

Local bone marrow renin-angiotensin system in the genesis of leukemia and other malignancies

I.C. HAZNEDAROGLU¹, U.Y. MALKAN²

¹Department of Hematology, Hacettepe University School of Medicine, Ankara, Turkey

²Department of Hematology, Hacettepe University School of Medicine, Ankara, Turkey

Abstract. – The existence of a local renin-angiotensin system (RAS) specific to the hematopoietic bone marrow (BM) microenvironment had been proposed two decades ago. Most of the RAS molecules including ACE, ACE2, AGT, AGTR1, AGTR2, AKR1C4, AKR1D1, ANPEP, ATP6AP2, CMA1, CPA3, CTSA, CTSD, CTSG, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP21A2, DPP3, EGFR, ENPEP, GPER, HSD11B1, HSD11B2, IGF2R, KLK1, LNPEP, MAS1, MME, NR3C1, NR3C2, PREP, REN, RNPEP, and THOP1 are locally present in the BM microenvironment. Local BM RAS peptides control the hematopoietic niche, myelopoiesis, erythropoiesis, thrombopoiesis and the development of other cellular lineages. Local BM RAS is important in hematopoietic stem cell biology and microenvironment. Angiotensin II regulates the proliferation, differentiation, and engraftment of hematopoietic stem cells. Activation of Mas receptor or ACE2 promotes proliferation of CD34+ cells. BM contains a progenitor that expresses renin throughout development. Angiotensin II attenuates the migration and proliferation of CD34+ Cells and promotes the adhesion of both MNCs and CD34+ cells. Renin cells in hematopoietic organs are precursor B cells. The renin cell requires RBP-J to differentiate. Mutant renin-expressing hematopoietic precursors can cause leukemia. Deletion of RBP-J in the renin-expressing progenitors enriches the precursor B-cell gene programme. Mutant cells undergo a neoplastic transformation, and mice develop a highly penetrant B-cell leukemia with multi-organ infiltration and early death. Many biological conditions during the development and function of blood cells are mediated by RAS, such as apoptosis, cellular proliferation, intracellular signaling, mobilization, angiogenesis, and fibrosis. The aim of this paper is to review recent developments regarding the actions of local BM RAS in the genesis of leukemia and other malignancies molecules.

Key Words:

Local bone marrow renin-angiotensin system, Leukemia, Malignancies.

Introduction

The existence of a local renin-angiotensin system (RAS) specific to the hematopoietic bone marrow (BM) microenvironment had been proposed by our group^{1,2}. The major RAS molecules including renin, angiotensinogen, angiotensin receptors, and angiotensin-converting enzymes (ACEs) have been detected at the BM microenvironment³. Locally active BM RAS affects the important stages of physiological and pathological blood cell production via autocrine, paracrine, and intracrine pathways^{4,5}. Local BM RAS peptides control the hematopoietic niche⁶, myelopoiesis⁷, erythropoiesis⁸, thrombopoiesis⁹ and the development of other cellular lineages^{6,10-12}. BM stromal niche contains local RAS^{4,5}, which controls the important hematopoietic functions^{3,13}. Furthermore, the BM stromal microenvironment contains angiotensin type 1 and type 2 receptors (AT1R and AT2R) and the inhibitory tetrapeptide N-Acetyl-Ser-Asp-Lys-Pro (AcSD-KP). Ang-II is the main RAS effector mediator, and it demonstrates its hematopoietic effects by stimulating angiotensin receptors, which are type 1 (AT1) and type 2 (AT2) receptors in the BM microenvironment^{4,5}. ACE/CD143 degrades AcSD-KP; as a result, the recruitment of primitive stem cells into S-phase is triggered^{9,14-17}. Moreover, Ang-II stimulates AT1/AT2 receptors, so that it has stimulatory/inhibitory effects on the JAK-STAT pathway, which is associated with physiologic functions of erythropoietin, thrombopoietin, and other hematopoietic cytokines throughout normal hematopoiesis and in myeloproliferative diseases^{9,18-20}. Local RAS is active even at the phase of primitive embryonic hematopoiesis²¹⁻²⁴. Recent developments regarding the actions of local bone marrow (BM) renin-angiotensin system (RAS) in the genesis of leukemia are depicted in Table I.

Table I. Recent developments regarding the actions of local bone marrow (BM) renin-angiotensin system (RAS) in the genesis of leukemia.

The findings	Conclusions	Perspectives	Reference
Renin cells in hematopoietic organs are precursor B cells	BM contains a progenitor that expresses renin throughout development and possesses a B-lymphocyte pedigree	Mutant cells undergo neoplastic transformation, and mice develop a highly penetrant B-cell leukemia with multi-organ infiltration and early death	101. Belyea et al, Nat Commun 2014; 5: 3273
Renin cell requires RBP-J to differentiate	Deletion of RBP-J in the renin-expressing progenitors enriches the precursor B-cell gene programme and constrains lymphocyte differentiation. Deletion of RBP-J in renin-lineage cells leads to enhanced cell cycle progression and increased cell proliferation.	Mutant renin-expressing hematopoietic precursors can cause leukemia	101. Belyea et al, Nat Commun 2014; 5: 3273
A transcriptomic meta-analysis revealed the atlas of BM RAS	ACE, ACE2, AGT, AGTR1, AGTR2, MAS1, REN, ANPEP and other critical molecules of RAS are locally present in the bone marrow	There is a local RAS in the BM affecting physiological and neoplastic cellular proliferation	52. Nehme et al, Sci Rep. 2015; 5: 10035
Ang II attenuates migration and proliferation of CD34+ Cells. Ang II promotes the adhesion of both MNCs and CD34+ cells	Activation of Mas receptor or ACE2 promotes proliferation of CD34+ cells	Local BM RAS is important in hematopoietic stem cell biology and microenvironment	77. Singh et al, Am J Physiol Heart Circ hysiol 2015; 309: P H1697-H1707
Specific immunoreactive renin-like peptide of 47 kDa isolated from AML blast cells	Renin-like enzyme activity converting angiotensinogen to angiotensin I in leukemic blast cells	Intracrine effects of renin is important in leukemogenesis	44. Wulf et al, Br J Haematol 1998; 100: 335-337
Over expression of ACE surface antigen in leukemic myeloid blast cells had been detected.	Renin expression could have a role on the leukemia development and angiotensin may act as an autocrine growth factor for AML cells	Autocrine effects of RAS is enhanced in leukemogenesis	35. Aksu et al, Leuk Lymphoma 2006; 47: 891-896 36. Beyazit et al, J Natl Med Ass 2007; 99: 57-63
Chronic Ang II infusion regulates HSC proliferation, mediated by angiotensin receptor type 1a	Ang II accelerates HSC to myeloid differentiation and Ang II impairs homing and reconstitution potentials of the donor HSCs	Angiotensin II regulates the proliferation, differentiation, and engraftment of hematopoietic stem cells	157. Kim S et al, Hypertension. 2016; 67: 574-584
Angiotensin II utilizes the JAK-STAT pathway	JAK-STAT pathway serves as a point of crosstalk between the components of the locally present RAS in the bone marrow and hematopoiesis	Local BM RAS is important in signal transduction of leukemia	20. Vrsalovic et al, Cancer Biol Ther 2007; 6: 1434-1436

Many biological conditions during the development and function of blood cells are mediated by RAS²⁵, such as apoptosis²⁶, cellular proliferation²⁷, intracellular signaling^{18,28}, mobilization²⁹, angiogenesis³⁰, fibrosis within the cytokine network³¹, and many others^{4,5,32,33}. Increased creation of neoplastic cells is the major characteristic feature of hematological clonal neoplastic diseases.

Besides, corrupted apoptosis, weakening of cell differentiation, uncontrolled signaling, and angiogenesis of cancer are the other factors that have roles in the clonal tumoral disease mechanism³⁴⁻³⁹. Many different pathological proliferative stages lead to the creation of neoplastic blood cells, which are derivative of leukemic stem cells. In the literature, it was stated that lo-

cal BM RAS could play a role in the development of neoplastic malignant blood cells^{34-36,40-45}. Local RAS functions in primitive embryonic hematopoiesis confirm the hypothesis that local autocrine BM RAS may play a role in neoplastic hematopoiesis²¹⁻²⁴.

The aim of this paper is to review recent developments regarding the actions of local BM RAS in the genesis of leukemia and other malignancies. The presence of renin⁴⁴, ACE³⁵, angiotensin II (Ang-II)⁴⁶, and angiotensinogen³⁶ have already been proven in leukemic blast cells. Besides, the formation of pathological tumoral blood cells is affected by RAS-modulating agents⁴⁷. The local BM RAS in leukemogenesis still needs to be clarified, and this issue is the main research subject^{4,5}. Currently, Phase I/II clinical trials of a pharmaceutical agent of peptide angiotensin 1-7 (Ang-1-7) have been conducted to evaluate the role of local BM RAS in different diseases^{33,48,49}.

The Local Bone Marrow Renin-Angiotensin System and Hematopoiesis

Entire blood cells are derived from hematopoietic BM, which is a very complex organic system. To preserve the management of hematopoietic cell growth, the main important growth factors are supplied by the local BM microenvironmental stromal cells that have contact with committed hematopoietic precursors and HSC. Cytokines and bioactive peptides are some examples of factors that control most of the processes in post-natal hematopoiesis within the BM microenvironment. The BM hematopoietic system is regulated by the local BM RAS in many different ways, such as autocrine, paracrine, intracrine. It was shown previously that the hematopoietic RAS regulates the evolution of blood cells^{1,4,5}. CD34+ hematopoietic cells contain Angiotensin II type 1a (AT1a) receptors that augment production of hematopoietic progenitors of BM and umbilical cord blood in different clinical conditions³². ACE is a regulator of hematopoiesis^{7,15,21,50,51}. Entire RAS molecules including ACE, ACE2, AGT, AGTR1, AGTR2, AKR1C4, AKR1D1, ANPEP, ATP6AP2, CMA1, CPA3, CTSA, CTSD, CTSG, CYP11A1, CYP11B1, CYP11B2, CYP17A1, CYP21A2, DPP3, EGFR, ENPEP, GPER, HSD11B1, HSD11B2, IGF2R, KLK1, LNPEP, MAS1, MME, NR3C1, NR3C2, PREP, REN, RNPEP, and THOP1 are locally present in the bone marrow, as represented by transcriptomic molecular studies⁵².

The role of Ang-II in the proliferation of all lineages in bone marrow was proved previously. When Ang-II was given externally, the colony development from HSC to CFU-GM and CFU-GEMM was enhanced¹². TNF-alpha production is managed by Ang-II as well as its secretion from bone marrow by the regulation the monocytic lineages⁵³. The function of Ang-II in the management of normal and non-functional hematopoiesis is not well understood. The study of Richmond et al⁵⁴ has greatly contributed to the knowledge on this issue. In the BM microenvironment, secretion of arachidonic acid is regulated by the local Ang-II. Arachidonic acid is secreted by the effect of Ang-II, and then it moves to a cellular section of BM. After then, arachidonic acid plays the role of a signalling molecule; thus, it regulates the production or inhibition of hematopoietic precursors. Arachidonic acid is known to have eicosanoid metabolites, and these two substances play important roles in the regulation of hematopoietic pathways⁵⁴. Local BM RAS has substantial effects on the hematopoietic mechanisms, especially on myeloid and eritroid cells^{1,4,5}. Local BM RAS plays its role through the regulation of important peptides, which controls hematopoiesis. With the help of ACE, Ang I transforms to Ang II, while bioactive SP, Ac-SDKP, and Ang 1-7 have been inactivated by ACE. Furthermore, during this process, Substance P (SP) is secreted from nerve endings, which are launched against the BM microenvironment. BM stromal and hematopoietic cells secrete RAS peptides by the AT1 and NK1 receptors that regulate the effect of Ang II and SP, respectively (Figure 1). Also, it has been proven that the important receptor of Ang 1-7, MAS is present in BM stroma¹².

RAS and Myelopoiesis

Local BM RAS contains ACE (CD143), which has an important role in myelopoiesis. In a study that was conducted by Lin et al⁷, myelopoietic disorders were shown to develop in ACE-knock-out mice. These myelopoietic disorders include augmented bone marrow myeloblasts, myeloid cells and amplified extramedullary myelopoiesis. Myeloid differentiation and development increases when AT1 receptor binds with Ang-II. The myelopoietic role of ACE and Ang-II was presented at the Hematopoietic Stem Cell (HSC) level previously⁷. Some leukocytes have the angiotensinogen gene; moreover, they secrete angiotensinogen. This finding also favors local RAS-modulating effects on myelopoiesis⁵⁵.

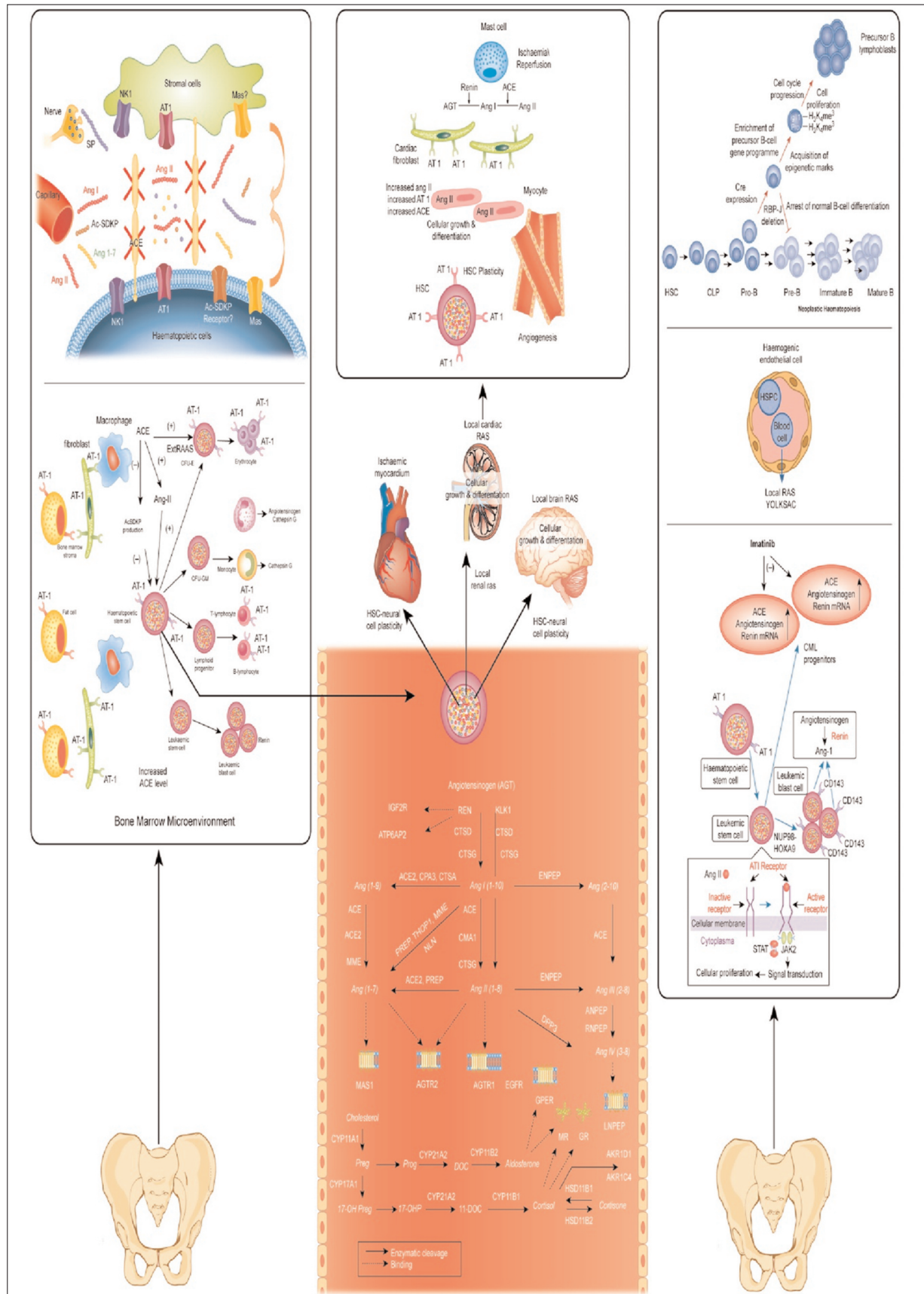


Figure 1. The role of RAS in normal and leukemic hematopoiesis, as well as the plasticity and systemic circulation, are depicted in Figure 1. BM local ACE controls peptides for hematopoiesis. Ang I, Ang II, Ac-SDKP, and Ang 1-7 are created in other tissues and transferred to the BM by circulation, and SP is secreted from the nerve ending projecting to the BM. ACE secretes Ang II from Ang I and reduces the bioactive SP, Ac-SDKP, and Ang 1-7. Both stromal cells and hematopoietic cells are equipped with AT1 and NK1 receptors and mediate the action of Ang II and SP, respectively. Mas, the receptor for Ang 1-7, can be detected in BM. These peptides thus can either directly stimulate hematopoietic cells or perform their actions through stromal cells. Local bone marrow RAS in association with the yolk sac embryonic hematopoiesis has a role in the development, creation, proliferation, and differentiation of the hematopoietic progenitors. The metabolic cascades of angiotensin peptides and corticoid and glucocorticoid pathways are shown using symbols of genes coding for the substrate, the enzymes, and the receptors involved in the pathway. Angiotensin peptides and steroid hormones are represented in gray using their usual abbreviation. Normal B-cell development proceeds from hematopoietic stem cells (HSC) by multiple phases to eventually convert mature B cells. A small subset of pro-B cells express renin and are named BRenin-cells. In this model, stimulation of the renin promoter in BRenin-cells results in cre recombinase expression and subsequently RBP-J deletion. These cells fail to differentiate along the normal B-cell pathway and undergo epigenetic initiation and enrichment of a precursor B-cell gene programme. Mutant cells additionally experience cell cycle progression and cell proliferation, ultimately resulting in expansion of a lymphoblast population and the development of precursor B cell leukemia (Refs; 4,12,52,80,101). *Abbreviations:* HSPC: Hematopoietic stem/progenitor cells; ACE: Angiotensin converting enzyme; CML: Chronic myeloid leukemia; Ang: Angiotensinogen; CFU-GM/E: Colony forming units-Granulocyte-Macrophage/erythroid; JAS/STAT: Janus kinase/Signal transduction and transcription; BC: Blood cell; Ang: Angiotensin; Preg: Pregnanolone; Prog: Progesterone; DOC: deoxycortisol; 17-OHP: 17-OH Progesterone; ACE: angiotensin I converting enzyme; ACE2: angiotensin I converting enzyme type 2; AGTR1: angiotensin II type 1 receptor; AGTR2: angiotensin II type 2 receptor; AKRIC4: aldo-keto reductase family 1, member C4; AKRID1: aldo-keto reductase family 1, member D1; ANPEP: alanyl-aminopeptidase; ATP6AP2: prorenin/renin receptor; CMA1: chymase 1; CPA3: carboxypeptidase A3; CTSA: cathepsin A; CTSD: cathepsin D; CTSG: cathepsin G; CYP11A1: cytochrome P450, family 11, subfamily A, polypeptide 1; CYP11B1: cortisol synthase; CYP11B2: aldosterone synthase; CYP17A1: cytochrome P450, family 17, subfamily A, polypeptide 1; CYP21A2: cytochrome P450 enzyme, family 21, subfamily A, polypeptide 2; DPP3: dipeptidyl-peptidase 3; ENPEP: glutamyl aminopeptidase (aminopeptidase A); GR: glucocorticoid receptor; HSD11B1: hydroxysteroid (11-beta) dehydrogenase 1; HSD11B2: hydroxysteroid (11-beta) dehydrogenase 2; IGF2R: insulin-like growth factor 2 receptor; KLK1: tissue kallikrein; LNPEP: leucyl/cystinylaminopeptidase; MAS1: MAS1 proto-oncogene; MME: membrane metallo-endopeptidase; MR: mineralocorticoid receptor; NLN: neurolysin (metallopeptidase M3 family); PREP: prolyl endopeptidase; REN: renin; RNPEP: arginyl aminopeptidase (aminopeptidase B); THOP1: thimetoligopeptidase 1. Images of IGF2R36, ATP6AP237, MR38, GR39, G-protein coupled receptors (AGTR1, AGTR2, GPER and MAS1)40 and LNPEP41.

The role ACE in myelopoiesis was revealed by Lin et al⁷. They found that the quantities of neutrophils and erythroid cells are decreased by 37% in ACE-knockout mice. Furthermore, in ACE-knockout mice, some myeloid precursors like myeloblasts, eosinophils, and immature myelocytes increased by 2.2, 2.3, and 2.5 times, respectively. Also, the nucleated erythroid precursors were found to be reduced to 77 % from normal standards; as a result, anemia was observed in these mice⁷. The clinical course of the ACE-knockout mice worsens because of the splenomegaly which is caused by extramedullary hematopoiesis. Mice without ACE had 10 times reduced Ang-II levels compared to wild mice. ACE and Ang-II play roles in myelopoiesis by increasing the central transcription factor, C/EBP⁷. ACE-KO mice had reduced C/EBP in its macrophages; however, this phenomenon can be normalized by giving Ang-II¹². It can be concluded that hematopoiesis is regulated by local BM RAS in two major ways. Firstly, local BM RAS controls the internal signals of transcription factors that change the gene expression. Second-

ly, local BM RAS modify the growth factors' signals that are produced from the BM microenvironment.

In the BM, the negative physiological regulator of hematopoiesis, *N*-acetyl seryl-aspartyl-lysyl-proline (AcSDKP) is inactivated by ACE¹⁵. The increase in ACE effects results in a decrease of AcSDKP by increasing its transformation into an inactive form; thus, the inhibitor effects of proliferation on hematopoiesis diminish. AcSDKP inhibits the production of hematopoietic progenitors and pluripotent HSCs by preventing them to enter the S phase of the cell cycle^{14,16,34}.

The function of AcSDKP in ACE activity and ACE expression were investigated by Oliveira et al¹⁷ in murine BM. In a kinin B1 receptor knockout (B1KO) mice model, a reduction in erythroid (Ter119+), granulocytic-macrophage (Gr1+/Mac1+), CD-220+, CD3+, and Lin-Sca1+c-Kit+ (LSK) cells were observed under ACE hyperfunction. Also, in B1 receptor knockout mice with ACE hyperfunction, after injection of Abz-YRK(Dnp)P-OH, B1KO LTBM ACE activity

was found to be increased compared to wild mice. The importance of these data is not yet clarified¹⁷.

Hematopoietic recovery following myelosuppression is increased by Angiotensin (1-7) (Ang 1-7). Ang 1-7 can be produced from Ang-II or Ang-I with the help of ACE2. The BM microenvironment includes Mas receptors, which regulate the proliferative role of Ang 1-7 on HSCs³². The therapeutic effect of Ang 1-7 on hematopoietic injury secondary to radiation after total body irradiation (TBI) has been investigated by Rodgers et al⁵⁶. In this study, subcutaneous injection of Ang 1-7 after TBI amended the survival from 60% to 92-97%. Moreover, thrombocytopenia frequency secondary to radiation was halved. Furthermore, Ang 1-7 increased the proliferation of various hematopoietic cells such as early mixed progenitors, erythroid progenitors, megakaryocytes and BM myeloid progenitors, approximately 4, 3.5, 2.5, and 4.5 folds, respectively⁵⁶. As a result, it is likely to name Ang 1-7 as a pan-hematopoietic cytokine proliferative agent as it boosts many important phases in hematopoiesis and myelopoiesis^{27,29,33,48,49,56,57}. So, nowadays many experimental studies are going to make an Ang 1-7 drug for the regulation of local BM RAS-mediated hematopoiesis in different clinical situations^{33,48,49}. The ACE2/Ang (1-7)/Mas receptor-axis-oriented drugs are especially promising³².

Another effect of Ang-II over BM AT1 receptors is the management of monocyte-lineage cells that implies proatherogenic effects in the cardiac microenvironment^{53,58}. Macrophage growth requires AT1 signaling. In a study which was conducted by Tsubakimoto et al⁵³ with BM chimeric apoE(-/-) mice re-populated with AT1-deficient (Agtr1(-/-)) or wild-type (Agtr1(+/+)) BM cells, Ang-II were found to control the c-Fms in HSCs and monocytic cells over BM stromal cell-derived TNF-alpha in order to increase macrophage-colony-stimulating factor (M-CSF)-induced management of monocytic cells. In this investigation, it was proposed that the M-CSF-induced transformation from HSCs (c-Kit(+)/Sca-1(+)/Lin(-)) to promonocytes (CD11b(high)/Ly-6G(low)) was decreased in HSCs from AT1-deficient Agtr1(-/-) mice⁵³.

RAS and Erythropoiesis

It is known that ACE-knockout mice develop anemia. The treatment of this anemia with an injection of Ang-II is the evidence of the main

role of Ang-II in erythropoiesis^{59,60}. Ang-II increases erythropoiesis by increasing erythroid progenitors^{8,61-63}. Kato et al⁸ suggested that persistent erythrocytosis develops in mice that have both the human renin and angiotensinogen genes. On the other hand, in BM transplantation studies, AT1a receptors on BM-derived cells were shown to be unnecessary for RAS linked erythrocytosis⁸. Kaneko et al⁶¹ found that in BM erythroid cells there are (Pro)renin receptors (PRRs), and these PRRs are amplified by IFN-gamma. So, IFN-gamma, an inflammatory cytokine seems to inhibit erythropoietin secretion and erythropoiesis. Erythroid cells contain PRR freely from their differentiation phases. After (pro)renin binds PRR, mitogen-activated protein kinase (MAPK) ERK1/2 signaling pathways are stimulated⁶¹. As a result, local BM RAS controls erythropoiesis by autocrine and intracrine ways. The (pro)renin receptor has recently come out as part of the RAS⁶⁴. The human renin/prorenin receptor (RER) has been found in the intracellular perinuclear zone. In addition, promyelocytic zinc finger protein (PLZF), which is a transcription factor, was recently acknowledged as a protein interaction partner of the renin receptor. After renin binds to RER, PLZF moves from the cytoplasm to the nucleus, enabling positive or negative control of target genes⁶⁵. PLZF in CD34(+) cells and early erythropoiesis manages the c-kit expression transcriptionally⁶⁶. Ang II-induced cellular effects through an AT2 receptor-dependent signaling pathway is controlled by PLZF over AT2 receptor. The angiotensin II-AT2-PLZF-GATA4 signal contributes in the control of Ang-II linked pathological changes⁶⁷. However, these issues still need to be clarified by future experimental studies. Savary et al⁶⁸ proposed that the local RAS exists in a primitive embryonic erythropoiesis located in the yolk sac of the chicken embryo. Yolk sac endoderm contains ACE, renin, angiotensinogen, and AT receptor alongside with the variation of blood islands in the adjacent yolk sac mesoderm. ACE and Ang-II receptor blockers were found to reduce erythroblast production, which was stimulated by RAS. As a result, it can be concluded that the local autocrine RAS plays a role in the regulation of both primitive and definitive erythropoiesis. ACE inhibitors or angiotensin receptor blockers decrease hematocrit levels. The reason for this may be the RAS inactivation by these drugs in the BM cellular autocrine RAS network⁶⁹.

RAS also has a role in the regulation of pathological and neoplastic erythropoiesis. Angiotensin II receptor type 1 in erythroid progenitors was thought to play a role in the postrenal transplant erythrocytosis⁶². It has also been suggested that in BM of polycythemia verae (PV), there are mRNAs that consist of augmented local production of the RAS elements. As a result in PV, there is an increase in local BM RAS while BM CD143 receptors decrease⁴⁰.

RAS and Thrombopoiesis

AGTRAP (i.e., Angiotensin II Receptor-Associated Protein) is an element of RAS systems that plays a role in hematopoiesis. It also amplifies the thrombopoietin receptor Mpl⁹. Megakaryocyte growth and thrombocyte development are mediated by the Mpl proto-oncogene. Also, Mpl proto-oncogene controls the HSC homeostasis and self-renewal⁷⁰. Furthermore, Mpl signaling is essential for HSC homeostasis. Retroviral insertional mutagenesis was achieved in a study by Kwiatkowski et al⁹. Kwiatkowski et al⁹ conducted this study by an MSCV established vector coding for a drug dependent, dimerizable, fusion protein, which has the cytoplasmic part of Mpl. With the help of this vector, the gene arrangement can be disturbed by insertion, and neighboring genes can be augmented by the intact long terminal repeats of the vector. In another study, a vector is used as a transducer of the human leukemia cell line K562 that contains all RAS components⁴⁵. Without Mpl signaling, the cell perished after erythroid differentiation.

Mutations that are synergistic with Mpl signaling are probably in cells that gain a proliferative state and need Mpl function. Over-represented clones are easily detected by cloning of retroviral integration sites (RIS) from particular populations. RIS indicates a gene that may cooperate with Mpl. A RAS protein named Angiotensin II Receptor-Associated Protein (AGTRAP) has been detected from these indicated genes⁹.

Kwiatkowski et al⁹ tried to clarify the role of AGTRAP. They proposed that Mpl signal stimulates K562 cells, and AGTRAP is highly present in K562 cells. The high presence of AGTRAP expression in K562 cells results in an increase in K562 cells by reducing the doubling time.

Mpl-dependent K562 cell production is amplified by Mpl signaling by AGTRAP. Mpl signaling and JAK2 is essential for Mpl dependent K562 cells that express AGTRAP. The proliferation of HEL cells that have the homozygous

Jak2V617F mutation is inhibited by the AGTRAP. The presence of AGTRAP over-sensitized UT7/TPO cells and recombinant human megakaryocyte growth and development factor (rhMGDF) increases the proliferation of cells by a little amount of rhMGDF⁹.

Thrombotic and inflammatory effects develop with the platelets that contain AT1 receptors⁷¹. Platelet production indicators and *in vivo* platelet activation are amplified by Ang-II⁷². When Ang-II was given, rolling thrombocytes, adhered thrombocytes on the leukocytes and the endothelial cells, rolling leukocytes, and adhered leukocytes, as well as an escalation in thrombocyte-leukocyte-endothelial cell relations by means of dose and time in the cerebral veins, were observed⁷¹.

RAS and Other Blood Cell Lineages: Dendritic Cells, Mast Cells, T-lymphocytes, Monocytes, Macrophages, and Antigen-Presenting Cells

There are many previous studies reporting that local RAS plays a role in hematopoietic cell production and development. Furthermore, local RAS is also involved in the development of antigen presenting cells, T-lymphocytes, dendritic cells, mast cells, monocytes, and macrophages^{4,5}. Cleavage of a C-terminal dipeptide or tripeptide is necessary for the degradation of substance P (SP) in the BM microenvironment, lymphoblasts, and lymphocytes by ACE¹².

Antigen-presenting cells (APCs) have local RAS in the cellular part of the immuno-hematological structure. T cells and APCs have AT1R⁵⁸. Dendritic cells need the Ang-II type 1 receptor for their normal growth and functionality⁷³⁻⁷⁵. T cells are stimulated via dendritic cells that are focused APCs on this function. If Ang-II binds the AT1 receptor, dendritic cell production is augmented; however, Ang-II and AT2 receptor creates inhibitory effects on this process^{12,75}.

Nahmod et al⁷⁵ investigated the role of Ang II and AT1 and AT2 receptors in dendritic cell development. Dendritic cell development is suppressed by pharmacologic inhibition of the AT1 receptor in a GM-CSF-amplified culture. As a result, surface maturation indicators reduced, endocytosis decreased, and allogeneic T cell production suppressed. However, AT2 inhibition or Ang II injection to culture had contrary function and augments progenitors in gaining the role of the dendritic cells⁷⁵. BM-derived dendritic cells with a low level of AT1a secreted greater amounts of

monocyte chemoattractant protein-1⁷⁴. The production of dendritic cells contains major modifications in their features without AT1a and/or AT1b subtypes⁷³. Dendritic cells are stimulated by Ang-II with autocrine and paracrine ways by AT1 that results in sustaining the inflammatory reactions⁷³.

The role of RAS on dendritic cells and APCs has a part in the underlying mechanism for immune-inflammatory diseases. Stegbauer et al⁵⁸ observed an increase in renin, ACE, and AT1R in the immune system in the myelin-oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis. Also, they detected an increase in renin, ACE, and AT1R in the immune system by quantitative RT-PCR method⁵⁸. In the course of inflammation, the local RAS is stimulated in the immune system. The local RAS controls the APC populations and the chemokines by AT1R through autocrine-paracrine-intracrine pathways. The amounts of CD11b+ or CD11c+ APC in the immune system and the spinal cord were decreased by the inhibition of AT1R. Also, inhibition of AT1R damages the presence of CCL2, CCL3, and CXCL10 as well as CCL2-stimulated APC⁵⁸.

Mast cells secrete an effective growth factor, preformed Ang-II. Hara et al¹⁰ proposed that the mast cells contain the pre-formed Ang-II and RAS system. Calcitonin gene-related peptide (CGRP) controls the Ang-II in mast cells. CGRP has two main effects. Firstly, the secretion of Ang-II is increased. Secondly, the amount of angiotensinogen mRNA in a human mast cell is augmented by CGRP. Neural activity controls mast cells, which could be named mobile RAS. Secretion of Ang-II in the organs correlates with the amount of mast cells¹⁰.

The Tissue Ras System in Other Organs

The RAS system is present in several tissues of the human body. Nehme et al⁵² proposed preliminary atlas for the organization of RAAS across 23 different normal human tissues. The extended RAAS (extRAAS) system is defined as a set of 37 genes encoding classical and novel RAAS participants, including glucocorticoids and mineralocorticoids. MAS1, prorenin, and renin receptors, as well as LNPEP-IRAP, are found to be important factors in RAS system among different tissues. For example, MAS1 and ACE2 were expressed in the kidney, whereas LNPEP-IRAP was not. This atlas has enabled us to understand the variability of RAS system for

each different tissue. As a result, it can be concluded that in the near future, tissue-specific targeted therapy may be possible.

The immune system has a major role in the pathogenesis of hypertension. T-lymphocytes, which are based on the vasculature and renal system, may augment elevated blood pressure if these lymphocytes are activated and gain pro-inflammatory features. Elevated sympathetic nerve activity and norepinephrine secretion is accused to be the main reasons for the activation of the immune system in hypertension onset. On the other hand, increased sympathetic activity is known to act as an immunosuppressor, and patients with hypertension have a vulnerability to infections. As a result, it may be interpreted that in hypertension, norepinephrine stimulates particular immune cells while inhibiting others.

Ang-II controls the activation of T-lymphocytes; thus, Ang-II actually regulates the immune system⁷⁶. However, the exact mechanism of action remains unclear. For the present, it seems that in the treatment of hypertension, targeting the immune system, which is manipulated by the sympathetic nervous system, will result in a decrease in blood pressure as well as immunosuppression unless specific treatment modalities are developed⁷⁶.

Both cardiovascular protective and deleterious arms of RAS modulate the vasoreparative functions of CD34 cells⁷⁷. The ACE2/Ang-(1-7)/Mas axis stimulates vasoprotection-relevant effects of these cells. In contrast, the ACE/Ang II/AT1 axis either directly or indirectly attenuates CD34 cell functions. As a result, relative expression of the two axes of local RAS in CD34 cells can be a good measure of their vasoreparative effects. Along similar lines, an imbalance to the augmented expression of the ACE/Ang II/AT1 axis would stimulate dysfunction of CD34 cells and can be a prognostic marker for an increased risk for the development of cardiovascular disease⁷⁷.

The bone marrow has been shown to have multiple roles in disease and tissue healing⁷⁸. Bone marrow-derived stem cells have been revealed to maintain tumor development and metastases by the release of mesenchymal stem cells and endothelial progenitor cells. Bone marrow cells assist as the progenitor for end-organ cells. Cardiac stem cells, which have important potential to advance cardiac function, are replenished after myocardial injury over proliferation and release of bone marrow-derived stem cells. Genotypic or phenotypic differences in bone

marrow stem cells can lead to the generation of inflammatory cells with varied activity leading to altered end-organ function⁷⁸.

BM contributes to hypertension by increasing peripheral inflammatory cells and their extravasation into the brain. Minocycline is an effective treatment to alter neurogenic elements of hypertension. BM-derived cells are involved in neuroinflammation, and targeting them may be an innovative strategy for neurogenic resistant hypertension therapy⁷⁹.

Bone marrow-derived hematopoietic stem cells (HSC) can show incredible differentiation activity in numerous non-hematopoietic organs. This enigmatic procedure is named 'stem cell plasticity' (SCP). HSC may endorse structural and functional repair in several organs, such as the heart, liver, brain, and skeletal muscle via the SCP⁸⁰.

Local Renin-Angiotensin System in Primitive Embryonic Hematopoiesis

First multipotent, hematopoietic cells that contain the stem cells of the fetal and postnatal blood elements develop in the human embryo. The umbilical cord blood (UCB), the fetal liver, embryonic para-aortic splanchnopleura, hematopoietic cells in the aorta gonad mesonephros (AGM) area is the primitive hematopoietic cells through embryonic hematopoiesis²¹. Many studies concentrated on the ACE (CD143) together with the local RAS²¹⁻²⁴ and human embryonic HSCs⁸¹. The development and function of the hematopoietic system are controlled by local RAS since embryogenesis²³. A HSC indicator, which is a somatic isoform of ACE (CD143), is detected by monoclonal antibody (mAb) BB9. BB9 has reactivity with embryonic cells at all phases of hematopoietic ontogeny²¹. Common yolk sac-like precursors such as ACE+CD45-CD34+/- cells have the role of progenitor for endothelium, primitive, and definitive human lymphohematopoietic stem cells²⁴.

Endothelial cells within the yolk sac, placenta, and aorta form the multilineage hematopoietic stem cells (HSC) and progenitor cells throughout embryogenesis⁸². Jokubaitis et al²¹ suggested that ACE, as detected by mAb BB9, is an indicator of primitive hematopoietic cells at all phases in the development of the hematopoietic system. In this study, it was found that during the formation of the human hematopoietic system, BB9/ACE was detected. Also, BB9 was detected in the somatic form of ACE. Moreover, disturbance of

RAS signaling changed the development of primitive hematopoietic progenitors²¹. Zambidis et al²⁴ found that the hemangioblast differentiation is controlled by RAS. The human hemangioblasts were found to contain AT1 and AT2²⁴. Moreover, the transformation of hemangioblasts to progenitors is associated with the regulation of signals over major Ang-II-binding receptors, AT1 and AT2²⁴. In this study, the primitive and definitive Yolk Sac (YS)-like hematopoiesis is stimulated by ACE that was found on the hemangioblast surface. Embryonic hematopoiesis' progenitors were detected by ACE expression and growth and development of human embryonic hemangioblasts were controlled by RAS. The growth of human hemangioblast colony is reduced by captopril because captopril decreases the ACE activity. Local RAS function leads to the stimulation of human angio-hematopoiesis from an ACE-hemangioblastic precursor of embryonic and definitive hematopoiesis²⁴.

Sinka et al²² investigated the existence of ACE in the earliest, pre-aorta-gonad-mesonephros (AGM) phases of human intraembryonic angio-hematopoiesis. In this research, in the initial phases of human development, the hematopoietic potential in the splanchnopleura is limited to evolving CD34-ACE+ precursors. ACE+CD34-CD45- mesodermal progenitors transferring from the splanchnopleura to the ventral aorta augment the CD34+ intra-aortic hematopoietic clusters. The yolk sac, splanchnopleura, aorta, fetal liver, and BM in the human embryo are the hematopoietic tissues that comprise ACE. ACE has important roles for the preservation of embryonic hematopoiesis²². These findings correlate with the statement of BM as a local RAS^{1,2}. Sinka et al²² detected the BM ACE presence in the long bones of human embryos and fetuses by flow cytometry. They found that the ACE present at the surface of CD34+CD45- cells and of some CD34-CD45+ cells, which are the first endothelial and hematopoietic (probably monocyte-macrophage) cells, create the marrow cavity. CD34-CD45, which are early hematopoietic precursors, are identified by ACE. Hematopoiesis present in the medullary cavity at the phases after 14 weeks and ACE identifies CD34+CD45- endothelial cells but also CD45+CD34+ hematopoietic cells. At this phase, some ACE+ cells do not have CD34 and CD45, and they represent mesenchymal cells

in the BM microenvironment. CD34+ACE+ cells are found in the fetal liver and BM long-term blood-founding cells²².

The hematopoietic stem cell niche can help the differentiation of hemangioblasts in YS or AGM²¹⁻²⁴. The selection of development of hemangioblasts into either hematopoietic precursors or vascular endothelial networks is decided by the antagonistic competition between AT2 and AT1 for Ang-II binding on developing hemangioblasts. In embryonic and definitive hematopoiesis, AT1/AT2-controlled stem cell development may be a widespread phenomenon. As a result, in order to develop the multipotent hematopoietic precursors from embryonic HSC, the angiotensin receptor signaling may be manipulated.

The phrase “stem cell plasticity” represents the hypotheses about local BM RAS and the cellular development function of HSCs¹⁹. Post-natal HSCs have marked ability for cellular differentiation in different tissues. These HSC functions imitating primitive hematopoiesis are dependent on and responsive to the definite signals existing in the local tissue microenvironment. The RAS hypothesis has been suggested about HSC homing and stem cell plasticity to create cardiomyocytes in the cardiac microenvironment, with the source of data regarding the local cardiac and BM RAS¹⁹. Renewing myocardial tissue could use monitoring roles on circulating or resident stem cells by the locally active RAS. Cardiac RAS and hematopoietic RAS could cooperate to sustain tissue roles since local RASs exist in different tissues¹⁹. On the other hand, there is no data to verify this hypothesis. The development and differentiation of BM mesenchymal stem cells into cardiomyocyte-like cells are stimulated by Ang-II and 5-azacytidine⁸³. The hypotheses regarding RAS and HSC plasticity in different tissues such as the heart, kidney, brain, muscle, nerves, and pancreas are supported by clarification of the existence and function of angiotensin peptides in primitive hematopoiesis²¹⁻²⁴. There is an association between angiotensin and transdifferentiation of epithelial cells into fibroblasts. Kidney growth is also mediated by local embryonic RAS. The renal capacity to create its blood cells concurrently with *in situ* blood vessel formation is pointed out by the course of hemovasculogenesis closely associated to the roles of the local RAS⁸⁴. Additional studies shall concentrate on these hypotheses in different experimental settings.

Renin-Angiotensin System in the Basic Pathobiological Events of Carcinogenesis and Cancer

Dysregulation in a complex series of neoplastic pathobiological actions leads to carcinogenesis. The associations of RAS in neoplasia symbolize a model for improved understanding of the place of local BM RAS in hematological tumoral diseases. The complex pathological network of neoplasia includes the inequity between cellular proliferation/differentiation and apoptosis related to the immunopathological modifications and the genomic dysregulation due to somatic and/or germline mutations, neoplastic intracellular signalling due to oncogenic autocrine-paracrine-intracrine possessions, neoplastic angiogenesis, fibrosis in the neoplasia microenvironment, and pathological mobilization of neoplastic cells^{50,85,86}. One of the critical elements in the tumor microenvironment is the local RAS, and it has vital effects in cancer metabolism, survival, angiogenesis, and invasion processes⁸⁷.

Local tissue RAS affects cancer development and metastases in an autocrine and paracrine way by the modulation of many neoplastic events, such as angiogenesis, apoptosis, cellular increase, immune answers, cell signaling, and extracellular matrix development. The development and stimulation of tumoral cells are controlled by locally formed Ang-II in intrahepatic cholangiocarcinoma tissues⁸⁸. Possible management of the local RAS with various enzymes, peptides, and feedback mechanisms can even symbolize a treatment target for the clinical control of neoplasia^{50,85,86}.

DNA damage with single and double strand breaks are stimulated by Ang-II. The evidence of AT1 mediated DNA injury has been shown in a study which proposes the AT1 receptor blocker candesartan avoids all kinds of damage due to Ang-II⁸⁹. The progression of pancreatic cancer may be postponed by enalapril together with aspirin⁹⁰. Moreover, the creation of invasive murine pancreatic cancer in a genetically engineered mouse cancer model can be somewhat prevented by enalapril and aspirin⁹⁰. Similarly, losartan increases the effectiveness of systemically administered nanotherapeutics to highly fibrotic solid neoplasias, such as pancreatic adenocarcinomas⁹¹.

The future of RAS blockers in cancer treatment has been described in two directions⁹². As a first approach, protocols using these drugs as chemo-prophylactic agents could be considered

to reduce cancer rates. The limited efficacy of long-term use to compensatory rises in renin of ACEIs and ARBs can be a limitation, where strategies such as the combination of RAS blockers with a renin inhibitor should be anticipated. Despite the multiple limitations, chemoprevention is thought to be a realistic method for decreasing the rate of cancer, and RAS blockers constitute a great potential approach. Another direction can be the use of RAS blockers as coadjuvant agents in cancer therapy; however, the side effects may be a major problem⁹².

RAS and Apoptosis and Leukemia

Whether neoplastic cells experience apoptosis or survive in response to RAS activation was decided by the biological actions of angiotensin receptors, AT1 and AT2, and pathological changes in their signaling⁸⁶. There are contradictory studies regarding apoptosis and RAS associations^{26,28,86}. Signaling over AT2 is always linked to the increase of apoptosis; however, stimulation of AT1 by Ang-II in neoplastic cells can improve pro-survival anti-apoptotic signaling⁹³. Different governing, biological, inflammatory, angiogenic, proliferative, and apoptotic activities are created by AT1 signaling relating with AT2 and/or the MAS receptor. Over activity of the RAS axis stimulates apoptosis in the cardiac microenvironment⁹³. The effect of angiotensin receptor relations in cellular apoptosis have been investigated in cardiomyocytes⁹⁴. Staining for Caspase-3, an apoptotic indicator, showed that increased the expression of AT1, as well as AT2, leads to cardiomyocyte apoptosis with a modifications in the expression of the apoptotic molecules annexin V, Bax, and Bcl2. AT1-related cardiomyocyte apoptosis could be somewhat controlled by the increase of endogenous AT2. AT2 over-expression related cardiomyocyte apoptosis by an increase of iNOS⁹⁴. Ghrelin could have an antagonistic effect in Ang II-related cardiomyocyte apoptosis by reducing AT1 receptor expression and hindering the stimulation of the endoplasmic reticulum stress pathway⁹⁵. In contrast, it was shown in mouse models that the RAS blockade normalized nephrotic the ACE2 expression and urinary Ang (1-7) levels, avoided tubular apoptosis, and decreased pro-fibrotic and pro-apoptotic gene expression⁹⁶. RAS signaling has been associated with improved survival and augmented proliferation of tumor cells. Apoptosis-increasing effects of the RAS are controlled by AT2 or the MAS receptor; however, apoptosis-reducing effects are

associated with AT1 signaling⁸⁶. RAS has been associated with the reduction of ERK signaling and the stimulation of cell death receptors that result in apoptosis. On the other hand, AT1 stimulates mitogenic signals together with MAPK or PI3K pathways and results in the downstream stimulation of transcription factors along with nuclear factor- κ B (NF- κ B), which is accountable for the production of different anti-apoptotic proteins, such as BCL-XL, survivin, and BCL2⁸⁶. While the role of RAS in the apoptotic course is not similar, those pathobiological data associated with apoptosis highlight the effect of the local RAS in carcinogenesis.

Telmisartan, an angiotensin II receptor blocker, induces apoptosis in Adult T-cell leukemia cells⁹⁷. Adult T-cell leukemia (ATL) is a T-cell malignancy that presents after human T-cell leukemia virus (HTLV-1) infection. The transcription factor PPAR plays various roles in lipid metabolism, immune response, cellular differentiation, and apoptosis. Telmisartan is well known for its unique ability to activate PPAR. It is found that telmisartan also induces significant growth inhibition and apoptosis in leukemia cell lines from ATL patients by caspase activation (caspase-3, 8, and 9) in leukemia cells. Also, telmisartan increases the LC3-II-enriched protein fraction, demonstrating autophagosome accumulation.

RAS, Cellular Proliferation-Differentiation and Leukemia

The development of progenitor cells is stimulated by RAS. The cellular renin, the Ang-II secretion, the presence of AT2 receptor, and a reduction in angiotensinogen and ACE expression are related to cellular development⁹⁸. DNA creation can be stimulated by Ang-II over AT1 as well as the generation of superoxide and phosphorylation of the important oncogenic signaling pathways JAK/STAT3 and p38 MAPK⁹⁹. The AT2 receptor has an inhibitory effect on cellular development⁹³. Throughout tumor development, angiotensin peptides have an effect in pathological cellular development. Developmental processes and homeostasis are regulated by angiotensin-generating cascades. Stimulation of the up-regulated AT1 receptor by Ang-II leads to the proliferation of breast cancer¹⁰⁰. The promotional roles of Ang-II on cancer development are reliant on modifications in cell cycle machinery and downstream AT1 signaling actions. Stimulation of the Ras-Raf-MAPK pathway and the tran-

scription factors NF-kappaB and CREB takes on a role in tumor cellular development amplified by Ang-II. AT1 blockers (ARBs) could inhibit the proliferative roles of angiotensin peptides. Activated AT1R in AT1R(+)-MCF-7 breast cancer cells *in vitro* controls p53, PCNA, and cyclin D1, which are also modified by Irbesartan¹⁰⁰.

Bone marrow contains a progenitor that expresses renin throughout development and possesses a B-lymphocyte pedigree that needs RBP-J to differentiate¹⁰¹. The precursor B-cell gene programme is enriched, and lymphocyte differentiation is constrained by the deletion of RBP-J in renin-expressing progenitors. This process is facilitated by H3K4me3-activating marks in genes that control the pre-B stage. As a result, neoplastic transformation occurs in mutant cells, and highly penetrant B-cell leukemia with multi-organ infiltration develops, which results in death.

RAS and Intracellular Signaling and Leukemia

An intracellular system is present in local tissue RAS, which takes part in cell signaling and function. Intracellular or nuclear RAS could have a significant effect in the pathobiology of RAS. The G-protein and the non-G protein associated signaling pathways can be stimulated by Ang-II with AT1 receptors. Local intracellular RAS requires different signaling pathways, such as MAPK kinases (ERK 1/2, JNK, p38MAPK), receptor tyrosine kinases (PDGF, EGFR, IRS-1), and non-tyrosine receptor kinases (Src, JAK/STAT, FAK). Focal adhesion and extracellular matrix development are related with scaffolding proteins, such as paxillin, talin, and p130Cas, which are increased by Ang-II. These signaling cascades cause cellular development, cell movement, and disease advancement²⁸. The JAK-STAT pathway, a significant intracellular signalling system for many hematopoietic growth factors, functions as a bridge between the elements of the local RAS in the bone marrow and neoplastic hematopoietic diseases^{18,20,53}. Intracellular presence of all angiotensin receptor subtypes is obvious in the nuclear compartment^{102,103}. The AT1 receptor is tied to the group of reactive oxygen species (ROS) over the stimulation of phosphoinositol-3 kinase signaling; however, the AT2 and Ang 1-7 receptors augment nitric oxide (NO) generation¹⁰². The gamma-aminobutyric acid (GABA) receptor-associated protein (GABARAP) is related to the AT1a receptor. GABARAP increases the stimulation of the Ang-

II-related phospho-ERK1/2 signaling pathway. Peptides that were intended to inhibit the AT1-GABARAP relationship efficiently decrease intracellular gathering of AT1 and receptor gathering, cell surface expression, and signaling¹⁰³.

Similarly, the biological actions of the endogenous RAS peptide, Ang (1-7), are controlled by suppression of the PI3K/Akt, P38, and JNK signaling pathways⁸⁷. Ang (1-7) and its receptor Mas inhibits proliferation. Ang (1-7) suppresses both the development of human lung neoplastic cells *in vitro* and cancer angiogenesis *in vivo* over stimulation of the Mas receptor. Ang (1-7) has an inhibitory role on metastasis, migration, and invasion in A549 human lung adenocarcinoma cells⁸⁷. Also, Ang (1-7) takes part in the mobilization of hematopoietic cells^{29,32}. Notably, Ang (1-7) has dual effects. Although Ang 1-7 inhibits the development of neoplastic cells, it stimulates the mobilization of hematopoietic cells. Ang (1-7) augments hematopoietic recovery after radiation therapy. Also, angiotensin peptides stimulate hematopoietic recovery after myelosuppression^{48,49,104}. The myelosuppressive treatments assessed included total body irradiation and intravenous administration of two dissimilar chemotherapeutic drugs. The rises were most reflective and longest lasting in the bone marrow, similar to the detected roles on early progenitors and effects on blood cell lineages, counting detected rises in red blood cell (BFU-E) and platelet (CFU-Meg) progenitors after Ang (1-7) therapy. Furthermore, Ang-(1-7) increases dendritic cell functions and takes a part in the development of human dendritic cells^{48,49}. The mechanism for the opposing cellular roles of Ang (1-7) is unclear, but Ang (1-7) modifies the balance and concentration among proliferative and anti-proliferative prostaglandins¹⁰⁵. Since Ang-II also uses eicosanoid pathways, the inconsistent cellular actions could be attributed to the dual roles on prostanoids.

The (pro)renin receptor ((P)RR) signaling is elaborate in many pathophysiology, ranging from cardiorenal end-organ damage to tumorigenesis. The transcription factor promyelocytic leukemia zinc finger (PLZF) is an adaptor protein of the (P)RR. (P)RR functions are mediated by its transmembrane and intracellular fragment that has a role as an accessory protein of V-AT-Pases. In a recent study, (P)R s signal transduction pathways have been shown to have roles in cardiovascular problems and tumorigenesis¹⁰⁶.

In the literature, the new role of RAS has been stated, in particular, Ang II distinct from other mutual functions, by considering its managing effect on the various signaling pathways involved in the cardiac and endothelial tissue as well as in stem cell transplantation¹⁰⁷. Stem cell therapy has been effective in avoiding and handling many diseases, including CVDs with a promising future¹⁰⁷.

RAS and Other Essential Pathobiological Events of Oncogenesis: Angiogenesis, Inflammation, Genomic Aberrations, and Immunological Dysregulation

Angiogenesis has an important role in carcinogenesis. Neoplastic angiogenesis is stimulated by local RAS. Vascular endothelial growth factor (VEGF) increases the pathological angiogenesis, and Ang-II stimulates VEGF¹⁰⁸. Benazepril has been shown to decrease the development of esophageal carcinoma xenografts. This effect has been shown to be created by the reduction of VEGF by benazepril, which eventually leads to inhibition of neoplastic angiogenesis. Similarly, the inhibition of the RAS by ACE inhibitors or ARBs noticeably decreased hepatocellular carcinoma (HCC) in addition to a reduction of angiogenesis¹⁰⁹. Also, in breast cancer and other tumors, the relationship between RAS and tumor angiogenesis has been detected^{85,108,110,111}. Ang-II escalates vascular permeability by secreting prostaglandins and the vascular endothelial cell growth factor or the reorganization of cytoskeletal proteins¹¹². Therefore, Ang-II has a major role in the cancer-related inflammatory process, cell growth, and matrix production. Moreover, Ang-II may have a role in the enrollment of inflammatory cells into the cancer tissue over the management of adhesion molecules and chemokines by resident cells. RAS stimulates the NF-kappaB and AP-1, which leads to the immunologically-induced inflammation and transcriptional regulation^{86,112}.

The effect of ACE gene polymorphism on gastric cancer development has been investigated¹¹³. ACE is present locally in the gastric tumor, and its gene polymorphism is related with metastasis. ACE genotypes are related to the metastases of lymph nodes and the Union for International Cancer Control (UICC) tumor stage. In that study, a few lymph node metastases and smaller UICC tumor stages ($p = 0.01$) were observed in gastric tumor patients with the II genotype than patients with the DD genotype¹¹³. Germline and

somatic mutations that result with local RAS dysregulation could stimulate neoplastic development in solid tumors, such as breast, lung, and gastric cancer^{86,114-116}. AT1 and AT2 are present locally in gastric tumor and the mixture of AT1 and ACE I/D gene polymorphism have an association with a nodal spread in intestinal type gastric tumors¹¹⁷. The DD genotype of ACE leads to an increased risk of squamous cell lung carcinoma¹¹⁸. Ang-II could stimulate cancer cell extravasation and metastasis¹¹⁹. The number of mice with metastases and the number and size of metastases per mouse were stimulated with the pre-treatment of cancer cells with Ang-II. *In vitro*, angiotensin II stimulates the cancer cell adhesion to endothelial cells, trans-endothelial immigration and tumor cell relocation across the extracellular matrix, thus expanding tumor metastasis. A total of 102 genes differentially expressed after Ang-II pre-treatment were detected by comparative DNA microarray¹¹⁹. Ang-II controls two groups of connected genes associated with its precursor angiotensinogen. Between those genes, the stimulated MMP2/MMP9 and ICAM1 are the most important ones that are involved in cell adhesion, migration, and invasion¹¹⁹.

Immunological dysregulation may lead to cancer development and progression. T and NK cells have the ability of secreting and delivering Ang-II to tissues since they have local RAS elements¹²⁰. By using the mRNA analysis, NK and T cells were shown to have renin, renin receptor, angiotensinogen, and angiotensin-converting enzyme. The co-stimulatory role of Ang-II and anti-CD3-induced T and NK cell development with Ang-II therapy were detected. AT1 and AT2 were present in monocytes, NK, and T cells. These receptors were effective in immunological actions, such as calcium signaling, chemotaxis, and development¹²⁰. Ang-II manages dendritic cell differentiation⁷⁵. Decreased functions of dendritic cells lacking in AT1 receptors have been detected⁷³. AT1 receptors regulate the differentiation and functions of dendritic cells and have a critical role in cellular immune actions where local angiotensinergic systems are stimulated.

Bernstein et al¹²¹ demonstrated a unique mouse model called ACE 10/10, presented high ACE in macrophages; however, ACE was missing from the blood vessels and kidney. It was detected that ACE 10/10 mice have a noticeable resistance to the development of an aggressive and usually used cancer model, B16 melanoma. ACE

10/10 mice reply to melanoma with a boosted inflammatory answer, counting augmented cancer-specific CD8+T cells. B16 tumor resistance is transferred directly with macrophages or the engraftment of wild-type mice with ACE 10/10 bone marrow¹²¹. ACE is the main peptidase that is involved in MHC class I antigen processing¹²¹. Moreover, ACE expression is increased with antigen presenting cell (APC) development, ACE controls surface MHC class I expression, ACE manages the MHC class I peptide repertoire, ACE edits self-antigens, ACE controls the exhibition of viral antigens, and ACE acts as a carboxyl dipeptidase on proteasome products, and therefore, ACE reduction or ACE over-expression affects immunogenicity¹²².

The Local Bone Marrow Renin-Angiotensin System in Neoplastic Hematopoiesis

Renin and Leukemia

The significance of renin presence as an abnormal leukemic indicator in acute leukemia has been detected by real-time PCR tests. Renin-like enzyme action changing angiotensinogen to angiotensin I has been identified in leukemic blast cells^{44,123,124}. A definite immunoreactive renin-like peptide of 47 kDa was obtained from acute myeloid leukemia (AML) blast cells. Renin is present in certain myeloid human leukemia cell lines, such as K562, KU812, and MEG-01⁴¹. The renin system is detected in the *in vitro* model of the K562 leukemic cell line. Renin, angiotensinogen, and ACE are detected in multipotential, hematopoietic neoplastic K562 leukemic blast cells⁴⁵. Renin expression was still present when K562 cells were put in the stimulators of growth inhibition and/or differentiation. Therefore, renin expression is related with a blastic phenotype rather than with cell development⁴¹. Casares et al⁴¹ suggested that renin is present in some myeloid blasts; however, normal BM does not have this expression. In this study, renin expression was detected in cells from AML, chronic myeloid leukemia (CML), and acute lymphoid leukemia (ALL). The highest renin presence was detected in AML cases, which was approximately 47.2% of the cases. After the complete remission of AML, renin presence was gone⁴¹. Inigo et al⁴² investigated 76 samples from AML cases, with follow-up of positive cases. At diagnosis, renin was present in thirty-one cases (41%). All

renin-positive cases at diagnosis have no expression throughout complete remission (CR); however, the expression returned in relapse and persistent cases, when the disease was refractory to therapy⁴². In AML and myelodysplastic syndromes, many different NUP98 fusions were detected, and the chimeric protein NUP98-HOXA9 was one of them. Primary human CD34+ hematopoietic cells are managed by NUP98-HOXA9 in terms of differentiation, proliferation, and gene expression. NUP98-HOXA9 may increase the numbers of erythroid precursors and harm myeloid and erythroid development. Augmented renin gene activity was observed during NUP98-HOXA9 boosted blast development^{125,126}.

The (pro)renin receptor [(P)RR] is very important in the RAS system since it has important functions in cardio-renal pathophysiology. (P)RR has angiotensin II-dependent and angiotensin II-independent effects. The catalytic activity of prorenin increases 5-fold when renin binds to (P)RR. The (P)RR cooperates with promyelocytic leukemia zinc finger protein (PLZF) and Wnt receptors and domains of the (P)RR are vital for V-ATPase activity. High glucose induces (P)RR signal transduction; however, deglycosylation of prorenin eliminates its intrinsic effect in neuronal and epithelial cells¹²⁷. In a study, the PLZF translocation blocker genistein and the specific V-ATPase inhibitor bafilomycin is used to separate three distinct sub-pathways downstream of the (P)RR¹²⁷. The V-ATPase is associated with robust pro-proliferative effects, but prorenin causes moderate proliferation *in vitro*. On the other hand, PLZF does not affect cell number.

RAS in bone marrow is suggested to increase cellular proliferation and differentiation. Renin in myeloid blast cells' cytosol has been demonstrated, and some blast cells from some types of AML have also expressed renin. 77 % of AML and 100% of ALL patients were detected as renin positive in a previous study¹²⁸. Renin expression disappeared with hematological remission and returned with relapse¹²⁹. ACE inhibitors and the AT1 receptor antagonist exert an antiproliferative and apoptotic activity on leukemic cells¹²⁹.

Angiotensin Converting Enzyme (ACE) and Leukemia

The existence of ACE in hematopoietic stem cells during hematopoietic ontogeny shows that embryonic hematopoiesis²¹⁻²⁴ characterizes the effect of the ACE in neoplastic hematological diseases, including neoplastic hematopoiesis.

The presence of ACE in human embryonic lymphohematopoietic cells, an embryonic, fetal, and adult hematopoietic tissue²¹⁻²⁴, shows the role of RAS on neoplastic tissues. Immunohistochemical investigations have revealed the potential effect of ACE/RAS in BM by assessing ACE presence in normal BM, several myeloproliferative diseases, and myelodysplasia⁵¹. ACE and p53 presence were observed in CD34+ cells in cases with acute leukemia throughout and after induction therapy⁴³. ACE presence in macrophages in lymph nodes of Hodgkin lymphoma has been observed¹³⁰, and the role of ACE was also related with multiple myeloma^{131,132}. ACE over-function results in quicker hydrolysis of the AcSDKP peptide that reduces in BM tissues, enabling HSC to go in the S phase of the cell cycle^{4,16,34}. ACE controls the serum concentration of AcSDKP, which is a negative controller of the development of normal hematopoietic stem cells^{14-16,133}. *In vitro* incubation of AML cells with an ACE inhibitor inhibits the development and colony-forming skill of AML cells. When Ang-II peptide added to AML cells, the colony-forming skills of those cells are decreased¹³³. A high presence of ACE (CD 143) surface antigen in leukemic myeloid blast cells has been observed with flow cytometric tests. Furthermore, a positive association has been detected among ACE and bone marrow blast count³⁵. ACE insertion/deletion (I/D) gene polymorphisms in cases with hematological malignancies were investigated together with acute and chronic leukemia, myelodysplastic syndrome, and multiple myeloma¹³⁴. In that study, 80.4% of the cases had an ID/II genotype versus 55.9% in the control group, and there were 3.2 times increased disease risk in the existence of the insertion allele (ID/II)¹³⁴.

The role of the ACE I/D gene polymorphism were investigated in 108 PV and essential thrombocytosis (ET) patients who were positive for the JAK2V617F mutation¹³⁵. It was found that the ACE II genotype and I allele could be associated with increased risk of ET and PV. On the other hand, the DD genotype and D allele could be associated with decreased risk of ET and PV. This study also revealed that the ACE I/D gene polymorphism was independent of thrombosis.

Angiotensinogen and Leukemia

Renin, angiotensinogen, and ACE mRNAs were found to be present in human umbilical cord blood cells¹³⁶. In PV, the presence of angiotensinogen, ACE, and renin mRNA were

found to be increased⁴⁰. The angiotensinogen gene is present in leukocytes that are producing and secreting angiotensinogen, with the capacity of producing angiotensin⁵⁵. CML cases had increased ACE, angiotensinogen, and renin mRNA levels, which are reduced after the administration of imatinib. The presence of RAS elements was investigated in cases with CML at diagnosis and at 3, 6, and 12 months after diagnosis by quantitative real-time PCR. After taking imatinib, ACE, angiotensinogen, and renin, mRNA levels are reduced in CML cases that are elevated before drug administration. The RAS effects were expressively varied between Sokal risk groups of CML, underlining the changed biological effect of RAS in cancer. Thus, the hematopoietic RAS has a role in neoplastic cell creation that may be able to be changed by tyrosine kinase inhibitors, such as imatinib mesylate¹³⁷.

Angiotensin Peptides and Leukemia

Human CD34+CD38- cells, CD34+CD38+ cells, lymphocytes, and stromal cells contain AT1a receptors. Ang-II is the major effector peptide of RAS, and it stimulates the angiotensin type 1a (AT1a) receptors exist on CD34+ hematopoietic stem cells; as a result, hematopoietic progenitor cell development is increased²⁷. JAK-STAT is managed by Ang-II¹⁸. Angiotensin (1-7) also has a role in hematopoietic cell development^{48,49,56,57}. Ang-II stimulates erythroid differentiation in the BM with AT1 receptors⁶³. Ang-II was detected as an autocrine growth factor for AML⁴⁶. The RAS member AGTRAP is significant in hematopoietic cell development and existence and has a synergistic role with the development stimulating role of thrombopoietin receptor Mpl⁹. BM AT1r levels in myeloma cases presented a positive association with their BM infiltration pattern and tumor load, as detected with beta-2 microglobulin¹³². AT1aR in BM have an in-atherosclerosis development, as detected by testing various BM chimeric mice that have BM cells that were positive or negative for AT1aR. The presence of AT1aR on BM-derived cells could affect atherosclerosis by stimulating the infiltration of BM-linked inflammatory cells in the vessel wall. Inhibition of AT1R was not only in vascular cells. Also, in BM, this may be a significant strategy to avoid progression and destabilization of atherosclerotic plaques. As a result, local RAS has a role in the development of atherosclerosis to provide very significant signs to better understand the roles of the local hematopoiet-

ic RAS on the growth of cancer^{53,138-146}. The equivalent role of local RASs over the human body (including the myocardium, pancreas, pituitary gland, ovary, and kidney) in health and diseases characterize the correct source for the plan of future experimental investigation that tests this hypothesis⁴.

AT2R is involved in pancreatic cancer¹⁴⁷. The examination of pancreatic ductal adenocarcinoma (PDAC) species by immunohistochemical analysis revealed that a relatively strong AT1R expression was detected consistently in both normal pancreas and PDAC areas, whereas moderate AT2R expression was detected in 78.5 % of PDAC specimens and 100 % of the normal area of the pancreas. AT1R mRNA levels were considerably higher in the PDAC area than in the normal pancreas; however, there is no such relationship in AT2R mRNA levels. AT2R mRNA levels had a negative correlation with overall survival. These advances may enable a novel AT2R agonist to serve as an important therapeutic for PDAC therapy in future.

Angiotensin II-linked inflammatory pathways were up-regulated in many organ systems by gamma radiation. Wang et al¹⁴⁸ showed that ACE inhibitors and ARBs can reduce radiation-linked injuries in animal models that are exposed to gamma radiation. Also, an active angiotensin peptide DAA-I (des-aspartate-angiotensin I) was found to attenuate the deleterious actions of angiotensin II¹⁴⁸. It acts as an agonist on the angiotensin AT1 receptor and produces responses that oppose those of angiotensin II. Radioprotection was facilitated via the angiotensin AT1 receptor¹⁴⁸. Moreover, the radioprotection linked with an increase in circulating PGE2, and this finding proposes that PGE2 elaborates with the radioprotection in DAA-I-treated mice.

Future Perspectives

Local tissue RAS, counting local hematopoietic BM RAS⁴, is dynamic from embryogenesis²² to adult ages¹⁴⁹. As a result, understanding the roles of local RAS can characterize an important treatment choice for controlling cancer¹⁵⁰. The present medical application contains RAS-managing agents for the management of cardiovascular diseases. The roles of RAS inhibitors on circulating RAS are identified; however, their roles in the origin and development of cancer are still unclear^{50,151-154}. Future treatment methods for the modification of local BM RAS may concentrate on locally active molecules. The tetrapeptide

AcSDKP acts as a blocker of embryonic hematopoietic cell development and stimulates angiogenesis in BM stroma. As a result, Goralatide (tetrapeptide Acetyl-N-Ser-Asp-Lys-Pro) may be proposed as a probable treatment method in many different phases of hematopoiesis¹⁵⁵. The new agent of angiotensin 1-7 (Ang-1-7) is by now in Phase I/II clinical studies for the control of BM RAS in different diseases^{33,48,49}. However, since the main roles of the local RAS are in an autocrine, paracrine, and intracrine manner, future agents proposed to control local RAS roles should be organized to have a local targeted roles in the tissue microenvironment, such as the BM. For example, Kawabata et al¹⁵⁶ developed a nanoparticle vector to influence the efficacy of this cell-penetrating method for tumor-aimed gene transfer in the setting of intratracheal application. In the study, they showed that the bolus application of dTAT NP-encapsulated angiotensin II type 2receptor (AT2R) or TNF-associated apoptosis-stimulating ligand (TRAIL) cDNA evidently decreased cancer development. As a result, in that study, a unique gene transfer system was proposed that enables an active intratracheal method for lung cancer gene treatment¹⁵⁵. Kim et al¹⁵⁷ further highlighted the important regulatory roles of Ang II on HSC proliferation, differentiation, and engraftment. Chronic Ang II infusion regulates HSC proliferation, mediated by angiotensin receptor type 1a, Ang II accelerates HSC to myeloid differentiation and Ang II impairs homing and reconstitution potentials of the donor HSCs¹⁵⁷. Besides the already known effects of RAS¹⁵⁸, future investigational and clinical trials are thus required to explain the puzzling roles of local tissue RASs, including local BM RAS. These actions must concentrate on separating local RAS connections with the complex pathobiological features of cancer and on influencing autocrine-paracrine-intracrine systems for the improved clinical handling of neoplastic cases.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

- 1) HAZNEDAROGLU IC, TUNCER S, GURSOY M. A local renin-angiotensin system in the bone marrow. *Med Hypotheses* 1996; 46: 507-510.

- 2) HAZNEDAROGLU IC. A local renin-angiotensin system in the bone marrow still awaits its Christopher Columbus. *Exp Hematol* 1998; 26: 279-279.
- 3) STRAWN WB, RICHMOND RS, ANN TALLANT E, GALLAGHER PE, FERRARIO CM. Renin-angiotensin system expression in rat bone marrow haematopoietic and stromal cells. *Br J Haematol* 2004; 126: 120-126.
- 4) HAZNEDAROGLU IC, BEYAZIT Y. Local bone marrow renin-angiotensin system in primitive, definitive and neoplastic hematopoiesis. *Clin Sci* 2013; 124: 307-323.
- 5) HAZNEDAROGLU IC, OZTURK MA. Towards the understanding of the local hematopoietic bone marrow renin-angiotensin system. *Int J Biochem Cell Biol* 2003; 35: 867-880.
- 6) HUBERT C, SAVARY K, GASC JM, CORVOL P. The hematopoietic system: a new niche for the renin-angiotensin system. *Nat Clin Pract Cardiovasc Med* 2006; 3: 80-85.
- 7) LIN C, DATTA V, OKWAN-DUODU D, CHEN X, FUCHS S, ALSABEH R, BILLET S, BERNSTEIN KE, SHEN XZ. Angiotensin-converting enzyme is required for normal myelopoiesis. *FASEB J* 2010; 25: 1145-1155.
- 8) KATO H, ISHIDA J, IMAGAWA S, SAITO T, SUZUKI N, MATSUKA T, SUGAYA T, TANIMOTO K, YOKOO T, OHNEDA O, SUGIYAMA F, YAGAMI K, FUJITA T, YAMAMOTO M, NANGAKU M, FUKAMIZU A. Enhanced erythropoiesis mediated by activation of the renin-angiotensin system via angiotensin II type 1a receptor. *FASEB J* 2005; 19: 2023-2025.
- 9) KWIATKOWSKI BA, RICHARD RE. Angiotensin II Receptor-Associated Protein (AGTRAP) synergizes with mpl signaling to promote survival and to increase proliferation rate of hematopoietic cells. *ASH Annual Meeting Abstracts* 2009; 114: 3606.
- 10) HARA M, ONO K, WADA H, SASAYAMA S, MATSUMORI A. Preformed angiotensin II is present in human mast cells. *Cardiovasc Drugs Ther* 2004; 18: 415-420.
- 11) PARK TS, ZAMBIDIS ET. A role for the renin-angiotensin system in hematopoiesis. *Haematologica* 2009; 94: 745-747.
- 12) SHEN XZ, BERNSTEIN KE. The peptide network regulated by angiotensin converting enzyme (ACE) in hematopoiesis. *Cell Cycle* 2011; 10: 1363-1369.
- 13) HUANG YL, KUANG J, HU YZ, SONG YB, QIU RF, MAI WY. Bone marrow stromal cell transplantation combined with angiotensin-converting enzyme inhibitor treatment in rat with acute myocardial infarction and the role of insulin-like growth factor-1. *Cytotherapy* 2012; 14: 563-569.
- 14) COMTE L, LORGEOT V, BIGNON J, VOLKOV L, DUPUIS F, WDZIECZAK-BAKALA J, PRALORAN V. In vivo modifications of AcSDKP metabolism and haematopoiesis in mice treated with 5-fluorouracil and Goralatide. *Eur J Clin Invest* 1998; 28: 856-863.
- 15) COMTE L, LORGEOT V, VOLKOV L, ALLEGRAUD A, ALDIGIER JC, PRALORAN V. Effects of the angiotensin-converting enzyme inhibitor enalapril on blood haematopoietic progenitors and acetyl-N-Ser-Asp-Lys-Pro concentrations. *Eur J Clin Invest* 1997; 27: 788-790.
- 16) LI J, VOLKOV L, COMTE L, HERVE P, PRALORAN V, CHARBORD P. Production and consumption of the tetrapeptide AcSDKP, a negative regulator of hematopoietic stem cells, by hematopoietic microenvironmental cells. *Exp Hematol* 1997; 25: 140-146.
- 17) OLIVEIRA CR, PAREDES-GAMERO EJ, BARBOSA CM, NASCIMENTO FD, BATISTA EC, REIS FC, MARTINS AH, FERREIRA AT, CARMONA AK, PESQUERO JB, TERSARIOL IL, ARAÚJO RC, BINCOLETTI C. Myelopoiesis modulation by ACE hyperfunction in kinin B(1) receptor knockout mice: relationship with AcSDKP levels. *Chem Biol Interact* 2010; 184: 388-395.
- 18) HAZNEDAROGLU IC, ARICI M, BUYUKASIK Y. A unifying hypothesis for the renin-angiotensin system and hematopoiesis: sticking the pieces together with the JAK-STAT pathway. *Med Hypotheses* 2000; 54: 80-83.
- 19) OZTURK MA, GUVEN GS, HAZNEDAROGLU IC. How hematopoietic stem cells know and act in cardiac microenvironment for stem cell plasticity? Impact of local renin-angiotensin systems. *Med Hypotheses* 2004; 63: 866-874.
- 20) VRSALOVIC MM, PEJSA V, VEIC TS, KOLONIC SO, AIDUKOVIC R, HARIS V, JAKSIC O, KUSEC R. Bone marrow renin-angiotensin system expression in polycythemia vera and essential thrombocythemia depends on JAK2 mutational status. *Cancer Biol Ther* 2007; 6: 1434-1436.
- 21) JOKUBAITIS VJ, SINKA L, DRIESSEN R, WHITTY G, HAYLOCK DN, BERTONCELLO I, SMITH I, PÉAULT B, TAVIAN M, SIMMONS PJ. Angiotensin-converting enzyme (CD143) marks hematopoietic stem cells in human embryonic, fetal, and adult hematopoietic tissues. *Blood* 2008; 111: 4055-4063.
- 22) SINKA L, BIASCH K, KHAZAAL I, PÉAULT B, TAVIAN M. Angiotensin-converting enzyme (CD143) specifies emerging lympho-hematopoietic progenitors in the human embryo. *Blood* 2012; 119: 3712-3723.
- 23) TAVIAN M, BIASCH K, SINKA L, VALLET J, PÉAULT B. Embryonic origin of human hematopoiesis. *Int J Dev Biol* 2010; 54: 1061-1065.
- 24) ZAMBIDIS ET, PARK TS, YU W, TAM A, LEVINE M, YUAN X, PRYZHKOVA M, PÉAULT B. Expression of angiotensin-converting enzyme (CD143) identifies and regulates primitive hemangioblasts derived from human pluripotent stem cells. *Blood* 2008; 112: 3601-3614.
- 25) PAUL M, POYAN MEHR A, KREUTZ R. Physiology of local renin-angiotensin systems. *Physiol Rev* 2006; 86: 747-803.
- 26) LEUNG PS. The peptide hormone angiotensin II: Its new functions in tissues and organs. *Curr Protein Pept Sci* 2004; 5: 267-273.
- 27) RODGERS KE1, XIONG S, STEER R, DIZEREGA GS. Effect of angiotensin II on hematopoietic progenitor cell proliferation. *Stem Cells* 2000; 18: 287-294.
- 28) MEHTA PK, GRIENDLING KK. Angiotensin II cell signaling: physiological and pathological effects in

- the Cardiovascular System. *Am J Physiol Cell Physiol* 2007; 292: C82-97.
- 29) ELLEFSON DD, DiZERE GA, ESPINOZA T, RODA N, MALDONADO S, RODGERS KE. Synergistic effects of co-administration of angiotensin 1-7 and Neupogen on hematopoietic recovery in mice. *Cancer Chemother Pharmacol* 2004; 53: 15-24.
- 30) SHI RZ, WANG JC, HUANG SH, WANG XJ, LI OP. Angiotensin II induces vascular endothelial growth factor synthesis in mesenchymal stem cells. *Exp Cell Res* 2009; 315: 10-15.
- 31) LI Y, ZHANG C, WU Y, HAN Y, CUI W, JIA L, CAI L, CHENG J, LI H, DU J. Interleukin-12p35 deletion promotes CD4 T-cell-dependent macrophage differentiation and enhances angiotensin II-induced cardiac fibrosis. *Arterioscler Thromb Vasc Biol* 2012; 32: 1662-1674.
- 32) DURIK M, SEVA PESSOA B, ROKS AJ. The renin-angiotensin system, bone marrow and progenitor cells. *Clin Sci (Lond)* 2012; 123: 205-223.
- 33) HERINGER-WALTHER S, ECKERT K, SCHUMACHER SM, UHAREK L, WULF-GOLDENBERG A, GEMBARDT F, FICHTNER I, SCHULTHEISS HP, RODGERS K, WALTHER T. Angiotensin-(1-7) stimulates hematopoietic progenitor cells in vitro and in vivo. *Haematologica* 2009; 94: 857-860.
- 34) ABALI H, HAZNEDAROGLU IC, GOKER H, CELIK I, OZATLI D, KORAY Z, CAGLAR M. Circulating and local bone marrow renin-angiotensin system in leukemic hematopoiesis: preliminary evidences. *Hematology* 2002; 7: 75-82.
- 35) AKSU S, BEYAZIT Y, HAZNEDAROGLU IC, CANPINAR H, KEKILLI M, UNER A, SAYINALP N, BÜYÜKA İK Y, GOKER H, OZCEBE OI. Over-expression of angiotensin-converting enzyme (CD 143) on leukemic blasts as a clue for the activated local bone marrow RAS in AML. *Leuk Lymphoma* 2006; 47: 891-896.
- 36) BEYAZIT Y, AKSU S, HAZNEDAROGLU IC, KEKILLI M, MISIRLIOGLU M, TUNCER S, KARAKAYA J, KOCA E, BUYUKASIK Y, SAYINALP N, GOKER H. Overexpression of the local bone marrow renin-angiotensin system in acute myeloid leukemia. *J Natl Med Assoc* 2007; 99: 57-63.
- 37) TUFAN A, UNAL N, KOCA E, ONAL I, AKSU S, HAZNEDAROGLU I. Spontaneous tumor lysis syndrome in a patient with diffuse large B cell lymphoma and Richter syndrome. *Ann Hematol* 2006; 85: 183-184.
- 38) SAYINALP N, CINAR H, UNER A, HAZNEDAROGLU IC, BÜYÜKA İK Y, GÖKER H, AKSU S, OZCEBE OI, KARAKU S, KIRAZLI S, DÜNDAR SV. Plasma basic fibroblast growth factor and bone marrow fibrosis in clonal myeloproliferative disorders. *Clin Lab Haematol* 2004; 26: 265-268.
- 39) DIZDAR O, YÜREKLİ BS, PÜRNAS T, AKSU S, HAZNEDAROGLU IC. Tumor lysis syndrome associated with fludarabine treatment in chronic lymphocytic leukemia. *Ann Pharmacother* 2004; 38: 1319-1320.
- 40) AKSU S, BEYAZIT Y, HAZNEDAROGLU IC, KEKILLI M, CANPINAR H, MISIRLIOGLU M, UNER A, TUNCER S, SAYINALP N, BÜYÜKA İK Y, GOKER H, OZCEBE OI. Enhanced expression of the local haematopoietic bone marrow renin-angiotensin system in polycythemia rubra vera. *J Int Med Res* 2005; 33: 661-667.
- 41) TERESA GOMEZ CASARES M, DE LA IGLESIA S, PERERA M, LEMES A, CAMPO C, GONZALEZ SAN MIGUEL JD, BOSCH JM, SUAREZ A, GUERRA L, RODRIGUEZ-PÉREZ JC, MOLERO T. Renin expression in hematological malignancies and its role in the regulation of hematopoiesis. *Leuk Lymphoma* 2002; 43: 2377-2381.
- 42) IÑIGO SDE L, CASARES MT, JORGE CE, LEIZA SM, SANTANA GS, BRAVO DE LAGUNA SJ, SAN MIGUEL JD, CABALLERO A, ALVAREZ MDL M, CASTELLANO AL, HENRÍQUEZ HL, LABARTA TM. Relevance of renin expression by real-time PCR in acute myeloid leukemia. *Leuk Lymphoma* 2006; 47: 409-416.
- 43) KHODUNOVA EE, PAROVICHNIKOVA EN, GAL'TSEVA IV, KULIKOV SM, ISAEV VG, SAVCHENKO VG. Dynamic study of Bcl-2, Bax, p53, and ACE expression in CD34+ cells of peripheral blood and bone marrow in acute leukemia patients in the course of induction chemotherapy. *Ter Arkh* 2011; 83: 32-37.
- 44) WULF GG, JAHNS-STREUBEL G, NOBILING R, STRUTZ F, HEMMERLEIN B, HIDDEMANN W, WÖRMANN B. Renin in acute myeloid leukaemia blasts. *Br J Haematol* 1998; 100: 335-337.
- 45) KOCA E, HAZNEDAROGLU IC, ACAR K, BEYAZIT Y, AKSU S, MISIRLIOGLU M, TUNCER S, SAYINALP N, OZCEBE OI, UNER A. Renin-angiotensin system expression in the K562 human erythroleukaemic cell line. *J Renin Angiotensin Aldosterone Syst* 2007; 8: 145-147.
- 46) RP PINTO, KK WANG, H KHOURY, AD SCHIMMER, MD MINDEN. Aberrant expression of angiotensin in acute myeloid leukemia. *Blood* 2004; 102: 2124A.
- 47) DE LA IGLESIA IÑIGO S, LÓPEZ-JORGE CE, GÓMEZ-CASARES MT, LEMES CASTELLANO A, MARTÍN CABRERA P, LÓPEZ BRITO J, SUÁREZ CABRERA A, MOLERO LABARTA T. Induction of apoptosis in leukemic cell lines treated with captopril, trandolapril and losartan: A new role in the treatment of leukaemia for these agents. *Leuk Res* 2009; 33: 810-816.
- 48) RODGERS K, XIONG S, DiZERE GA. Effect of angiotensin II and angiotensin(1-7) on hematopoietic recovery after intravenous chemotherapy. *Cancer Chemother Pharmacol* 2003; 51: 97-106.
- 49) RODGERS KE, OLIVER J, DiZERE GA. Phase I/II dose escalation study of angiotensin 1-7 [A(1-7)] administered before and after chemotherapy in patients with newly diagnosed breast cancer. *Cancer Chemother Pharmacol* 2006; 57: 559-568.
- 50) ABALI H, GÜLLÜ IH, ENGİN H, HAZNEDAROGLU IC, ERMAN M, TEKUZMAN G. Old antihypertensives as novel antineoplastics: angiotensin-I-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists. *Med Hypotheses* 2002; 59: 344-348.
- 51) MARUSIC-VRSALOVIC M, DOMINIS M, JAKSIC B, KUSEC R. Angiotensin I-converting enzyme is expressed by

- erythropoietic cells of normal and myeloproliferative bone marrow. *Br J Haematol* 2003; 123: 539-541.
- 52) NEHME A, CERUTTI C, DHAOUADI N, GUSTIN MP, COURAND PY, ZIBARA K, BRICCA G. Atlas of tissue renin-angiotensin-aldosterone system in human: A transcriptomic meta-analysis. *Sci Rep* 2015; 5: 10035.
- 53) TSUBAKIMOTO Y, YAMADA H, YOKOI H, KISHIDA S, TAKATA H, KAWAHITO H, MATSUI A, URAO N, NOZAWA Y, HIRAI H, IMANISHI J, ASHIHARA E, MAEKAWA T, TAKAHASHI T, OKIGAKI M, MATSUBARA H. Bone marrow angiotensin AT1 receptor regulates differentiation of monocyte lineage progenitors from hematopoietic stem cells. *Arterioscler Thromb Vasc Biol* 2009; 29: 1529-1536.
- 54) RICHMOND RS, TALLANT EA, GALLAGHER PE, FERRARIO CM, STRAWN WB. Angiotensin II stimulates arachidonic acid release from bone marrow stromal cells. *J Renin Angiotensin Aldosterone Syst* 2004; 5: 176-182.
- 55) GOMEZ RA, NORLING LL, WILFONG N, ISAKSON P, LYNCH KR, HOCK R, QUESENBERRY P. Leukocytes synthesize angiotensinogen. *Hypertension* 1993; 21: 470-475.
- 56) RODGERS KE, ESPINOZA T, RODA N, MEEKS CJ, HILL C, LOUIE SG, DIZEREGA GS. Accelerated hematopoietic recovery with angiotensin-(1-7) after total body radiation. *Int J Radiat Biol* 2012; 88: 466-476.
- 57) RODGERS KE, XIONG S, DIZEREGA GS. Accelerated recovery from irradiation injury by angiotensin peptides. *Cancer Chemother Pharmacol* 2002; 49: 403-411.
- 58) STEGBAUER J, LEE DH, SEUBERT S, ELLRICHMANN G, MANZEL A, KVAKAN H, MULLER DN, GAUPP S, RUMP LC, GOLD R, LINKER RA. Role of the renin-angiotensin system in autoimmune inflammation of the central nervous system. *Proc Natl Acad Sci USA* 2009; 106: 14942-14947.
- 59) COLE J, ERTOY D, BERNSTEIN KE. Insights derived from ACE knockout mice. *J Renin Angiotensin Aldosterone Syst* 2000; 1: 137-141.
- 60) COLE J, ERTOY D, LIN H, SUTLIFF RL, EZAN E, GUYENE TT, CAPECCHI M, CORVOL P, BERNSTEIN KE. Lack of angiotensin II-facilitated erythropoiesis causes anemia in angiotensin-converting enzyme-deficient mice. *J Clin Invest* 2000; 106: 1391-1398.
- 61) KANEKO K, SHIBASAKI A, NISHIYAMA H, HIROSE T, OHBA K, TOTSUNE K, FURUYAMA K, TAKAHASHI K. Expression of (pro)renin receptor in human erythroid cell lines: the effect of interferon- γ . *ASH Annual Meeting Abstracts* 2011; 118: 3172.
- 62) MRUG M, JULIAN BA, PRCHAL JT. Angiotensin II receptor type 1 expression in erythroid progenitors: Implications for the pathogenesis of postrenal transplant erythrocytosis. *Semin Nephrol* 2004; 24: 120-130.
- 63) Mrug M, Stopka T, Julian BA, Prchal JF, Prchal JT. Angiotensin II stimulates proliferation of normal early erythroid progenitors. *J Clin Invest* 1997; 100: 2310-2314.
- 64) BATENBURG WW, DANSER AH. (Pro)renin and its receptors: pathophysiological implications. *Clin Sci (Lond)* 2012; 123: 121-33.
- 65) DE MELLO WC. On the pathophysiological implications of an intracellular renin receptor. *Circ Res* 2006; 99: 1285-1286.
- 66) SPINELLO I, QUARANTA MT, PASQUINI L, ET AL. PLZF-mediated control on c-kit expression in CD34(+) cells and early erythropoiesis. *Oncogene* 2009; 28: 2276-2288.
- 67) WANG N, FRANK GD, DING R, TAN Z, RACHAKONDA A, PANDOLFI PP, SENBONMATSU T, LONDON EJ, INAGAMI T. Promyelocytic leukemia Zinc finger protein activates GATA4 transcription and mediates cardiac hypertrophic signaling from angiotensin II receptor 2. *PLoS One* 2012; 7: e35632.
- 68) SAVARY K, MICHAUD A, FAVIER J, LARGER E, CORVOL P, GASC JM. Role of the renin-angiotensin system in primitive erythropoiesis in the chick embryo. *Blood* 2005; 105: 103-110.
- 69) MARATHIAS KP, AGROYANNIS B, MAVROMOUSTAKOS T, MATSOUKAS J, VLAHAKOS DV. Hematocrit-lowering effect following inactivation of renin-angiotensin system with angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Curr Top Med Chem* 2004; 4: 483-486.
- 70) HAZNEDAROGLU IC, GOKER H, TURGUT M, BUYUKASIK Y, BENEKLI M. Thrombopoietin as a drug: biologic expectations, clinical realities, and future directions. *Clin Appl Thromb Hemost* 2002; 8: 193-212.
- 71) ISHIKAWA M, SEKIZUKA E, YAMAGUCHI N, NAKADATE H, TERAOKA S, GRANGER DN, MINAMITANI H. Angiotensin II type 1 receptor signaling contributes to platelet-leukocyte-endothelial cell interactions in the cerebral microvasculature. *Am J Physiol Heart Circ Physiol* 2007; 292: H2306-2315.
- 72) LARSSON PT, SCHWIELER JH, WALLEN NH. Platelet activation during angiotensin II infusion in healthy volunteers. *Blood Coagul Fibrinolysis* 2000; 11: 61-69.
- 73) NAHMOD K, GENTILINI C, VERMEULEN M, UHAREK L, WANG Y, ZHANG J, SCHULTHEISS HP, GEFFNER J, WALTHER T. Impaired function of dendritic cells deficient in angiotensin II type 1 receptors. *J Pharmacol Exp Ther* 2010; 334: 854-862.
- 74) NAHMOD KA, GEFFNER JR, WALTHER T. Angiotensin II type 1a-deficient bone marrow-derived dendritic cells produce higher levels of monocyte chemoattractant protein 1. *Hypertension* 2010; 56: e6-7.
- 75) NAHMOD KA, VERMEULEN ME, RAIDEN S, SALAMONE G, GAMBERALE R, FERNÁNDEZ-CALOTTI P, ALVAREZ A, NAHMOD V, GIORDANO M, GEFFNER JR. Control of dendritic cell differentiation by angiotensin II. *FASEB J* 2003; 17: 491-493.
- 76) ADAM J, CASE, MATTHEW C. ZIMMERMAN. Sympathetic-mediated activation versus suppression of the immune system: consequences for hypertension. *J Physiol* 2016; 594: 527-536.
- 77) SINGH N, JOSHI S, GUO L, BAKER MB, LI Y, CASTELLANO RK, RAIZADA MK, JARAJAPU YP. ACE2/Ang-(1-7)/Mas axis stimulates vascular repair-relevant functions

- of CD34+ cells. *Am J Physiol Heart Circ Physiol* 2015; 309: H1697-1707.
- 78) PENN MS, SWAMINATH D. Novel role of bone marrow stem cells in systemic disease. *Circ Res* 2015; 117: 119-120.
- 79) SANTISTEBAN MM, AHMARI N, CARVAJAL JM, ZINGLER MB, Qi Y, KIM S, JOSEPH J, GARCIA-PEREIRA F, JOHNSON RD, SHENOY V, RAIZADA MK, ZUBCEVIC J. Involvement of bone marrow cells and neuroinflammation in hypertension. *Circ Res* 2015; 117: 178-191.
- 80) ÖZTÜRK MA, GÜVEN GS, HAZNEDAROGLU IC. How hematopoietic stem cells know and act in cardiac microenvironment for stem cell plasticity? Impact of local renin-angiotensin systems. *Med Hypotheses* 2004; 63: 866-874.
- 81) TAVIAN M, PEAULT B. The changing cellular environments of hematopoiesis in human development in utero. *Exp Hematol* 2005; 33: 1062-1069.
- 82) HIRSCHI KK. Hemogenic endothelium during development and beyond. *Blood* 2012; 119: 4823-4827.
- 83) XING Y, LV A, WANG L, YAN X. The combination of angiotensin II and 5-azacytidine promotes cardiomyocyte differentiation of rat bone marrow mesenchymal stem cells. *Mol Cell Biochem* 2011; 360: 279-287.
- 84) SEQUEIRA LOPEZ ML, GOMEZ RA. The role of angiotensin II in kidney embryogenesis and kidney abnormalities. *Curr Opin Nephrol Hypertens* 2004; 13: 117-122.
- 85) AGER EI, NEO J, CHRISTOPHI C. The renin-angiotensin system and malignancy. *Carcinogenesis* 2008; 29: 1675-1684.
- 86) GEORGE AJ, THOMAS WG, HANNAN RD. The renin-angiotensin system and cancer: old dog, new tricks. *Nat Rev Cancer* 2010; 10: 745-759.
- 87) NI L, FENG Y, WAN H, MA Q, FAN L, QIAN Y, LI Q, XIANG Y, GAO B. Angiotensin-(1-7) inhibits the migration and invasion of A549 human lung adenocarcinoma cells through inactivation of the PI3K/Akt and MAPK signaling pathways. *Oncol Rep* 2011; 27: 783-790.
- 88) OKAMOTO K, TAJIMA H, OHTA T, NAKANUMA S, HAYASHI H, NAKAGAWARA H, ONISHI I, TAKAMURA H, NINOMIYA I, KITAGAWA H, FUSHIDA S, TANI T, FUJIMURA T, KAYAHARA M, HARADA S, WAKAYAMA T, ISEKI S. Angiotensin II induces tumor progression and fibrosis in intrahepatic cholangiocarcinoma through an interaction with hepatic stellate cells. *Int J Oncol* 2010; 37: 1251-1259.
- 89) URSULA SCHMID, HELGA STOPPER, FRANK SCHWEDA, NINA QUEISSER, NICOLE SCHUPP. Angiotensin II Induces DNA Damage in the Kidney. *Cancer Res* 2008; 68: 9239-9246.
- 90) FENDRICH V, CHEN NM, NEEF M, WALDMANN J, BUCHHOLZ M, FELDMANN G, SLATER EP, MAITRA A, BARTSCH DK. The angiotensin-I-converting enzyme inhibitor enalapril and aspirin delay progression of pancreatic intraepithelial neoplasia and cancer formation in a genetically engineered mouse model of pancreatic cancer. *Gut* 2010; 59: 630-637.
- 91) DIOP-FRIMPONG B, CHAUHAN VP, KRANE S, BOUCHER Y, JAIN RK. Losartan inhibits collagen I synthesis and improves the distribution and efficacy of nanotherapeutics in tumors. *Proc Natl Acad Sci U S A* 2011; 108: 2909-2914.
- 92) WEGMAN-OSTROSKY T, SOTO-REYES E, VIDAL-MILLÁN S, SÁNCHEZ-CORONA J. The renin-angiotensin system meets the hallmarks of cancer. *J Renin Angiotensin Aldosterone Syst* 2015; 16: 227-233.
- 93) VELEZ RUEDA JO, PALOMEQUE J, MATTIAZZI A. Early apoptosis in different models of cardiac hypertrophy induced by high renin-angiotensin system activity involves CaMKII. *J Appl Physiol* 2012; 112: 2110-2120.
- 94) WANG X, LU J, KHAIDAKOV M, MITRA S, DING Z, GOYAL T, MEHTA JL. Delineation of the effects of angiotensin type 1 and 2 receptors on HL-1 cardiomyocyte apoptosis. *Apoptosis* 2012; 17: 908-915.
- 95) YANG C, WANG Y, LIU H, LI N, SUN Y, LIU Z, YANG P. Ghrelin protects H9c2 cardiomyocytes from angiotensin II-induced apoptosis through the endoplasmic reticulum stress pathway. *J Cardiovasc Pharmacol* 2012; 59: 465-471.
- 96) LO CS, LIU F, SHI Y, MAACHI H, CHENIER I, GODIN N, FILEP JG, INGELFINGER JR, ZHANG SL, CHAN JS. Dual RAS blockade normalizes angiotensin-Converting Enzyme-2 expression and prevents hypertension and tubular apoptosis in Akita angiotensinogen-transgenic mice. *Am J Physiol Renal Physiol* 2011; 302: F840-852.
- 97) KOZAKO T, YOSHIMITSU M, ARIMA N, SOEDA S, HIRATA S, TANAKA H, HONDA S, SOEDA S. Telmisartan, angiotensin II receptor blocker, induces apoptosis and autophagy in adult T-cell leukemia cells from patients and leukemia cell lines. *Blood* 2015; 126: 2055.
- 98) MATSUSHITA K, WU Y, OKAMOTO Y, PRATT RE, DZAU VJ. Local renin angiotensin expression regulates human mesenchymal stem cell differentiation to adipocytes. *Hypertension* 2006; 48: 1095-1102.
- 99) ISHIZUKA T, GOSHIMA H, OZAWA A, WATANABE Y. Effect of angiotensin II on proliferation and differentiation of mouse induced pluripotent stem cells into mesodermal progenitor cells. *Biochem Biophys Res Commun* 2012; 420: 148-155.
- 100) DU N, FENG J, HU LJ, SUN X, SUN HB, ZHAO Y, YANG YP, REN H. Angiotensin II receptor type 1 blockers suppress the cell proliferation effects of angiotensin II in breast cancer cells by inhibiting AT1R signaling. *Oncol Rep* 2012; 27: 1893-1903.
- 101) BELYEA BC, XU F, PENTZ ES, MEDRANO S, LI M, HU Y, TURNER S, LEGALLO R, JONES CA, TARIO JD, LIANG P, GROSS KW, SEQUEIRA-LOPEZ ML, GOMEZ RA. Identification of renin progenitors in the mouse bone marrow that give rise to B-cell leukaemia. *Nat Commun* 2014; 5: 3273.
- 102) GWATHMEY TM, ALZAYADNEH EM, PENDERGRASS KD, CHAPPELL MC. Novel roles of nuclear angiotensin

- receptors and signaling mechanisms. *Am J Physiol Regul Integr Comp Physiol* 2011; 302: R518-530.
- 103) VITKO JR, RE RN, ALAM J, COOK JL. Cell-penetrating peptides corresponding to the angiotensin II Type 1 receptor reduce receptor accumulation and cell surface expression and signaling. *Am J Hypertens* 2011; 25: 24-28.
- 104) RODGERS KE, XIONG S, STEER R, DI ZEREGA GS. Effect of angiotensin II on hematopoietic progenitor cell proliferation. *Stem Cells* 2000; 18: 287-294.
- 105) MCCOLLUM LT, GALLAGHER PE, TALLANT EA. Angiotensin-(1-7) abrogates mitogen-stimulated proliferation of cardiac fibroblasts. *Peptides* 2012; 34: 380-388.
- 106) ZAADE D, SCHMITZ J, BENKE E, KLARE S, SEIDEL K, KIRSCH S, GOLDIN-LANG P, ZOLLMANN FS, UNGER T, FUNKE-KAISER H. Distinct signal transduction pathways downstream of the (P)RR revealed by microarray and ChIP-chip analyses. *PLoS One* 2013; 8: e57674.
- 107) AHMADIAN E, JAFARI S, YARI KHOSROUSHAH A. Role of angiotensin II in stem cell therapy of cardiac disease. *J Renin Angiotensin Aldosterone Syst* 2015; 16: 702-711.
- 108) CARBAJO-LOZOYA J, LUTZ S, FENG Y, KROLL J, HAMMES HP, WIELAND T. Angiotensin II modulates VEGF-driven angiogenesis by opposing effects of type 1 and type 2 receptor stimulation in the microvascular endothelium. *Cell Signal* 2012; 24: 1261-1269.
- 109) KAJI K, YOSHUI H, IKENAKA Y, NOGUCHI R, AIHARA Y, SHIRAI Y, DOUHARA A, FUKUI H. Possible involvement of angiogenesis in chronic liver diseases: interaction among renin-angiotensin-aldosterone system, insulin resistance and oxidative stress. *Curr Med Chem* 2012; 19: 1889-1898.
- 110) JETHON A, PULA B, PIOTROWSKA A, WOJNAR A, RYS J, DZIEGIEL P, PODHORSKA-OKOLOW M. Angiotensin II type 1 receptor (AT-1R) expression correlates with VEGF-A and VEGF-D expression in invasive ductal breast cancer. *Pathol Oncol Res* 2012; 18: 867-873.
- 111) VINSON GP, BARKER S, PUDDEFOOT JR. The renin-angiotensin system in the breast and breast cancer. *Endocr Relat Cancer* 2011; 19: 1-19.
- 112) SUZUKI Y, RUIZ-ORTEGA M, LORENZO O, RUPEREZ M, ESTEBAN V, EGIDO J. Inflammation and angiotensin II. *Int J Biochem Cell Biol* 2003; 35: 881-900.
- 113) RÖCKEN C, LENDECKEL U, DIERKES J, WESTPHAL S, CARL-MCGRATH S, PETERS B, KRÜGER S, MALFERTHEINER P, ROESSNER A, EBERT MP. The number of lymph node metastases in gastric cancer correlates with the angiotensin I-converting enzyme gene insertion/deletion polymorphism. *Clin Cancer Res* 2005; 11: 2526-2530.
- 114) YAREN A, OZTOP I, TURGUT S, TURGUT G, DEGIRMENCIOGLU S, DEMIRPENCE M. Angiotensin-converting enzyme gene polymorphism is associated with anemia in non-small-cell lung cancer. *Exp Biol Med (Maywood)* 2008; 233: 32-37.
- 115) YAREN A, TURGUT S, KURSUNLUOGLU R, OZTOP I, TURGUT G, DEGIRMENCIOGLU S, KELTEN C, ERDEM E. Insertion/Deletion polymorphism of the angiotensin I-converting enzyme gene in patients with breast cancer and effects on prognostic factors. *J Investig Med* 2007; 55: 255-261.
- 116) YIGIT B, BOZKURT N, NARTER F, YILMAZ H, YUCEBAS E, ISBIR T. Effects of ACE I/D polymorphism on prostate cancer risk, tumor grade and metastasis. *Anticancer Res* 2007; 27: 933-936.
- 117) RÖCKEN C, RÖHL FW, DIEBLER E, LENDECKEL U, PROSS M, CARL-MCGRATH S, EBERT MP. The angiotensin II/angiotensin II receptor system correlates with nodal spread in intestinal type gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 1206-1212.
- 118) DEVI PAVLI S, RISTI S, FLEGO V, KAPOVI M, RADOJIC BADOVINAC A. Angiotensin-Converting Enzyme insertion/deletion gene polymorphism in lung cancer patients. *Genet Test Mol Biomarkers* 2012; 16: 722-725.
- 119) RODRIGUES-FERREIRA S, ABDELKARIM M, DILLENBURG-PILLA P, LUISANT AC, DI-TOMMASO A, DESHAYES F, PONTES CL, MOLINA A, CAGNARD N, LETOURNEUR F, MOREL M, REIS RI, CASARINI DE, TERRIS B, COURAUD PO, COSTA-NETO CM, DI BENEDETTO M, NAHMIA S. Angiotensin II facilitates breast cancer cell migration and metastasis. *PLoS One* 2012; 7: e35667.
- 120) JUREWICZ M, MCDERMOTT DH, SECHLER JM, TINCKAM K, TAKAKURA A, CARPENTER CB, MILFORD E, ABDI R. Human T and natural killer cells possess a functional renin-angiotensin system: further mechanisms of angiotensin II-induced inflammation. *J Am Soc Nephrol* 2007; 18: 1093-1102.
- 121) XIAO Z, SHEN, PING LI, DAIANA WEISS, SEBASTIEN FUCHS, HONG D. XIAO, JON A. ADAMS, IFOR R. WILLIAMS, MARIO R. CAPECCHI, W. ROBERT TAYLOR, KENNETH E. BERNSTEIN. Mice with enhanced macrophage angiotensin-converting enzyme are resistant to melanoma. *Am J Pathol* 2007; 170: 2122-2134.
- 122) SHEN XZ, BILLET S, LIN C, OKWAN-DUODU D, CHEN X, LUKACHER AE, BERNSTEIN KE. The carboxypeptidase angiotensin converting enzyme (ACE) shapes the MHC class I peptide repertoire. *Nat Immunol* 2012; 12: 1078-1085.
- 123) WULF GG, JAHNS-STREUBEL G, STRUTZ F, BASENAU D, HÜFNER M, BUSKE C, WÖRMANN B, HIDDEMANN W. Paraneoplastic hypokalemia in acute myeloid leukemia: a case of renin activity in AML blast cells. *Ann Hematol* 1996; 73: 139-141.
- 124) HAZNEDAROGLU IC, SAVAS MC, BENEKLİ M. Renin-like activity in leukemic blast cells: an initial clue to a local renin-angiotensin system in the bone marrow. *Ann Hematol* 1997; 75: 69-70.
- 125) TAKEDA A, GOOLSBY C, YASEEN NR. NUP98-HOXA9 induces long-term proliferation and blocks differentiation of primary human CD34+ hematopoietic cells. *Cancer Res* 2006; 66: 6628-6637.
- 126) YASSIN ER, ABDUL-NABI AM, TAKEDA A, YASEEN NR. Effects of the NUP98-DDX10 oncogene on primary

- human CD34+cells: role of a conserved helicase motif. *Leukemia* 2010; 24: 1001-1011.
- 127) KIRSCH S, SCHREZENMEIER E, KLARE S, ZAADE D, SEIDEL K, SCHMITZ J, BERNHARD S, LAUER D, SLACK M, GOLDIN-LANG P, UNGER T, ZOLLMANN FS, FUNKE-KAISER H. The (pro)renin receptor mediates constitutive PLZF-independent pro-proliferative effects which are inhibited by bafilomycin but not genistein. *Int J Mol Med* 2014; 33: 795-808.
- 128) UZ B, TATONYAN SC, SAYITOGLU M, ERBILGIN Y, NG OH, BUYUKASIK Y, SAYINALP N, AKSU S, GOKER H, OZCEBE OI, OZBEK U, HAZNEDAROGLU IC. Local hematopoietic renin-angiotensin system in myeloid versus lymphoid hematological neoplastic disorders. *J Renin Angiotensin Aldosterone Syst* 2013; 14: 308-314.
- 129) DE LA IGLESIA S, GÓMEZ CASARES MT, LÓPEZ-JORGE CE. Renin expression in acute leukaemia. *J Renin Angiotensin Aldosterone Syst* 2013; 14: 91-92.
- 130) KOCA E, HAZNEDAROGLU IC, UNER A, SAYINALP N, SAGLAM AE, GOKER H, OZCEBE OI. Angiotensin-converting enzyme expression of the lymphoma-associated macrophages in the lymph nodes of Hodgkin's disease. *J Natl Med Assoc* 2007; 99: 1243-1244, 1246-1247.
- 131) ALBAYRAK M, CELEBI H, ALBAYRAK A, SAYILIR A, YESIL Y, BALCIK OS, YOKUS O, CELIK T. Elevated serum angiotensin converting enzyme levels as a reflection of bone marrow renin-angiotensin system activation in multiple myeloma. *J Renin Angiotensin Aldosterone Syst* 2012; 13: 259-264.
- 132) SAKA B, DOGAN O, TASCIOGLU C, BESISIK SK, KARAN MA, SAYITOGLU M, GENÇ S. Bone marrow renin-angiotensin system in multiple myeloma. *Clin Lymphoma Myeloma Leuk* 2009; 9: 10
- 133) BRUNET DE LA GRANGE P, IVANOVIC Z, LEPRIVEY-LORGEOT V, PRALORAN V. Angiotensin II that reduces the colony-forming ability of hematopoietic progenitors in serum free medium has an inverse effect in serum-supplemented medium. *Stem Cells* 2002; 20: 269-271.
- 134) AKALIN I, KOCA E., KARABULUT HG, HAZNEDAROGLU IC, CETINER D, HAYRAN M, ONAL IK, OZCEBE OI, TUKUN A. Angiotensin Converting Enzyme insertion/deletion gene polymorphisms in leukemic hematopoiesis. *UHOD* 2011; 21: 1-9.
- 135) GORUKMEZ O, SAG O, GORUKMEZ Ö, TURE M, TOPAK A, SAHINTURK S, OZKAYA G, GULTEN T, ALI R, YAKUT T. Association of the ACE I/D gene polymorphisms with JAK2V617F-positive polycythemia vera and essential thrombocythemia. *Genet Test Mol Biomarkers* 2015; 19: 303-308.
- 136) GOKER H, HAZNEDAROGLU IC, BEYAZIT Y, AKSU S, TUNCER S, MISIRLIOGLU M, BAYRAMOGLU F, KEKILLI M, BÜYÜKASIK Y, SAYINALP N, OZCEBE O, DUNDAR S, MOLLAMAHMUTOGLU L. Local umbilical cord blood renin-angiotensin system. *Ann Hematol* 2005; 84: 277-281.
- 137) SAYITOGLU M, HAZNEDAROGLU IC, HATIRNAZ O, ERBILGIN Y, AKSU S, KOCA E, ADIGUZEL C, BAYIK M, AKALIN I, GÜLBAS Z, AKAY M, UNAL A, KAYNAR L, OVALI E, YILMAZ M, YENEREL M, DAGDAS S, OZET G, AR C, AYDIN Y, SOYSAL T, DURGUN B, OZCEBE O, TUKUN A, ILHAN O, OZBEK U. Effects of Imatinib mesylate on renin-angiotensin system (RAS) activity during the clinical course of chronic myeloid leukaemia. *J Int Med Res* 2009; 37: 1018-1028.
- 138) BEYAZIT Y, PURNAK T, GUVEN GS, HAZNEDAROGLU IC. Local bone marrow renin-angiotensin system and atherosclerosis. *Cardiol Res Pract* 2010; 2011: 714515.
- 139) FERRARIO CM, RICHMOND RS, SMITH R, LEVY P, STRAWN WB, KIVLIGHN S. Renin-angiotensin system as a therapeutic target in managing atherosclerosis. *Am J Ther* 2004; 11: 44-53.
- 140) FUKUDA D, SATA M. Role of bone marrow renin-angiotensin system in the pathogenesis of atherosclerosis. *Pharmacol Ther* 2008; 118: 268-276.
- 141) FUKUDA D, SATA M, ISHIZAKA N, NAGAI R. Critical role of bone marrow angiotensin II type 1 receptor in the pathogenesis of atherosclerosis in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol* 2008; 28: 90-96.
- 142) KATO H, ISHIDA J, NAGANO K, HONJO K, SUGAYA T, TAKEDA N, SUGIYAMA F, YAGAMI K, FUJITA T, NANGAKU M, FUKAMIZU A. Deterioration of atherosclerosis in mice lacking angiotensin II type 1A receptor in bone marrow-derived cells. *Lab Invest* 2008; 88: 731-739.
- 143) SATA M, FUKUDA D. Crucial role of renin-angiotensin system in the pathogenesis of atherosclerosis. *J Med Invest* 2010; 57: 12-25.
- 144) MATSUBARA H. Clinical pathology and treatment of renin-angiotensin system - 3. Atherosclerosis and the renin-angiotensin system. *Intern Med* 2007; 46: 1299-1301.
- 145) STRAWN W, RICHMOND R, FERRARIO C. A new understanding of atherosclerosis: The bone marrow response-to-lipid hypothesis. In: *Heart Disease: Pathogenesis, Diagnosis and Treatment*. Washington, DC: 3rd World Congress on Heart Disease, 2003: p183-188.
- 146) STRAWN WB, FERRARIO CM. Angiotensin II AT(1) receptor blockade normalizes CD11b(+) monocyte production in bone marrow of hypercholesterolemic monkeys. *Atherosclerosis* 2008; 196: 624-632.
- 147) ISHIGURO S, YOSHIMURA K, TSUNEDOMI R, OKA M, TAKAO S, INUI M, KAWABATA A, WALL T, MAGAFA V, CORDOPATIS P, TZAKOS AG, TAMURA M. Involvement of angiotensin II type 2 receptor (AT2R) signaling in human pancreatic ductal adenocarcinoma (PDAC): a novel AT2R agonist effectively attenuates growth of PDAC grafts in mice. *Cancer Biol Ther* 2015; 16: 307-316.
- 148) WANG H, SETHI G, LOKE WK, SIM MK. Des-aspartate-angiotensin I attenuates mortality of mice exposed to gamma radiation via a novel mechanism of action. *PLoS One* 2015; 10: e0138009.
- 149) STEGBAUER J, COFFMAN TM. New insights into angiotensin receptor actions: from blood pressure to aging. *Curr Opin Nephrol Hypertens* 2011; 20: 84-88.

- 150) PURCLUTEPE O, ISKENDER G, KIPER HD, TEZCANLI B, SELVI N, AVCI CB, KOSOVA B, GOKBULUT AA, SAHIN F, BARAN Y, SAYDAM G. Enalapril-induced apoptosis of acute promyelocytic leukaemia cells involves STAT5A. *Anticancer Res* 2012; 32: 2885-2893.
- 151) BHASKARAN K, DOUGLAS I, EVANS S, VAN STAA T, SMEETH L. Angiotensin receptor blockers and risk of cancer: cohort study among people receiving antihypertensive drugs in UK General Practice Research Database. *Br Med J* 2012; 344: e2697.
- 152) GAO M, WANG Y, SHI Y, LIU D, LIANG Y, YU Y, ZHAOBIN J, ZHU L, JIN S. The relationship between three well-characterized polymorphisms of the angiotensin converting enzyme gene and lung cancer risk: a case-control study and a meta-analysis. *J Renin Angiotensin Aldosterone Syst* 2012; 13: 455-460.
- 153) HALLAS J, CHRISTENSEN R, ANDERSEN M, FRIIS S, BJERRUM L. Long-term use of drugs affecting the renin-angiotensin system and the risk of cancer. A population-based case-control study. *Br J Clin Pharmacol* 2012; 74: 180-188.
- 154) MC MENAMIN ÚC, MURRAY LJ, CANTWELL MM, HUGHES CM. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in cancer progression and survival: a systematic review. *Cancer Causes Control* 2011; 23: 221-230.
- 155) LIU JM, LAWRENCE F, KOVACEVIC M, BIGNON J, PAPADIMITRIOU E, LALLEMAND JY, KATSORIS P, POTIER P, FROMES Y, WDZIECZAK-BAKALA J. The tetrapeptide AcSDKP, an inhibitor of primitive hematopoietic cell proliferation, induces angiogenesis in vitro and in vivo. *Blood* 2003; 101: 3014-3020.
- 156) KAWABATA A, BAOUM A, OHTA N, JACQUEZ S, SEO GM, BERKLAND C, TAMURA M. Intratracheal administration of a nanoparticle-based therapy with the angiotensin II type 2 receptor gene attenuates lung cancer growth. *Cancer Res* 2012; 72: 2057-2067.
- 157) KIM S, ZINGLER M, HARRISON JK, SCOTT EW, COGLE CR, LUO D, RAIZADA MK. Angiotensin II regulation of proliferation, differentiation, and engraftment of hematopoietic stem cells. *Hypertension* 2016; 67: 574-584.
- 158) SESTITO A. Hypertension therapy and cardiovascular protection. Effects of angiotensin II receptor block with Valsartan. *Eur Rev Med Pharmacol Sci* 2011; 15: 1247-1255.