LDL receptor knock-out mice by transplantation with BM from AT1a receptor knock-out mice (Cassis et al. 2007), different from the studies indicating that (Kato et al. 2005; Yamada et al. 2007) AT1 receptor inhibition in BM cells may prevent atherosclerosis. In study it was also demonstrated that the beneficial effects of angiotensin receptor blocker (ARB) in end-organ injuries are because of the inhibition of AT1 receptor expressed in the end organs, but not in BM derived cells (Kato et al. 2008). The investigators proposed that distinct results detected in the kidney injury and atherosclerosis is possibly from the alterations in the pathogenesis of mouse models. Furthermore they have wondered that depending upon the tissues and model systems inspected, AT1 receptor activity in BM originated cells may have differential action points. Numerous physiological and pathophysiological stimuli or drugs control endothelial progenitor cell (EPC) mobilization. Furthermore, it was shown in a study levels of circulating EPCs is related with cardiovascular risk and left ventricular remodeling after myocardial infarction (Leone et al. 2009). Moreover, EPC pool in the myocardial microenvironment is associated to the bone marrow cellular proliferation. Vessel development and endothelial regeneration is affected by bone marrow-derived endothelial progenitor cells, monocytic cells, and mature endothelial cells (Steinmetz et al. 2010). Our current knowledge indicates that there are both cells that integrate into the vasculature, true EPC, and cells

with hematopoietic indicators that stimulate neo-vascularization. The interrogation of RAS activity on vasculogenesis-associated progenitor cells is also significant in the optimization of RAS intervention or regenerative treatment (Roks et al. 2011). To summarize the hematopoietic BM RAS and local vasculature RAS, manages the beginning and advancement of atherosclerosis, therefore effect the development of cardiovascular diseases.

## 5 The Role of RAS in Atherosclerotic Lesions

Cardiovascular risk factors are related with stimulation of the tissue renin–angiotensin system. It is widely accepted that the inhibition of the RAS can effectively delay the development of vascular diseases and related clinical events, including myocardial infarction. Cardiovascular protection has been predominantly confirmed with angiotensin converting enzyme inhibitors however also angiotensin receptor antagonists seem to be effective. It is notable that not only for vascular diseases but also for renal diseases these agents are very important therapeutic options. This makes us to think that stimulation of the RAS per se is one of the key factors defining initiation and development of abnormal cell growth and actions in the cardiovascular system, resulting in vascular and cardiac hypertrophy, mesangial cell growth and development of atherosclerosis. Atherosclerosis is characterized with chronic inflammation of the vascular wall including gathering of lipids, lipoproteins and mononuclear cells such as monocytes and T cells in the sub-endothelial space. This process results in a series of events in blood vessels leading to a remodeling of the arterial wall and a decrease in lumen size. Recent advances in biotechnology and molecular techniques have enabled us to discover the molecular pathways which initiate and stimulate the inflammatory activity in the development of atherosclerotic lesions. Even though RAS have a part in the control of cardiovascular and renal function, over-stimulation of this system contrib-

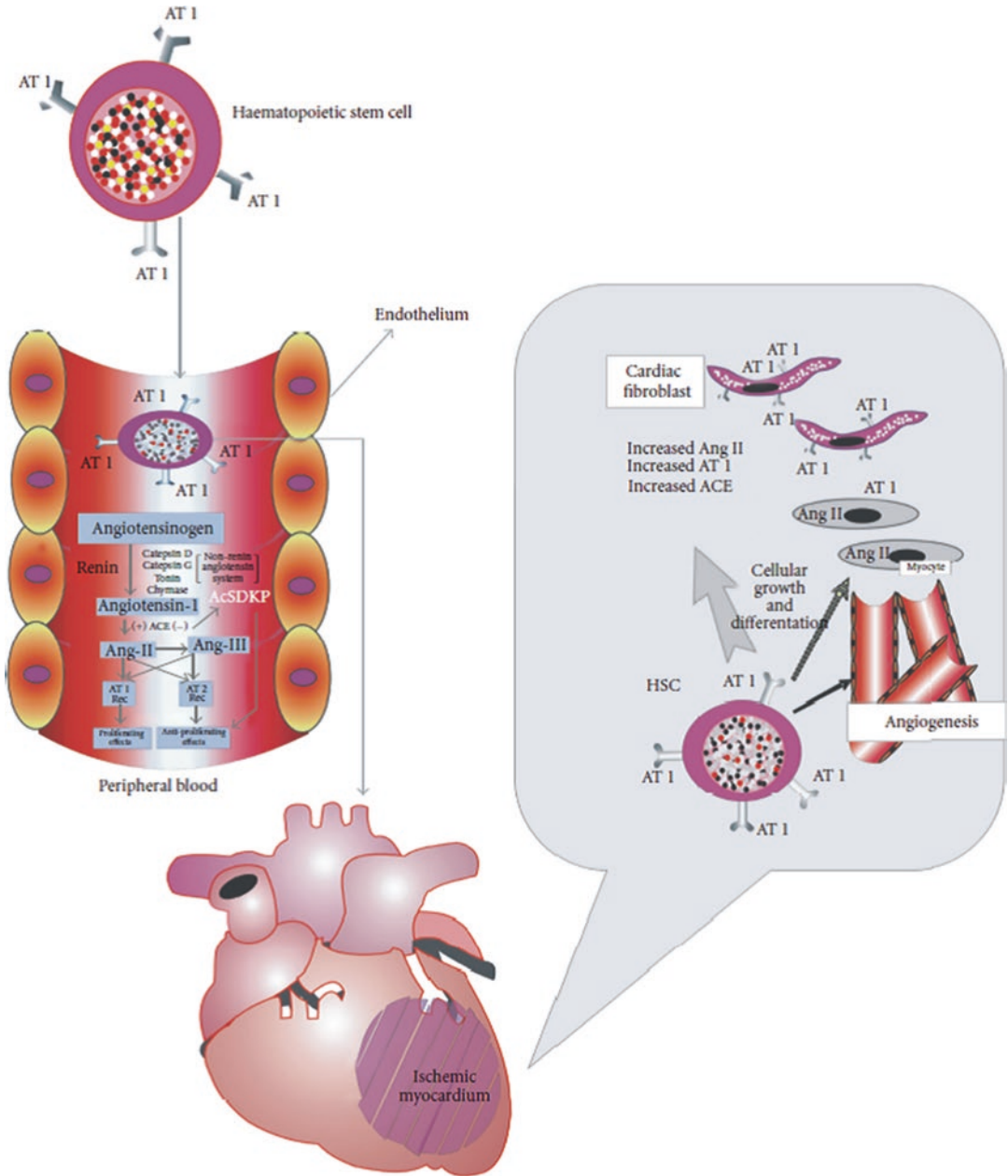
utes atherosclerotic process by triggering a series of cellular and molecular reactions detecting in the atherosclerotic lesions (Pastore et al. 1999).

Previously, Ang II was thought to effect atherosclerosis through its hemodynamic features however recently it has been proven that, the structural alterations in the vessel wall seen in atherosclerosis was a direct cellular effect of Ang II (Sata and Fukuda 2010). All of the elements of the RAS are expressed in the vessel wall and the activity of Ang II are generally controlled by the G-protein coupled receptors AT1 and AT2 (Iwai and Inagami 1992). Both AT1R and AT2R have been detected in the vessel wall, AT1R is thought to be accountable from most of the atherogenic activity of Ang II (Sayeski and Bernstein 2001). In a study, it has been showed that in hypercholesterolemic atherosclerosis in rabbits, the density of AT1 receptors in the media of diseased blood vessels is enlarged five-fold compared to healthy animals (Yang et al. 1998). In this study it was also showed that there is a significant AT1R binding capacity in the neointima of the diseased arteries. The most high receptor density in the vessel wall was detected on vascular smooth muscle cells (VSMCs); however cell culture investigations also established a important AT1R facilitated reactions in endothelial cells and macrophages and AT2Rs include only about 10% of total angiotensin receptors in healthy blood vessels (Yang et al. 1998). These data proposed that not only systemic but also local Ang II–AT1R pathway may contribute to beginning and advancement of atherosclerosis in blood vessels. It has been detected that serum ACE levels were considerably higher in cases with hepatportal sclerosis (HPS) in comparison to the healthy controls (Beyazit et al. 2011). This data was obtained by measuring circulating ACE concentrations. Therefore it seems that ACE may be related with the pathological thrombotic events in the microenvironment of the portal circulation in HPS. Furthermore, it may be suggested that intracellular processes which controls the secretion/expression of vasoactive substances such as angiotensin peptides may stimulate the vasculopathy in portal hypertension (Beyazit et al. 2011).

## 6 RAS Effect on Vascular Endothelial Cells and Obesity

Ang II is directly related with endothelial function. Ang II is secreted by endothelium and it has significant effects on the endothelium. It is shown that Ang II has a direct role on endothelial function (Ruiz-Ortega et al. 2001). Vascular endothelium is considered as a metabolically active secretory tissue. It functions as a thrombo-resistant surface to blood and makes a macromolecular block between blood and the vessel. Structural functional defects of endothelial cells are the reason of not only vascular diseases containing atherosclerosis but also definite visceral diseases (Robinson et al. 1995). Vessel tonus, coagulation state, cell development and apoptosis, and leukocyte trafficking are controlled by the factor that are secreted from endothelial cells., VSMCs which are managed by endothelium and other factors, are also able to secrete cytokines and growth factors which may affect vascular cellular phenotype and development (Ruiz-Ortega et al. 2001). The cytokines control inflammation and immunity which may apply both pro-and anti-atherogenic effects on vascular wall cells. The actions of vascular wall cells controlled by cytokines can affect the beginning, development, or complication of the atherosclerotic lesions. Therefore, cytokines may influence multiple stages of atherogenesis and offer novel and interesting targets for treatment approaches. Endothelial cells control vascular tonus in a firm balance between nitric oxide (NO) and Ang II. This equilibrium is significant for to sustain a healthy endothelium. The inequality to Ang II by itself may result in several vital alterations in the endothelium which set the development of atherosclerosis (Neutel 2004). In several studies it has been proved that Ang-II stimulates the adhesion molecules, growth factors, cytokines and chemokines and applies a proinflammatory action on leucocytes, endothelial cells and VSMCs (Sata and Fukuda 2010; Han et al. 1999). Furthermore it has been shown that Ang II augments the expression of vascular endothelial growth factor (VEGF) that considerably

stimulates the adventitial angiogenesis (Williams et al. 1995). Ang II starts an inflammatory cascade of decreased nicotinamide-adenine dinucleotide phosphate oxidase, reactive oxygen species (ROS) and nuclear factor-kappa B via type 1 receptor, that controls the transcription and gene expression and stimulates chemokines and adhesion molecules (Dandona et al. 2007). Augmented ROS and reduced MMP-9 effects in bone marrow decreases EPC mobilization in the initial post-infarction stage. ACE blockade or statin therapy stimulates EPC levels with distinct drug-specific actions on bone marrow molecular changes (Thum et al. 2006). The Ang II type 1a (AT1a) receptor is present on multiple cell types in atherosclerosis, containing BM-originated cells and vascular wall cells, and controls inflammation and development. Certainly, Ang II stimulates atherogenesis in hyperlipidemic mice via producing monocytes and by triggering vascular wall cells. In advanced atherosclerotic lesions, Ang II augments matrix metalloproteinases (MMPs) and plasminogen activator inhibitor-1, thus leading to destabilization of atherosclerotic plaque and changes of fibrinolytic equilibrium (Galis and Khatri 2002). Ang II has roles in vascular remodeling separately from stimulating oxidative stress, endothelial damage, thrombosis and inflammation. It acts as a bifunctional growth factor which triggers secretion of growth factors and vasoactive peptides in VSMCs (Itoh et al. 1993). Ang II can stimulate vascular remodeling and development of vascular lesions by modulating of vascular cell migration, reducing vascular smooth muscle apoptosis and extracellular matrix deposition (Scott-Burden et al. 1990). These effects of Ang II are controlled by complex intracellular signaling pathways containing triggering of the PLC-IP3-DAG cascade, tyrosine kinases, MAP kinases, and RhoA/Rho kinase (Touyz 2005). Intracellular signaling pathways which are augmented afterwards binding of the peptide to its cell-surface receptors, of which two main subtypes have been described, AT1R and AT2R (Murphy et al. 1991). While Ang IV receptor was recognized in recent times, as insulin-controlled aminopeptidase, but, its actions in angiogenesis yet not clarified. AT1R is



**Fig. 20.1** RAS plays role on vascular endothelial cells, myocardial ischemia, angiogenesis, cellular differentiation and development of cardiac fibroblasts (Beyazit et al. 2010)

broadly present in blood vessels, kidney, heart, liver and adrenal glands; however AT2R is expressed mainly in foetal tissue, reducing after birth, with comparatively low quantities normally present in adult tissue. AT1R controls pro-angiogenic actions by boost of inflammation and leukocytes infiltration; however AT2R manages anti-angiogenic actions by control of apoptosis.

Presence of AT2R is stimulated in pathological conditions related with cardiac and vascular remodeling or inflammation. Both of the receptors have critic actions in managing VSMC actions, although they differ in their unique effects. The RAS effects on vascular endothelial cells are summarized in Fig. 20.1 (Beyazit et al. 2010).



## 7 Inflammation and Development of Atherosclerosis

Atherosclerosis is a pathological process that initiates during fetal life. The early lesion of the atherosclerotic plaque, the fatty streak, could be observed in the fetal aorta and formation is stimulated by maternal hypercholesterolemia. This suggests that plasma lipids have an essential role for onset and development of early fetal atherosclerosis and in children. It is possible that unfavorable nutritional features and behavior (overeating, unbalanced lipid-rich diets) alone or in combination with unfavorable alterations in lifestyle such as lack of physical activity will stimulate the development of juvenile obesity, unfavorable alterations in plasma lipids, and the development of atherosclerotic lesion formation. One of the main reasons of atherosclerosis is considered as chronic inflammation. Noticeable cellular elements of atherothrombosis are lymphocytes, platelets, and endothelial cells but in latest studies it was suggested that myeloid leukocytes, specifically monocyte subsets, polymorphonuclear leukocytes, and mast cells play critical role in atherothrombosis (Soehnlein and Weber 2009). These elements are present in the vascular wall and trigger and maintain core mechanisms in plaque development and destabilization. Mesenchymal progenitor cells may also have critical effects in the beginning of myocardial fibrosis (Sopel et al. 2011). Various data suggest a role for oxidative stress in the development of endothelial dysfunction and atherogenesis, apart from the hemodynamic stress of blood pressure (Laursen et al. 1997). Furthermore plenty of data support that vascular reactive oxygen species (ROS) have a critical effect in atherogenesis. In addition to its vasoconstrictive features, novel *in vivo* and *in vitro* investigations suggest that Ang II, by the AT1 receptor, stimulates O<sub>2</sub><sup>-</sup> production in endothelial cells, adventitial fibroblasts, vascular smooth muscle cells (VSMC), and mesangial cells by triggering of nicotinamide adenine dinucleotide (reduced form)/NADH phosphate (reduced form) (NADH/NAD(P)H) oxidase resulting in endothelial dys-

function, growth, and inflammation (Lassègue and Clempus 2003). Latest studies have also proven that in endothelial cells in addition to in VSMCs, NAD(P)H-dependent oxidase characterizes the most important O<sub>2</sub><sup>-</sup> source. In a study it was shown that NAD(P)H oxidase is essential in the development of atherosclerosis via investigating the genetically changed mice which are lacking both apolipoprotein E (ApoE) and p47phox, one subunit of NAD(P)H oxidase. Noteworthy decrease in atherosclerotic lesion was detected in the double knockout mice, compared with that of ApoE-lacking mice. Also, ACE inhibitor-related blockade of plaque-infiltrating immune cells are related with suppression of the C-C chemokine receptor 9 (CCR9). The chemokine ligand 25 (CCL25)-CCR9 axis stimulates atherosclerosis, since blocking of CCR9 by RNA interference in hematopoietic progenitors of apoE-lacking mice slowed the atherosclerotic process (Abd Alla et al. 2010). ROS stimulated mitogen activated protein kinase, Akt and JAK/STAT pathways (Schieffer et al. 2000). Pharmacological inhibition of AT1R with Angiotensin receptor inhibitors could not be sufficient to prevent cytokine secretion completely; even though Ang II stimulates NF-kappa B and triggers formation of cytokines such as interleukin-6 and tumor necrosis factor- $\alpha$ , (Han et al. 1999). ROS secreted by Ang II effects the development of vascular diseases by inhibiting nitric oxide, damaging endothelial function, augmenting VSMC growth, and triggering proatherogenic, inflammatory, and adhesion molecule expression (Desideri et al. 2003). Ang II-related increase in O<sub>2</sub><sup>-</sup> production in the vessel wall is not associated with the hemodynamic activities of Ang II, since norepinephrine-related hypertension did not have parallel activities (Katusic and Vanhoutte 1989). Furthermore, it has been detected that Ang II effects neointimal monocyte infiltration by NF-kappa B stimulation and monocyte chemoattractant protein-1 (MCP-1) expression a significant outcome that is inhibited via angiotensin converting enzyme (ACE) blockers (Hernández-Presa et al. 1997). Ang II controls the presence of vascular cellular adhesion molecule-1 (VCAM-

1), intercellular adhesion molecule-1 (ICAM-1) and P selectin as well as cytokine, chemokine, and growth factor production within the vessel walls (Graninger et al. 2004). Also, RAS may affect the stimulation of complement system in both atherosclerosis and renal damage (Epstein 2001). This inflammatory pathway triggers the vascular inflammatory reaction by increasing the inflammatory cell infiltration to vessel walls. Monocytes convert into macrophages and increase the lipid deposition in the plaque, just after transferring into the vessel wall (Cathcart 2004). Chemokines and MMPs generated from monocytes/macrophages leads to the augmentation of atherosclerotic lesions. Besides, angiotensin II stimulates the intraplaque recruitment of monocytes and lymphocytes and increases the TNF- $\alpha$ , IL-6 and cyclooxygenase-2 expression in atherosclerotic vessels (Cathcart 2004). Moreover, Ang II stimulated increase of transcription factor nuclear factor-kappa B by redox-sensitive cascades, triggers cell adhesion molecules, chemokines MCP-1 and interleukin-8. These molecules augment monocyte and T lymphocyte adherence and accumulation in atherosclerotic plaques (Hernández-Presa et al. 1997). All of these evidences make us to suggest that a local stimulated RAS in vessel walls which triggers infiltration of inflammatory cells into the vessel walls is a significant characteristic of atherosclerosis.

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## 8 RAS, Obesity and Other Mechanisms

The mechanisms by which obesity augments the risk for cardiovascular syndromes, as well as for related diseases such as augmented insulin resistance, diabetes, dyslipidemia, and hypertension is not clarified yet. These risk factors are interaction which are also detected in the “metabolic syndrome X”, that includes of augmented insulin resistance, dyslipidemia, and hypertension in conjunction with obesity, and which is provoked by sedentary life style. Adipocyte, that characterizes the main element of fat tissue, not only comprises a functional local RAS, but also elements

of the endothelin system such as endothelin receptors. Thus, a rise of body fat mass will lead to a local net rise in actions and/or expression of vasoactive systems. Furthermore, both angiotensin II and endothelin-1 stimulates adipocyte gene expression, comprising leptin and PAI-1 (Ailhaud et al. 2000). Actions and/or expression of genes encoding for vasoactive proteins of the RAS is managed in adipocytes. The actions of renin, that control development of angiotensin I from angiotensinogen, is augmented in plasma of obese cases as well as in obese dogs, make us to think that obesity systemically stimulates RAS (Henegar et al. 2001). In contrast to humans and dogs, obesity in most rodent models is related with decreased plasma renin actions, representing significant species alterations. Experimental obesity in many concerns still parallels pathophysiological alterations seen in human obesity such as rises in insulin resistance and blood pressure. Like renin stimulation, species alteration exists between humans and rodents with regard to atherosclerosis and dyslipidemia. Therefore, when matching animal data to human disease it should be underlined that rodents are typically resistant to atherosclerosis unless exposed to highly unphysiological diets comprising cholic acid or after genetic manipulation. Natural resistance to atherosclerosis in mice could be somewhat associated to the fact that mice—unlike humans—have high plasma levels of HDL cholesterol relative to LDL cholesterol levels that continue even after high-fat diet treatment. Whether endothelin has effects in development of obesity is not yet clarified. In experimental obesity, there is stimulation in gene and protein expression of endothelin in the cardiovascular system, comprising vasculature and kidney (Barton et al. 2000). In humans, it is like to be a genetic tendency for obesity in some cases, that may position these patients at increased risk for vascular diseases as well. Augmented endothelin-1 plasma levels have been detected in obese normotensive and hypertensive cases (Tiret et al. 1999). As obesity is commonly related with rises in arterial blood pressure, it has been asked whether mutations of the preproendothelin-1 gene could be related with the predisposition to

development of hypertension. Without a doubt, the Lys198Asn polymorphism of the preproendothelin-1 gene was detected to be associated with obesity-related hypertension in Caucasians as well as in Japanese cases of obese patients (Tiret et al. 1999). Therefore, variations of the gene encoding for vasoconstrictor proteins could affect predisposition to hypertension in obese cases. Obesity is associated with the risk of renal disease, in which the RAS has a significant pathogenetic role. It was recently investigated whether obesity locally plays a role regarding expression or stimulation of elements of the RAS in the cardiovascular system. It was proven that diet-related obesity by giving C57 mice with a high fat, low cholesterol diet for 7 months, a treatment period that matches to 20 years in humans by means of maximal lifespan (Surwit et al. 1998). Animals on a high fat-diet were found to be obese and revealed a five times greater rise in body weight as compared to control group (Barton et al. 2000). In normotensive animals obesity was related with augmented ACE actions in the kidney, however not in lung or liver, and likewise with boosted angiotensin II-mediated vascular contractility. Chronic usage of an agent that is orally active antagonist of endothelin ETA receptors completely stopped these alterations, representing that endothelin locally manages RAS actions within the “obese” kidney. Obesity is a part of metabolic syndrome, which is affected by various features of endothelium. The risk for atherosclerotic vascular disease and following cardiovascular events is affected by several risk factors. These risk factors may be evaluated in two major groups which are endogenous and exogenous. Endogenous risk factors include genetic predisposition, hormonal influences, gender, age, and blood pressure. On the other hand exogenous risk groups include modifiable factors such as cigarette smoking, nutritional factors comprising dietary fat, body weight, physical activity, psychological stress and several others. Among variable risk factors, obesity has considered as a major health problem bearing significant social and economic implications. Aldosterone has roles in obesity-related disorders also (Kawarazaki and Fujita 2016). Obese sub-

jects often have hypertension and related cardiovascular and renal diseases, and this has become a serious worldwide health problem. In obese subjects, impaired renal-pressure natriuresis causes sodium retention, leading to the development of salt-sensitive hypertension. Physical compression of the kidneys by visceral fat and activation of the sympathetic nervous system, RAS, and aldosterone/mineralocorticoid receptor (MR) system are involved in this mechanism. Obese subjects often exhibit hyperaldosteronism, with increased salt sensitivity of blood pressure (BP). Adipose tissue excretes aldosterone-releasing factors, thereby stimulating aldosterone secretion independently of the systemic RAS, and aldosterone/MR activation plays a key role in the development of hypertension and organ damage in obesity. In obese subjects, both salt sensitivity of BP, enhanced by obesity-related metabolic disorders including aldosterone excess, and increased dietary sodium intake are closely related to the incidence of hypertension. Some salt sensitivity-related gene variants affect the risk of obesity, and together with salt intake, its combination is possibly associated with the development of hypertension in obese subjects. With high salt levels common in modern diets, salt restriction and weight control are undoubtedly important. However, not only MR blockade but also new diagnostic modalities and therapies targeting and modifying genes that are related to salt sensitivity, obesity, or RAS regulation are expected to prevent obesity and obesity-related hypertension (Kawarazaki and Fujita 2016). Genetic polymorphisms regarding RAS are also blamed for the development of metabolic syndrome. It recent studies the association of polymorphisms within the RAS with metabolic syndrome in a cohort of Chilean subjects is reported (Herrera et al. 2016). Metabolic syndrome (MetS) is associated with hypertension, obesity and dyslipidemia. Thus, genetic variants related with these conditions may modulate its development. The effects of polymorphisms in the renin-angiotensin system (RAS) on metabolic syndrome risk in a cohort of Chilean subjects were evaluated (Herrera et al. 2016). In the study, a total of 152 subjects, 83 with MetS and 69 with-

out MetS of both genders were included, according to the ATP III update criteria (Herrera et al. 2016). The rs4340 Insertion/Deletion (I/D), rs699 (T > C) and rs5186 (A > C) of the ACE, AGT and AGTR1 genes, respectively, were genotyped. After adjusting for age and gender, it was detected that the DD genotype of rs4340 associated with MetS. Specifically, the DD genotype was associated with MetS risk in women. In males, the AA genotype for rs5186 variant was associated with an increased risk for developing MetS when compared with women carrying the same genotype. In subjects without MetS, DD genotype was associated with increased waist circumference while subjects with MetS carrying the rs5186 TT genotype showed higher levels of HDL-cholesterol (Herrera et al. 2016). Therefore it can be concluded that there is a role for RAS polymorphisms in predisposing to metabolic syndrome. Recently, it has been shown that free fatty acids activate RAS in 3T3-L1 adipocytes through Nuclear Factor-kappa B pathway (Sun et al. 2016). RAS stimulation is related with impaired differentiation of preadipocytes and augmented lipolysis and enhanced oxidative stress and inflammatory answer (Sun et al. 2016). Defects in the system are related with obesity, type 2 diabetes, and cardiovascular diseases. It is known that RAS present in a number of tissues, comprising kidneys, heart, and nervous and immune systems. It is also known that elements of RAS, comprising renin, angiotensinogen, ACE, and angiotensins I, II, and III have also been exist in adipose tissue (Sun et al. 2016). It is well established that free fatty acids (FFAs) are stimulators of RAS in leukocytes (Sun et al. 2016). But, whether FFAs has a role in the stimulation of RAS in adipocytes was a debate. It has been shown that the levels of FFAs generating from lipolysis in adipocytes are considerably augmented in peripheral circulation as well as local tissues in obese humans and animals (Sun et al. 2016). It has been proposed that RAS can manage adipocyte differentiation by Ang II and the adipocyte AT1R in mice (Sun et al. 2016). So, FFAs can directly manage RAS stimulation in adipose tissue which might be a stimulating mechanism of glucose and lipid metabolism dis-

order and obesity-associated diseases. FFA components such as palmitic acid (PA) and lauric acid can bind to Toll-like receptor 4 (TLR4) with the assistance of the endogenous ligand, fetuin A (Fet A), therefore facilitating the stimulation of TLR4 and NF- $\kappa$ B pathways and resulting in the inflammatory cascade (Sun et al. 2016). TLR4 is a member of the family of Toll-like receptors (TLRs) that could stimulate mitogen-activated protein kinase and nuclear factor  $\kappa$ B (NF- $\kappa$ B) to regulate inflammatory and immune responses after binding to ligands (Sun et al. 2016). Moreover, recently in a study it was demonstrated that active TLR4 can trigger the stimulation of RAS in hepatocytes and cardiac muscle cells (Sun et al. 2016). Therefore, it has been suggested that palmitic acid (PA) stimulates the TLR4 signaling pathway, resulting in RAS stimulation in adipocytes. Recently in a study, it was detected that palmitic acid (PA), one kind of free fatty acid, stimulates the actions of RAS in 3T3-L1 adipocytes (Sun et al. 2016). In the presence of fetuin A (Fet A), PA upregulated the expression of angiotensinogen (AGT) and angiotensin type 1 receptor (AT<sub>1</sub>R) and stimulated the secretion of angiotensin II (ANG II) in 3T3-L1 adipocytes. Moreover, the activation of RAS in 3T3-L1 adipocytes was blocked when Toll-like receptor 4 (TLR4) signaling pathway using TAK242 or NF- $\kappa$ B signaling pathway using BAY117082 is inhibited. So it was identified that there are critical molecular mechanisms linking PA/TLR4/NF- $\kappa$ B signaling pathway to the activity of the local renin-angiotensin system in adipose tissue (Sun et al. 2016). In recent times it was found that Angiotensin II activates different calcium signaling pathways in adipocytes (Dolgacheva et al. 2016). It is well known that Ang II is an important mammalian neurohormone involved in RAS. Ang II is produced both constitutively and locally by RAS systems, including white fat adipocytes. The influence of Ang II on adipocytes is complex, affecting different systems of signal transduction from early Ca(2+) responses to cell proliferation and differentiation, triglyceride accumulation, expression of adipokine-encoding genes and adipokine secretion (Dolgacheva et al. 2016). It is known that white fat adipocytes

express all RAS components and Ang II receptors (AT1 and AT2). In a recent study which was carried out with the primary white adipocytes culture, and Ca(2+) signaling pathways activated by Ang II were investigated using fluorescent microscopy (Dolgacheva et al. 2016). Ca(2+)-oscillations and transient responses of differentiated adipocytes to Ang II were registered in cells with both small and multiple lipid inclusions. Using inhibitory analysis and selective antagonists, it was shown that Ang II initiates periodic Ca(2+)-oscillations and transient responses by activating AT1 and AT2 receptors and involving branched signaling cascades; in these cascades, AT1 receptors play the leading role (Dolgacheva et al. 2016). These studies open a perspective of using Ang II for correction of signal resistance of adipocytes often observed during obesity and type 2 diabetes. Recently it was detected that inactivation of adipose angiotensinogen reduces adipose tissue macrophages and increases metabolic activity (LeMieux et al. 2016). The adipose RAS has been linked to obesity-induced inflammation, though mechanisms are not completely understood. In a recent study, adipose-specific angiotensinogen knockout mice (Agt-KO) were generated to determine whether Agt inactivation reduces inflammation and alters the metabolic profile of the Agt-KO mice compared to wild-type (WT) littermates (LeMieux et al. 2016). In this study adipose tissue-specific Agt-KO mice were created using the Cre-LoxP system with both Agt-KO and WT littermates fed either a low-fat or high-fat diet to assess metabolic changes. White adipose tissue was used for gene/protein expression analyses and WAT stromal vascular cells for metabolic extracellular flux assays. No significant differences were observed in body weight or fat mass between both genotypes on either diet. However, improved glucose clearance was observed in Agt-KO compared to WT littermates, consistent with higher expression of genes involved in insulin signaling, glucose transport, and fatty acid metabolism (LeMieux et al. 2016). Furthermore, Agt inactivation reduced total macrophage infiltration in Agt-KO mice fed both diets. Lastly, stroma vascular cells from Agt-KO mice revealed higher

metabolic activity compared to WT mice. These findings indicate that adipose-specific Agt inactivation leads to reduced adipose inflammation and increased glucose tolerance mediated in part via increased metabolic activity of adipose cells. In a recent study it was detected that intrarenal renin-angiotensin system mediates fatty acid-induced ER stress in the kidney (Li et al. 2016). It is known that obesity-related kidney disease is related to caloric excess promoting deleterious cellular responses. Accumulation of saturated free fatty acids in tubular cells produces lipotoxicity involving significant cellular dysfunction and injury. In a recent study it was aimed to elucidate the role of RAS activation in saturated fatty acid-induced endoplasmic reticulum (ER) stress in cultured human proximal tubule epithelial cells (HK2) and in mice fed with a high-fat diet (Li et al. 2016). Treatment with saturated fatty acid palmitic acid for 24 h induced ER stress in HK2, leading to an unfolded protein response as reflected by increased expressions of the ER chaperone binding immunoglobulin protein (BiP) and proapoptotic transcription factor C/EBP homologous protein (CHOP) protein as evaluated by immunoblotting. PA treatment also induced increased protein expression of inositol requiring protein 1 $\alpha$  (IRE1 $\alpha$ ), phosphorylated eukaryotic initiation factor- $\alpha$  (eIF2 $\alpha$ ), and activating transcription factor 4 (ATF4) as well as activation of caspase-3. PA treatment was associated with increased angiotensin II levels in cultured medium. The angiotensin II type 1 receptor (AT1R) blocker valsartan or renin inhibitor aliskiren dramatically suppressed PA-induced upregulation of BiP, CHOP, IRE1 $\alpha$ , p-eIF2 $\alpha$ , and ATF4 in HK2 cells. In contrast, valsartan or aliskiren did not prevent ER stress induced by tunicamycin. C57BL/6 mice fed with a high-fat diet for 14 weeks exhibited increased protein expressions of BiP and CHOP compared with control mice, which were significantly attenuated by the valsartan treatment. Increased angiotensin II levels in serum and urine were observed in mice fed with a high-fat diet when compared with controls. Therefore it is suggested that the intrarenal RAS activation may play an important role in diabetic kidney injury via mediating ER

stress induced by saturated fatty acid (Li et al. 2016). In a recent investigation it was shown that combined angiotensin receptor modulation is effective in the management of cardio-metabolic disorders (Paulis et al. 2016). It is well-known that cardiovascular and metabolic disorders, such as hypertension, insulin resistance, dyslipidemia or obesity are linked with chronic low-grade inflammation and dysregulation of the RAS. Consequently, RAS inhibition by ACE inhibitors or angiotensin AT1 receptor blockers is the evidence-based standard for cardiovascular risk reduction in high-risk patients, including diabetics with albuminuria. In addition, RAS inhibition reduces the new onset of diabetes mellitus. Yet, the high and increasing prevalence of metabolic disorders, and the high residual risk even in properly treated patients, calls for additional means of pharmacological intervention. In the past decade, the stimulation of the angiotensin AT2 receptor (AT2R) has been shown to reduce inflammation, improve cardiac and vascular remodeling, enhance insulin sensitivity and increase adiponectin production (Paulis et al. 2016). Therefore, a concept of dual AT1R/AT2R modulation emerges as a putative means for risk reduction in cardio-metabolic diseases. The approach employing simultaneous RAS blockade (AT1R) and RAS stimulation (AT2R) is distinct from previous attempts of double intervention in the RAS by dual blockade. Dual blockade abolishes the AT1R-linked RAS almost completely with subsequent risk of hypotension and hypotension-related events, i.e. syncope or renal dysfunction. Such complications might be especially prominent in patients with renal impairment or patients with isolated systolic hypertension and normal-to-low diastolic blood pressure values. In contrast to dual RAS blockade, the add-on of AT2R stimulation does not exert significant blood pressure effects, but it may complement and enhance the anti-inflammatory and antifibrotic/de-stiffening effects of the AT1R blockade and improve the metabolic profile. Further studies will have to investigate these putative effects in particular for settings in which blood pressure reduction is not primarily desired (Paulis et al. 2016). In a recent study it was proposed that

ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity (Patel et al. 2016). It is well known that obesity is increasing in prevalence and is strongly associated with metabolic and cardiovascular disorders. RAS has emerged as a key pathogenic mechanism for these disorders; ACE2 negatively regulates RAS by metabolizing Ang II into Ang 1-7. In a recent study the role of ACE2 in obesity-mediated cardiac dysfunction was investigated (Patel et al. 2016). ACE2 null (ACE2KO) and wild-type (WT) mice were fed a high-fat diet (HFD) or a control diet and studied at 6 months of age. Loss of ACE2 resulted in decreased weight gain but increased glucose intolerance, epicardial adipose tissue (EAT) inflammation, and polarization of macrophages into a proinflammatory phenotype in response to HFD. Similarly, human EAT in patients with obesity and heart failure displayed a proinflammatory macrophage phenotype. Exacerbated EAT inflammation in ACE2KO-HFD mice was associated with decreased myocardial adiponectin, decreased phosphorylation of AMPK, increased cardiac steatosis and lipotoxicity, and myocardial insulin resistance, which worsened heart function. Ang 1-7 (24 µg/kg/h) administered to ACE2KO-HFD mice resulted in ameliorated EAT inflammation and reduced cardiac steatosis and lipotoxicity, resulting in normalization of heart failure. Therefore these data make us to think that ACE2 plays a novel role in heart disease associated with obesity wherein ACE2 negatively regulates obesity-induced EAT inflammation and cardiac insulin resistance (Patel et al. 2016). In another study it was shown that oxidative stress causes imbalance of renal renin angiotensin system components and hypertension in obese zucker rats (Luo et al. 2015). It is well-known that oxidative stress plays an important role in the pathogenesis of hypertension, especially in obesity-related hypertension. The natriuretic and antinatriuretic components of the renal renin angiotensin system maintain sodium homeostasis and blood pressure. In a recent study it was aimed to test the hypothesis that increased oxidative stress leads to the imbalance of RAS components and hypertension in

obese Zucker rats (Luo et al. 2015). Lean and obese rats received vehicle or tempol, a superoxide dismutase mimetic in the drinking water for 4 weeks. Compared with vehicle-treated lean rats, vehicle-treated obese rats exhibited higher blood pressure and increased renal oxidative stress, accompanied by increased diuretic and natriuretic responses to AT1R antagonist (Candesartan) and AT2R agonist (CGP-42112A) and reduced diuretic and natriuretic response to MasR agonist (Ang-[1-7]). Moreover, obese rats had higher ACE, AT1R and AT2R, lower ACE2 and MasR expressions in the kidney. All of the above-mentioned abnormalities were reversed to some degree by tempol treatment. In primary cultures of renal proximal tubular (RPT) cells from lean and obese rats, tempol treatment also increased AT2R, ACE2, and MasR expressions but decreased AT1R and ACE expressions in obese rats. Taken together, in this recent study it was shown that the imbalance of renal RAS components was associated with increased oxidative stress in obese rats (Luo et al. 2015). Moreover, antioxidant treatment with tempol reversed the imbalance of renal RAS components and led to diuresis and natriuresis, which, at least in part, explains the blood pressure-lowering effect of antioxidant supplementation in obesity-related hypertension. In another study, the inhibitory effect of angiotensin II on BKCa channels in podocytes via oxidative stress had been shown (Gao et al. 2015). It has been well-known that Ang II is an important active substance of the RAS. In a recent study it has confirmed that abnormalities of Ang II may be related with cerebrovascular diseases, endocrine diseases, cardiovascular diseases, liver diseases, such as: cerebral hypoxia, diabetes, obesity, atrial fibrillation, and liver cirrhosis (Gao et al. 2015). However, understanding effects of Ang II on podocytes is not enough. In the study it has been aimed to investigate the effects of oxidative stress on the large conductance, Ca(2+)-activated K(+) channels (BKCa). Results from the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay showed that Ang II induced podocyte death in a concentration-dependent manner (Gao et al. 2015). The measurement of

superoxide dismutase (SOD) generation demonstrated that Ang II decreased the total SOD of cellular levels. Meaningfully, pretreatment of a type of ROS scavenger formulations named N-(mercaptopyronyl)-glycine (N-MPG) could inhibit podocyte apoptosis induced by Ang II. Meanwhile, patch-clamp technique was used in this study to detect the effects of Ang II on currents of BKCa channel in podocytes. The results indicated that Ang II inhibited the current amplitude of BKCa channel and decreased the slope of I-V curve. Ang II also made the activation curves of BKCa channel shift to the left. These results may provide a theoretical basis for potential treatment of chronic glomerular disease in the future.

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## 9 Conclusion

Metabolic syndrome constitutes a constellation of findings including central obesity, insulin resistance/type 2 diabetes mellitus (DM), dyslipidemia and hypertension (Karmali et al. 2015). Metabolic syndrome affects 1 in 4 adults in the United States and is rapidly rising in prevalence, largely driven by the dramatic rise in obesity and insulin resistance/DM. Being central to the development of metabolic syndrome and its other related diseases, much focus has been placed on identifying the mitogenic effects of obesity and insulin resistance/DM as mechanistic clues of the link between metabolic syndrome and cancer. Pertinent mechanisms identified include altered lipid signaling, adipokine and inflammatory cytokine effects, and activation of PI3K/Akt/mTOR and RAS/RAF/MAPK/ERK pathways via dysregulated insulin/insulin-like growth factor-1 (IGF-1) signaling (Karmali et al. 2015). Through variable activation of these multiple pathways, obesity and insulin resistance/DM predispose to hematologic malignancies, imposing the aggressive and chemo-resistant phenotypes typically seen in cancer patients with underlying metabolic syndrome. Growing understanding of these pathways has identified druggable cancer targets, rationalizing the development and testing of agents like PI3K inhibitor idelalisib, mTOR

inhibitors everolimus and temsirolimus, and IGF-1 receptor inhibitor linsitinib. It has also led to exploration of obesity and diabetes-directed therapies including statins and oral hypoglycemic for the management of metabolic syndrome-related hematologic neoplasms (Karmali et al. 2015).

The positive regulatory role of plasma LDL on AT1 receptor-mediated hematopoietic stem cell (HSC) differentiation and the production of pro-atherogenic monocytes had been described (Strawn and Ferrario 2008). LDL-regulated HSC function may explain in part hypercholesterolemia-induced inflammation as well as the anti-inflammatory and anti-atherosclerotic effects of AT1 receptor blockers (Ferrario et al. 2004; Ferrario and Strawn 2006). The role of local adipose tissue RAS is directly related to the pathogenesis of metabolic derangements in obesity (Kalupahana and Moustaid-Moussa 2012a). There may be a crosstalk between local BM RAS (Ozturk et al. 2004) and local adipose tissue RAS (Kalupahana and Moustaid-Moussa 2012b) at the genomics and transcriptomics levels (Nehme et al. 2015). In the future regenerative medicine may be used for tissue-specific progenitor cells for vascular repair process. Mononuclear blood cell populations are capable of transforming into endothelial cells and incorporate into ischemic tissue. Most of the clinical investigations on human cell treatment for ischemic vascular disease are constructed on the presence of cell surface antigen like CD34 or VEGFR2 to detect endothelial progenitor cells (Becher et al. 2010). Further studies may clarify functional relations of local BM RAS driving CD34+ stem cells, and distinct local RAS in the vasculature in health and in disease (Zucker and Zimmerman 2011). Studies focusing on genomics and transcriptomics will help us to improve our knowledge regarding these issues.

## References

Abd Alla, J., et al. 2010. Angiotensin-converting enzyme inhibition down-regulates the pro-atherogenic chemokine receptor 9 (CCR9)-chemokine ligand 25 (CCL25) axis. *Journal of Biological Chemistry* 285: 23494–23503.

- Acar, K., Y. Beyazit, A. Sucak, et al. 2007. Alterations in the 'local umbilical cord blood renin-angiotensin system' during pre-eclampsia. *Acta Obstetrica et Gynecologica Scandinavica* 86: 1–7.
- Ailhaud, G., A. Fukamizu, F. Massiera, R. Negrel, P. Saint-Marc, and M. Teboul. 2000. Angiotensinogen, angiotensin II and adipose tissue development. *International Journal of Obesity and Related Metabolic Disorders* 24: 33–35.
- Aksu, S., Y. Beyazit, I.C. Haznedaroglu, et al. 2006. Overexpression of angiotensin-converting enzyme (CD 143) on leukemic blasts as a clue for the activated local bone marrow RAS in AML. *Leukemia & Lymphoma* 47: 891–896.
- Arakawa, K., and H. Urata. 2000. Hypothesis regarding the pathophysiological role of alternative pathways of angiotensin II formation in atherosclerosis. *Hypertension* 36: 638–641.
- Aryan, M., A. Kepez, E. Atalar, et al. 2009. Association of plasma osteopontin levels with coronary calcification evaluated by tomographic coronary calcium scoring. *Journal of Bone and Mineral Metabolism* 27(5): 591–597.
- Atalar, E., I.C. Haznedaroglu, H. Kilic, et al. 2005. Increased soluble glycoprotein V concentration during the acute onset of unstable angina pectoris in association with chronic cigarette smoking. *Platelets* 16(6): 329–333.
- Barton, M., R. Carmona, H. Morawietz, L. d'Uscio, W. Goettsch, H. Hillen, C. Haudenschild, J. Krieger, K. Munter, T. Lattmann, T. Luscher, and S. Shaw. 2000. Obesity is associated with tissue-specific activation of renal angiotensin-converting enzyme in vivo: Evidence for a regulatory role of endothelin. *Hypertension* 35: 329–336.
- Becher, M.U., et al. 2010. Regeneration of the vascular compartment. *Herz* 35: 342–350.
- Becher, U.M., et al. 2011. Endothelial damage and regeneration: The role of the Renin-Angiotensin-aldosterone system. *Current Hypertension Reports* 13: 86–92.
- Beyazit, Y., S. Aksu, I.C. Haznedaroglu, et al. 2007. Overexpression of the local bone marrow renin-angiotensin system in acute myeloid leukemia. *Journal of the National Medical Association* 99: 57–63.
- Beyazit, Y., T. Purnak, G.S. Guven, and I.C. Haznedaroglu. 2010. Local bone marrow Renin-Angiotensin system and atherosclerosis. *Cardiology Research and Practice* 2011: 714515. doi:10.4061/2011/714515.
- Beyazit, Y., M. Ibis, T. Purnak, et al. 2011. Elevated levels of circulating angiotensin converting enzyme in patients with hepatoportal sclerosis. *Digestive Diseases and Sciences* 56(7): 2160–2165. doi:10.1007/s10620-011-1580-7.
- Cassidy, L.A., D.L. Rateri, H. Lu, and A. Daugherty. 2007. Bone marrow transplantation reveals that recipient AT1a receptors are required to initiate angiotensin II-induced atherosclerosis and aneurysms. *Arteriosclerosis, Thrombosis, and Vascular Biology* 27: 380–386.



- Cathcart, M.K. 2004. Regulation of superoxide anion production by NADPH oxidase in monocytes/macrophages: Contributions to atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* 24: 23–28.
- Coppo, M., et al. 2008. Angiotensin II upregulates renin-angiotensin system in human isolated T lymphocytes. *Regulatory Peptides* 151: 1–6.
- Crowley, S.D., et al. 2010. A role for angiotensin II Type 1 receptors on bone marrow-derived cells in the pathogenesis of angiotensin II-dependent hypertension. *Hypertension* 55: 99–U180.
- Dandona, P., S. Dhindsa, H. Ghanim, and A. Chaudhuri. 2007. Angiotensin II and inflammation: The effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. *Journal of Human Hypertension* 21: 20–27.
- Daugherty, A., et al. 2010. Genetic variants of the renin-angiotensin system: Effects on atherosclerosis in experimental models and humans. *Current Atherosclerosis Reports* 12: 167–173.
- De Gasparo, M., K.J. Catt, T. Inagami, J.W. Wright, and T. Unger. 2000. International union of pharmacology. XXIII. The angiotensin II receptors. *Pharmacological Reviews* 52: 415–472.
- Desideri, G., M.C. Bravi, M. Tucci, G. Croce, M.C. Marinucci, A. Santucci, et al. 2003. Angiotensin II inhibits endothelial cell motility through an AT1-dependent oxidant-sensitive decrement of nitric oxide availability. *Arteriosclerosis, Thrombosis, and Vascular Biology* 23: 1218–1223.
- Dolgacheva, L.P., M.V. Turovskaya, V.V. Dynnik, et al. 2016. Angiotensin II activates different calcium signaling pathways in adipocytes. *Archives of Biochemistry and Biophysics* 593: 38–49.
- Epstein, M. 2001. Aldosterone and the hypertensive kidney: Its emerging role as a mediator of progressive renal dysfunction: A paradigm shift. *Journal of Hypertension* 19: 829–842.
- Erdem, Y., C. Usalan, I.C. Haznedaroglu, et al. 1999. Effects of angiotensin converting enzyme and angiotensin II receptor inhibition on impaired fibrinolysis in systemic hypertension. *American Journal of Hypertension* 12: 1071–1076.
- Ferrario, C.M., and W.B. Strawn. 2006. Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. *The American Journal of Cardiology* 98: 121–128.
- Ferrario, C.M., R.S. Richmond, R. Smith, et al. 2004. Renin-angiotensin system as a therapeutic target in managing atherosclerosis. *American Journal of Therapeutics* 11: 44–53.
- Galis, Z.S., and J.J. Khatri. 2002. Matrix metalloproteinases in vascular remodeling and atherogenesis: The good, the bad, and the ugly. *Circulation Research* 90: 251–262.
- Gao, N., H. Wang, X. Zhang, and Z. Yang. 2015. The inhibitory effect of angiotensin II on BKCa channels in podocytes via oxidative stress. *Molecular and Cellular Biochemistry* 398: 217–222.
- Goker, H., I.C. Haznedaroglu, Y. Beyazit, et al. 2005. Local umbilical cord blood renin-angiotensin system. *Annals of Hematology* 84: 277–281.
- Graninger, M., R. Reiter, C. Drucker, E. Minar, and B. Jilma. 2004. Angiotensin receptor blockade decreases markers of vascular inflammation. *Journal of Cardiovascular Pharmacology* 44: 335–339.
- Guven, G.S., A. Kilicaslan, S.G. Oz, et al. 2006. Decrements in the thrombin activatable fibrinolysis inhibitor (TAFI) levels in association with orlistat treatment in obesity. *Clinical and Applied Thrombosis/Hemostasis* 12(3): 364–368.
- Han, Y., M.S. Runge, and A.R. Brasier. 1999. Angiotensin II induces interleukin-6 transcription in vascular smooth muscle cells through pleiotropic activation of nuclear factor-kappa B transcription factors. *Circulation Research* 84: 695–703.
- Hara, M., K. Ono, H. Wada, S. Sasayama, and A. Matsumori. 2004. Preformed angiotensin II is present in human mast cells. *Cardiovascular Drugs and Therapy* 18: 415–420.
- Haznedaroglu, I.C., and Y. Beyazit. 2010. Pathobiological aspects of the local bone marrow renin-angiotensin system: A review. *Journal of the Renin-Angiotensin-Aldosterone System* 11(4): 205–213.
- — —. 2013. Local bone marrow renin-angiotensin system in primitive, definitive and neoplastic haematopoiesis. *Clinical Science (London, England)* 124(5): 307–323.
- Haznedaroglu, I.C., and M.A. Ozturk. 2003. Towards the understanding of the local hematopoietic bone marrow renin-angiotensin system. *The International Journal of Biochemistry & Cell Biology* 35: 867–880.
- Haznedaroglu, I.C., S. Tuncer, and M. GURSOY. 1996. A local renin-angiotensin system in the bone marrow. *Medical Hypotheses* 46: 507–510.
- Haznedaroglu, I.C., M. Arici, and Y. Buyukasik. 2000. A unifying hypothesis for the renin-angiotensin system and hematopoiesis: Sticking the pieces together with the JAK-STAT pathway. *Medical Hypotheses* 54: 80–83.
- Henegar, J., S. Bigler, L. Henegar, S. Tyagi, and J. Hall. 2001. Functional and structural changes in the kidney in the early stages of obesity. *Journal of the American Society of Nephrology* 12: 1211–1217.
- Hernández-Presa, M., C. Bustos, M. Ortego, et al. 1997. Angiotensin-converting enzyme inhibition prevents arterial nuclear factor-kappa B activation, monocyte chemoattractant protein-1 expression, and macrophage infiltration in a rabbit model of early accelerated atherosclerosis. *Circulation* 95: 1532–1541.
- Herrera, C.L., W. Castillo, P. Estrada, et al. 2016. Association of polymorphisms within the Renin-Angiotensin System with metabolic syndrome in a cohort of Chilean subjects. *Archives of Endocrinology and Metabolism* 60(3): 190–198. doi:10.1590/2359-399700000134.
- Itoh, H., M. Mukoyama, R.E. Pratt, G.H. Gibbons, and V.J. Dzau. 1993. Multiple autocrine growth factors modulate vascular smooth muscle cell growth response

- to angiotensin II. *The Journal of Clinical Investigation* 91: 2268–2274.
- Iwai, N., and T. Inagami. 1992. Identification of two subtypes in the rat type I angiotensin II receptor. *FEBS Letters* 298: 257–260.
- Jurewicz, M., et al. 2007. Human T and natural killer cells possess a functional renin-angiotensin system: Further mechanisms of angiotensin II-induced inflammation. *Journal of the American Society of Nephrology* 18: 1093–1102.
- Kalupahana, N.S., and N. Moustaid-Moussa. 2012a. The renin-angiotensin system: A link between obesity, inflammation and insulin resistance. *Obesity Reviews* 13: 136–149.
- . 2012b. The adipose tissue renin-angiotensin system and metabolic disorders: A review of molecular mechanisms. *Critical Reviews in Biochemistry and Molecular Biology* 47: 379–390.
- Karmali, R., A. Dalovisio, J.A. Borgia, et al. 2015. All in the family: Clueing into the link between metabolic syndrome and hematologic malignancies. *Blood Reviews* 29: 71–80.
- Kato, H., J. Ishida, S. Imagawa, et al. 2005. Enhanced erythropoiesis mediated by activation of the renin-angiotensin system via angiotensin II type 1a receptor. *The FASEB Journal* 19: 2023–2025.
- Kato, H., J. Ishida, K. Nagano, et al. 2008. Deterioration of atherosclerosis in mice lacking angiotensin II type 1A receptor in bone marrow-derived cells. *Laboratory Investigation* 88: 731–739.
- Katusic, Z.S., and P.M. Vanhoutte. 1989. Superoxide anion is an endothelium-derived contracting factor. *The American Journal of Physiology* 257: 33–37.
- Kawarazaki, W., and T. Fujita. 2016. The Role of aldosterone in obesity-related hypertension. *American Journal of Hypertension* 29: 415–423.
- Kim, J.A., M. Montagnani, S. Chandrasekran, and M.J. Quon. 2012. Role of lipotoxicity in endothelial dysfunction. *Heart Failure Clinics* 8(4): 589–607.
- Koca, E., I.C. Haznedaroglu, A. Uner, et al. 2007. Angiotensin-converting enzyme expression of the lymphoma-associated macrophages in the lymph nodes of Hodgkin's disease. *Journal of the National Medical Association* 99: 1243–1247.
- Kvakan, H., et al. 2009. Regulatory T cells ameliorate angiotensin II-induced cardiac damage. *Circulation* 119: 2904–U2983.
- Lassègue, B., and R.E. Clempus. 2003. Vascular NAD(P) H oxidases: Specific features, expression, and regulation. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* 285: 277–297.
- Laursen, J.B., S. Rajagopalan, Z. Galis, M. Tarpey, B.A. Freeman, and D.G. Harrison. 1997. Role of superoxide in angiotensin II-induced but not catecholamine-induced hypertension. *Circulation* 95: 588–593.
- LeMieux, M.J., L. Ramalingam, R.L. Mynatt, et al. 2016. Inactivation of adipose angiotensinogen reduces adipose tissue macrophages and increases metabolic activity. *Obesity (Silver Spring)* 24: 359–367.
- Leone, A.M., et al. 2009. From bone marrow to the arterial wall: The ongoing tale of endothelial progenitor cells. *European Heart Journal* 30: 890–899.
- Li, C., Y. Lin, R. Luo, et al. 2016. Intrarenal renin-angiotensin system mediates fatty acid-induced ER stress in the kidney. *American Journal of Physiology. Renal Physiology* 310: 351–363.
- Luo, H., X. Wang, C. Chen, et al. 2015. Oxidative stress causes imbalance of renal renin angiotensin system (RAS) components and hypertension in obese Zucker rats. *Journal of the American Heart Association* 4(2): e001559. doi:10.1161/JAHA.114.001559.
- Murphy, T.J., R.W. Alexander, K.K. Griendling, M.S. Runge, and K.E. Bernstein. 1991. Isolation of a cDNA encoding the vascular type-1 angiotensin II receptor. *Nature* 351: 233–236.
- Nehme, A., C. Cerutti, N. Dhaouadi, et al. 2015. Atlas of tissue renin-angiotensin-aldosterone system in human: A transcriptomic meta-analysis. *Scientific Reports* 5: 10035. doi:10.1038/srep10035.
- Neutel, J.M. 2004. Effect of the renin-angiotensin system on the vessel wall: Using ACE inhibition to improve endothelial function. *Journal of Human Hypertension* 18: 599–606.
- Ozturk, M.A., G.S. Guven, and I.C. Haznedaroglu. 2004. How hematopoietic stem cells know and act in cardiac microenvironment for stem cell plasticity? Impact of local renin-angiotensin systems. *Medical Hypotheses* 63: 866–874.
- Pastore, L., A. Tessitore, S. Martinotti, et al. 1999. Angiotensin II stimulates intercellular adhesion molecule-1 (ICAM-1) expression by human vascular endothelial cells and increases soluble ICAM-1 release in vivo. *Circulation* 100: 1646–1652.
- Patel, V.B., J. Mori, B.A. McLean, et al. 2016. ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity. *Diabetes* 65: 85–95.
- Paul, M., A. Poyan Mehr, and R. Kreutz. 2006. Physiology of local renin-angiotensin systems. *Physiological Reviews* 86: 747–803.
- Paulis, L., S. Foulquier, P. Namsolleck, et al. 2016. Combined angiotensin receptor modulation in the management of cardio-metabolic disorders. *Drugs* 76: 1–12.
- Pinto, R.P., K.K. Wang, H. Khoury, A.D. Schimmer, and M.D. Minden. 2004. Aberrant expression of angiotensin in acute myeloid leukemia. *Blood* 102: 2124.
- Robinson, K.A., F.J. Candal, N.A. Scott, and E.W. Ades. 1995. Seeding of vascular grafts with an immortalized human dermal microvascular endothelial cell line. *Angiology* 46: 107–113.
- Roks, A.J.M., et al. 2011. Effects of the renin angiotensin system on vasculogenesis-related progenitor cells. *Current Opinion in Pharmacology* 11: 162–174.
- Ruiz-Ortega, M., O. Lorenzo, M. Rupérez, et al. 2001. Role of the renin-angiotensin system in vascular dis-

- eases: Expanding the field. *Hypertension* 38: 1382–1387.
- Sata, M., and D. Fukuda. 2010. Crucial role of renin-angiotensin system in the pathogenesis of atherosclerosis. *The Journal of Medical Investigation* 57: 12–25.
- Sayeski, P.P., and K.E. Bernstein. 2001. Signal transduction mechanisms of the angiotensin II type AT(1)-receptor: Looking beyond the heterotrimeric G protein paradigm. *Journal of the Renin-Angiotensin-Aldosterone System* 2: 4–10.
- Sayitoglu, M., I.C. Haznedaroglu, O. Hatirnaz, et al. 2009. Effects of imatinib mesylate on renin-angiotensin system (RAS) activity during the clinical course of chronic myeloid leukaemia. *The Journal of International Medical Research* 37: 1018–1028.
- Schieffer, B., M. Luchtefeld, S. Braun, A. Hilfiker, D. Hilfiker-Kleiner, and H. Drexler. 2000. Role of NAD(P)H oxidase in angiotensin II-induced JAK/STAT signaling and cytokine induction. *Circulation Research* 87: 1195–1201.
- Scott-Burden, T., A.W. Hahn, T.J. Resink, and F.R. Bühler. 1990. Modulation of extracellular matrix by angiotensin II: Stimulated glycoconjugate synthesis and growth in vascular smooth muscle cells. *Journal of Cardiovascular Pharmacology* 16: 36–41.
- Slukvin, I.I. 2009. Renin angiotensin system and hemangioblast development from human embryonic stem cells. *Expert Review of Hematology* 2: 137–143.
- Soehnlein, O., and C. Weber. 2009. Myeloid cells in atherosclerosis: Initiators and decision shapers. *Seminars in Immunopathology* 31: 35–47.
- Sopel, M.J., et al. 2011. Myocardial fibrosis in response to Angiotensin II is preceded by the recruitment of mesenchymal progenitor cells. *Laboratory Investigation* 91: 565–578.
- Steinmetz, M., et al. 2010. Endothelial-regenerating cells an expanding universe. *Hypertension* 55: 593–599.
- Strawn, W.B., and C.M. Ferrario. 2008. Angiotensin II AT(1) receptor blockade normalizes CD11b(+) monocyte production in bone marrow of hypercholesterolemic monkeys. *Atherosclerosis* 196: 624–632.
- Strawn, W., R. Richmond, and C. Ferrario. 2003. A new understanding of atherosclerosis: The bone marrow response-to-lipid hypothesis. In *Heart Disease: Pathogenesis, Diagnosis and Treatment (3rd World Congress on Heart Disease)*, 183–188. Washington, DC.
- Sun, J., J. Luo, Y. Ruan, et al. 2016. Free fatty acids activate renin-angiotensin system in 3T3-L1 adipocytes through nuclear factor-kappa B pathway. *Journal of Diabetes Research* 2016: 1587594. doi:10.1155/2016/1587594.
- Surwit, R.S., S. Wang, A.E. Petro, S. Raimbault, D. Ricquier, and S. Collins. 1998. Diet-induced changes in uncoupling proteins in obesity-prone and obesity-resistant strains of mice. *Proceedings of the National Academy of Sciences of the United States of America* 95: 4061–4065.
- Takeda, A., C. Goolsby, and N.R. Yaseen. 2006. NUP98-HOXA9 induces long-term proliferation and blocks differentiation of primary human CD34+ hematopoietic cells. *Cancer Research* 66: 6628–6637.
- Thum, T., et al. 2006. Bone marrow molecular alterations after myocardial infarction: Impact on endothelial progenitor cells. *Cardiovascular Research* 70: 50–60.
- Tiret, L., O. Poirier, V. Hallet, T. McDonagh, C. Morrison, J. McMurray, H. Dargie, D. Arveiler, J. Ruidavets, G. Luc, A. Evans, and F. Cambien. 1999. The Lys198Asn polymorphism in the endothelin-1 gene is associated with blood pressure in overweight people. *Hypertension* 33: 1169–1174.
- Touyz, R.M. 2005. Intracellular mechanisms involved in vascular remodelling of resistance arteries in hypertension: Role of angiotensin II. *Experimental Physiology* 90: 449–455.
- Urata, H., H. Nishimura, and D. Ganten. 1996. Chymase-dependent angiotensin II forming systems in humans. *American Journal of Hypertension* 9: 277–284.
- Williams, B., A.Q. Baker, B. Gallacher, and D. Lodwick. 1995. Angiotensin II increases vascular permeability factor gene expression by human vascular smooth muscle cells. *Hypertension* 25: 913–917.
- Wulf, G.G., G. Jahns-Streubel, F. Strutz, et al. 1996. Paraneoplastic hypokalemia in acute myeloid leukemia: A case of renin activity in AML blast cells. *Annals of Hematology* 73: 139–141.
- Yamada, T., T. Kondo, Y. Numaguchi, et al. 2007. Angiotensin II receptor blocker inhibits neointimal hyperplasia through regulation of smooth muscle-like progenitor cells. *Arteriosclerosis, Thrombosis, and Vascular Biology* 27: 2363–2369.
- Yang, B.C., M.I. Phillips, D. Mohuczy, H. Meng, L. Shen, P. Mehta, and J.L. Mehta. 1998. Increased angiotensin II type 1 receptor expression in hypercholesterolemic atherosclerosis in rabbits. *Arteriosclerosis, Thrombosis, and Vascular Biology* 18: 1433–1439.
- Yildiz, B.O., and I.C. Haznedaroglu. 2006. Rethinking leptin and insulin action: Therapeutic opportunities for diabetes. *The International Journal of Biochemistry & Cell Biology* 38: 820–830.
- Zambidis, E.T., T. Soon Park, W. Yu, et al. 2008. Expression of angiotensin-converting enzyme (CD143) identifies and regulates primitive hemangioblasts derived from human pluripotent stem cells. *Blood* 112: 3601–3614.
- Zucker, I.H., and M.C. Zimmerman. 2011. The renin-angiotensin system in 2011: New avenues for translational research. *Current Opinion in Pharmacology* 11: 101–104.