

Local Bone Marrow Renin-Angiotensin System and COVID-19

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ABSTRACT

For the first time on December 31, 2019, 27 cases of pneumonia of unknown etiology were detected in Wuhan City, Hubei province, China. The factor that caused this clinic was called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). In the following days, WHO officially named the disease caused by the new coronavirus as Coronavirus Disease 2019 (COVID-19). Patients infected with SARS-CoV-2 mostly applied to health centers with symptoms of dry cough, shortness of breath and fever. Some patients have developed death-causing complications such as organ failure, septic shock, pulmonary edema, severe pneumonia, and Acute Respiratory Distress Syndrome (ARDS). SARS-CoV-2 infects patients by binding human Angiotensin Converting Enzyme 2 (ACE 2), causing to severe pneumonia and high mortality. Circulating RAS and local paracrin-autocrin-intracrin tissue-based RAS participate in numerous pathobiological events. Pro-inflammatory, pro-fibrotic, and pro-thrombotic consequences associated with local RAS activation have been detected at cellular and molecular level. Regenerative progenitor cell therapy in response to RAS-modulating pharmacotherapy in context of endothelial cell damage and regeneration emerged as an auxiliary therapy to improve regeneration of the vascular endothelium. The aim of this article is to evaluate the relationship between circulating and local angiotensin systems and COVID-19.

Keywords: Covid-19, Renin Angiotensin System, Hematopoiesis, Acute Respiratory Syndrome Coronavirus 2

ÖZET

Lokal Kemik İliği Renin Anjiyotensin Sistem ve COVID-19

İlk kez 31 Aralık 2019'da, Çin'in Hubei eyaleti, Wuhan şehrinde etyolojisi bilinmeyen 27 pnömoni vakası tespit edildi. Bu kliniğe neden olan ajana Şiddetli Akut Solunum Yolu Sendromu Coronavirus 2 (SARS-CoV-2) adı verildi. Sonraki günlerde DSÖ, yeni koronavirüsün neden olduğu hastalığı Coronavirus Hastalığı 2019 (COVID-19) olarak adlandırdı. SARS-CoV-2 ile enfekte hastalar çoğunlukla kuru öksürük, nefes darlığı ve ateş semptomları olan sağlık merkezlerine başvurdu. Bazı hastalarda organ yetmezliği, septik şok, pulmoner ödem, şiddetli pnömoni ve Akut Solunum Sıkıntısı Sendromu (ARDS) gibi ölüme neden olan komplikasyonlar geliştiği gözlemlendi. SARS-CoV-2, hastaları insan Anjiyotensin Dönüştürücü Enzim 2'yi (ACE 2) bağlayarak enfekte ederek ciddi pnömoniyeye ve yüksek mortaliteye neden olur. Dolaşımdaki RAS ve lokal parakrin-otokrin-intrakrin doku kaynaklı RAS birçok patobiyolojik olaya katılır. Lokal RAS aktivasyonu ile ilişkili pro-enflamatuar, pro-fibrotik ve pro-trombotik sonuçlar hücresel ve moleküler düzeyde tespit edilmiştir. Endotelial hücre hasarı ve rejenerasyonu bağlamında RAS modüle edici farmakoterapiye yanıt olarak rejeneratif progenitör hücre tedavisi, vasküler endotelin rejenerasyonunu iyileştirmek için yardımcı bir tedavi olarak ortaya çıkmıştır. Bu makalenin amacı, dolaşımdaki ve lokal anjiyotensin sistemleri ile COVID 19 arasındaki ilişkiyi değerlendirmektir.

Anahtar Kelimeler: COVID-19, Renin Anjiyotensin Sistem, Hematopoez, Akut Respiratuvar Sendrom Coronavirus 2

INTRODUCTION

For the first time on December 31, 2019, 27 cases of pneumonia of unknown etiology were detected in Wuhan City, Hubei province, China.¹ The causative agent was identified from throat swab specimen conducted by the Chinese Centre for Disease Control and Prevention on 7th January 2020. The factor that caused this clinic was called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).² In the following days, WHO officially named the disease caused by the new coronavirus as Coronavirus Disease 2019 (COVID-19).³ Patients infected with COVID-19 mostly applied to health centers with symptoms of dry cough, shortness of breath and fever. The symptoms of most of the cases resolved spontaneously. However, some patients have developed death-causing complications such as organ failure, septic shock, pulmonary edema, severe pneumonia, and Acute Respiratory Distress Syndrome (ARDS).⁴ COVID-19 infects patients by binding human Angiotensin Converting Enzyme 2 (ACE 2), causing to severe pneumonia and high mortality.⁵ Increased ACE and Ang II have been shown to be poor prognostic factors for severe pneumonia.⁶ Many important pathobiological events such as apoptosis, cellular proliferative events, mobilization, angiogenesis, fibrosis in the cytokine network are affected by Renin Angiotensin System (RAS) molecules.⁷⁻¹⁰ If the RAS system is not in balance, this can lead to an exacerbation of acute severe pneumonia. All major RAS molecules including Renin, angiotensinogen, angiotensin receptors and ACE have been shown to be found in the BM microenvironment.¹¹ Haznedaroglu et al. hypothesized that there is a locally active RAS in the BM that affects the growth, production, proliferation, and differentiation of hematopoietic cells.¹² The aim of this article is to evaluate the relationship between circulating and local angiotensin systems, COVID-19 and hematopoiesis.

1. COVID-19

Coronaviruses were first defined in 1966 by Tyrell and Bynoe.¹³ Coronaviruses are enveloped, positive single-stranded large RNA viruses that infect many animals and humans.¹⁴ Based on their

morphology as spherical virions with a core shell and surface projections resembling a solar corona. Therefore, they were called as coronaviruses. SARS-CoV-2 appears to be transmitted from animals to humans on the Huanan seafood market in Wuhan, China.¹⁴ The first clinical sign of SARS-CoV-2-related disease COVID-19 was pneumonia. Gastrointestinal symptoms and asymptomatic infections were also described.¹⁵ Studies to date have shown that a median incubation period of 3 days (range: 0-24 days).¹⁶ There are also people infected with SARS-CoV-2, which remain asymptomatic throughout the infection. In symptomatic patients, clinical manifestations of the disease usually begin in less than a week. Clinical symptoms such as fever, cough, nasal congestion, fatigue and other upper respiratory infections are observed in patients. Infection can progress to serious illness, accompanied by severe chest symptoms corresponding to dyspnea and pneumonia. These findings can be seen with computed tomography.¹⁶ Pneumonia usually occurs in the second or third week of a symptomatic infection. Important signs of viral pneumonia are decreased oxygen saturation and blood gas deviations. Changes that can be seen with chest x-rays and other imaging techniques, ground glass abnormalities, irregular consolidation, alveolar exudates and interlobular involvement are observed. Lymphopenia is common in patients and C-reactive protein and pro-inflammatory cytokines are elevated.¹⁴

2. COVID-19 and Renin Angiotensin System

In a recent hypothesis, it has been published that angiotensin receptor 1 (AT1R) inhibitors may be useful for COVID-19 infected patients with pneumonia.⁵ Based on this published knowledge, it was assumed that angiotensin II receptor blockers (ARB) present for clinical use may be potential drugs to control viral spread of the COVID-19. In a published observation, patients with hypertension using Losartan or Telmisartan tablets as anti-hypertensive have been shown to experience fewer cold and flu-like disease attacks.¹⁷ Losartan and Telmisartan severely bind to the AT1 receptors.¹⁸ The receptor binding domain for the spike protein of SARS-CoV-2, ACE2 was reported to be similar to the coronavirus strain involved in the 2002-

2003 SARS outbreak.¹⁹ The receptor binding domains of these two coronaviruses show 72% amino acid sequence similarity. The molecular simulation also showed similar ternary structures.²⁰ However, SARS-CoV-2 has higher affinity for ACE2 compared with SARS-CoV.²⁰ It has been reported that binding of the coronavirus spike protein to ACE2, its cellular binding site, leads to ACE2 downregulation, which in turn results in excessive production of angiotensin by the related enzyme ACE, while less ACE2 is capable of converting it to the vasodilator heptapeptide angiotensin.¹⁻⁷ Thus, lung damage increases because AT1R due to angiotensin increases pulmonary vascular permeability and ultimately mediates increased lung pathology.^{21,22} Therefore, by treating patients infected with SARS-CoV-2 chronically with AT1R blockers, higher ACE2 expression, although seemingly paradoxical, can protect them against acute lung damage.²³

3. COVID-19 and Hematopoiesis

Fan et al. has shown that most patients have normal complete blood count (normal Hb, WBC and platelet count) and lactate dehydrogenase (LDH) when patients first apply to the hospital. Moderate or severe thrombocytopenia, which is common in other viral diseases, has not been observed in COVID-19. The study reported that, 28% of all patients presented with lymphopenia (acute lymphocyte count $< 1 \times 10^9/L$).²⁴ Additionally, it was shown that patients in intensive care units have significantly lower CD45+, CD3+, CD4+, CD8+, CD19+ and CD16/56+ counts.²⁴ Another study observed that most patients had high C reactive protein, erythrocyte sedimentation rate and normal procalcitonin level. In severe cases, D-dimer increased and lymphocytes gradually decreased. It was shown to have high inflammatory parameters in severe and critical patients.²⁵ Another study showed that SARS-CoV-2 directly infects secondary lymphoid organs to cause cell death. Immunofluorescence staining confirmed that viral nucleospicy protein can be found in ACE2 + cells, CD169 + macrophages.²⁶ It can be considered as one of the causes of lymphopenia. Moreover, Wang et al. showed that T-cell lines were remarkably more susceptible to SARS-CoV-2 infection when compared with SARS-CoV.²⁷ In some other studies, patients had normal

or lower white blood cell count, lymphopenia or thrombocytopenia, prolonged active thromboplastin time and increased C-reactive protein level.^{4,28,29} High white blood cell count, high neutrophil count, low lymphocyte count and high LDH values were observed in patients who were referred to intensive care unit.³⁰

Inflammation is the characteristic process of chronic inflammation that has been defined in elderly individuals, with an increase of inflammatory cytokine levels that correlate with morbidity and age-related diseases.^{31,32} The HSC network is closely linked to inflammatory processes as a manufacturer of congenital immune cells. Furthermore, HSCs express receptors required for the identification of dangers and a variety of cytokines and their receptors.^{33,34} In elderly individuals, a variety of factors such as interleukin 6, interleukin 1 receptor antagonist, interleukin 18, fibrinogen and C reactive protein all increase significantly.³² Aging is a proinflammatory condition. The immune response in older people is very exaggerated and insufficient to settle early.³⁵ Leukocytosis, neutrophilia, cytokinemia are more prominent in patients with severe COVID-19. Therefore, various immunomodulatory treatments (chloroquine, anti IL-6 agents, corticosteroids) are thought to be successful in COVID-19. Of the cytokines produced by HSCs and progenitors, interleukin 6 appears to be important as a regulator of paracrine-style proliferations and myeloid differentiation, and as a myelopoiesis driver both in vitro and in vivo.³⁴ Furthermore, tumor necrosis factor (TNF) added to cycling human HSCs both in vitro and in vivo compromises their ability to reconstitute immunodeficient mice and long-term cultures. This effect is mediated by the TNF receptor p55, which seems to assist HSC differentiation.³⁶

4. Hematopoiesis and Bone Marrow Renin Angiotensin System

Circulating RAS and local paracrin-autocrin-intracrin tissue-based RAS participate in numerous pathobiological events. Pro-inflammatory, profibrotic, and pro-thrombotic consequences associated with local RAS activation have been detected at cellular and molecular level. Regenerative pro-

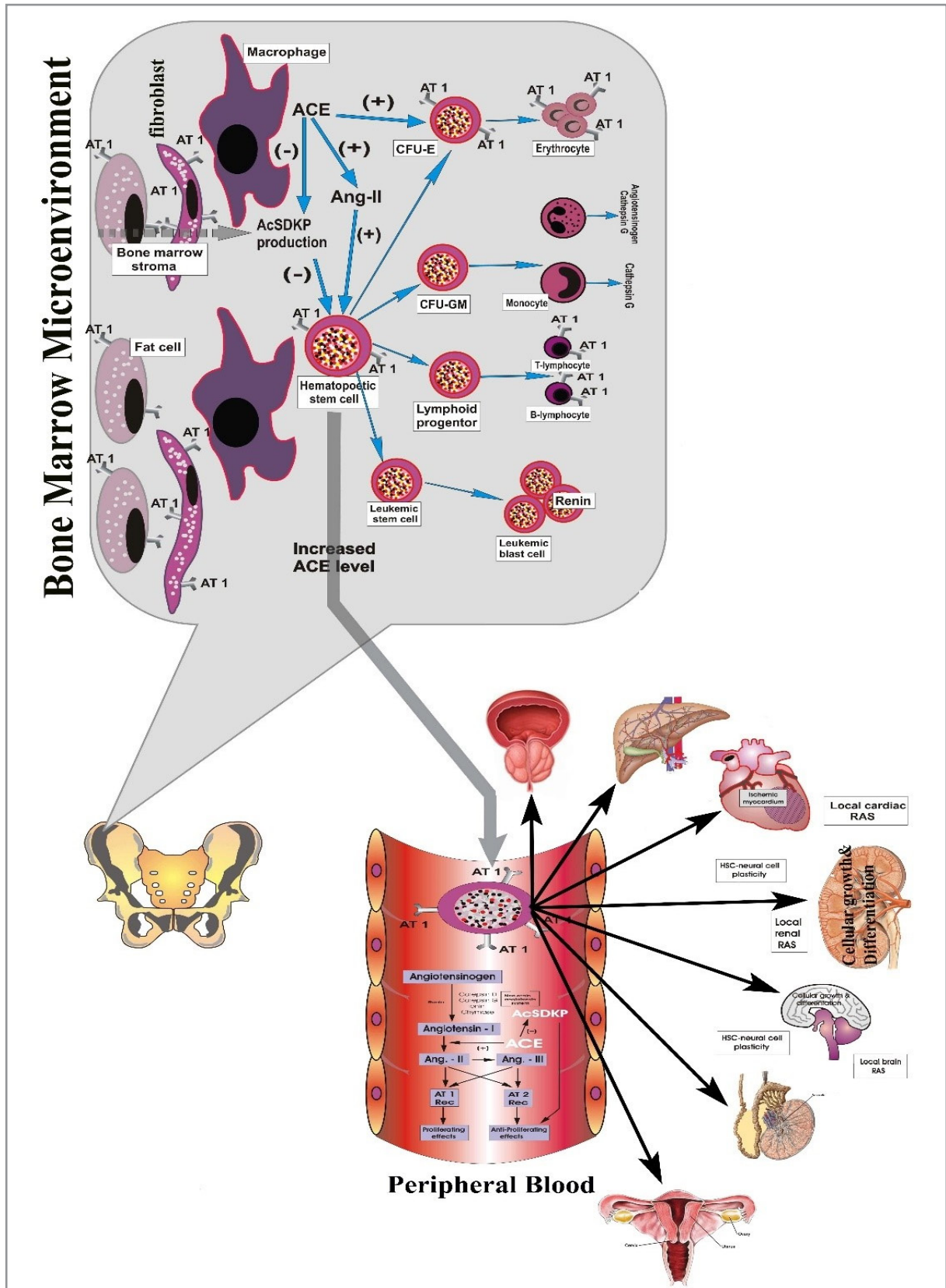


Figure 1. The effect of local RAS on hematopoiesis, as well as systemic circulation. (modified with permission from <https://www.hindawi.com/journals/crp/2011/714515/fig1/>).

genitor cell therapy in response to RAS-modulating pharmacotherapy in context of endothelial cell damage and regeneration emerged as an auxiliary therapy to improve regeneration of the vascular endothelium. Major RAS molecules, including renin, angiotensinogen, angiotensin receptors and ACE are all found in the BM microenvironment.¹¹ Haznedaroglu et al. first hypothesized that there exists a locally active RAS in the BM affecting the growth, production, proliferation and differentiation of hematopoietic cells as depicted in Figure 1.¹² Later, evidence of a local RAS in the bone marrow increased day by day. Locally active BM RAS affects important steps in physiological and pathological blood cell production by autocrine, paracrine and intracrine routes.^{7,8} The development of hematopoietic niche, myelopoiesis, erythropoiesis, thrombopoiesis and other cellular lineage is controlled by local BM RAS peptides.³⁷⁻⁴⁰ Local RAS in the BM stromal niche controls important hematopoietic functions.^{8,11,37-39,41,42} Many important pathobiological events such as apoptosis, cellular proliferative events, mobilization, angiogenesis, fibrosis in the cytokine network are affected by RAS molecules.⁷⁻¹⁰ BM stromal microenvironment includes AT1R and AT2R (angiotensin type 1 and type 2 receptors, respectively) and inhibitory tetrapeptide AcSDKP (N-acetyl-Ser-Asp-Lys-Pro). The major RAS effector agent angiotensin II (Ang II) exerts its effects on the hematopoietic system by activating the AT1Rs and AT2Rs, along with the BM microenvironment.^{7,8}

Ang I, Ang II, Ac-SDKP and Ang 1-7 are secreted in different tissues and transferred to the BM through circulation. ACE converts Ang II from Ang I and reduces bioactive SP, Ac-SDKP and Ang 1-7. Mas, with the Ang 1-7 receptor, is detected in the BM. Peptides in RAS can stimulate hematopoietic cells. Furthermore, local BM RAS plays a role in the development, formation, proliferation and differentiation of hematopoietic progenitors.

5. COVID-19, Renin Angiotensin System and Hematopoiesis

ACE2 has a significant role in the RAS. The imbalance between ACE/Ang II/AT1R pathway and ACE2/Ang (1-7)/Mas receptor pathway in the

RAS leads to multi-system inflammation.⁵ Furthermore, local BM RAS is involved in the regulation of important peptides that control hematopoiesis. Local BM RAS has significant effects on hematopoietic systems, particularly on myeloid and eritroid cells.^{8,12,41} It has been proven in previous studies that there are important receptors of Ang 1-7 and MAS in the bone marrow stroma.⁴³ BM hematopoietic stem/progenitor cells (HSPCs) interact with the cells of secondary lymphoid organs, which control HSPC differentiation and maturation.^{44,45} On the other hand, ACE2 is the common binding site of both the SARS-CoV of the 2002-2003 SARS outbreak and possibly the SARS-CoV-2 strain underlying the current COVID-19 outbreak.¹⁹ Moreover, angiotensin-induced AT1R causes increased pulmonary vascular permeability and thus mediates increased lung pathology.^{21,22} In the light of all these findings, it is thought that RAS has great importance in terms of therapeutic targets in COVID-19. In a recent study, Liu et al. evaluated COVID-19 patients used ACEI, ARB, calcium channel blockers (CCB), beta blockers (BB), or thiazide to treat preexisting hypertension prior to the hospital and patients who did not take any of those drugs. In their meta-analysis, it was concluded that the use of ARB has positive effects on the morbidity and mortality of pneumonia. As a result of this metanalysis, elderly (age > 65) COVID-19 patients with hypertension comorbidity taking ARB medications commented that they may be less likely to develop severe lung disease compared to patients not taking antihypertension medication.⁴⁶

6. Promising Treatment of COVID-19 with Soluble ACE2

It is reported that the genome structure of SARS-CoV-2 looks like those of other betacoronaviruses.⁴⁷ The long replicase ORF1ab gene of SARS-CoV-2 is over 21 kb in length. It includes 16 predicted non-structural proteins and a number of downstream ORFs likely of similar function to those of SARS-CoV.⁴⁷ Many drug development projects, including the development of vaccines, focus on ACE2-SARS-CoV-2 Spike interactions. Wang et al. reported that the crystal structure of C-terminal domain of SARS-CoV-2 spike protein

in complex with human ACE2 (hACE2), which shows a hACE2-binding style alike overall to that observed for SARS-CoV.⁴⁸ ACE2 protects the lung from injury from the SARS-CoV infections. ACE2 has also been identified as a key receptor for SARS-CoV-2 infections.⁴⁹ ACE2 is expressed in various tissues including heart, kidneys, blood vessels, intestine and alveolar epithelial cells.⁵⁰⁻⁵⁶ It has been suggested that inhibition of this interaction can be used in the treatment of patients with COVID-19. Monteil et al. showed that clinical grade human recombinant soluble (hrs) ACE2 can significantly inhibit SARS-CoV-2 infections and reduce viral load by a factor of 1,000-5,000. It has also been shown that SARS-CoV-2 can directly infect human blood vessel organoids and human kidney organoids designed to be inhibited by hrsACE2.⁴⁹

7. Hypotheses

In the light of all this data, the initial stage of viral attack to the body shall be called as “COVID-19 infection” but following ‘virus induced immune depression’ and impaired disproportionate macrophage activation’ should be called as “COVID-19 syndrome”, which is an immune disorder rather than infection. A temporary recommendation based on existing therapeutics that will probably be resistant to new coronavirus mutations can be used to reduce the aggression and mortality rate of SARS-CoV-2 virus infections. This idea is based on observations that the ACE2 very likely serves as the binding site for SARS-CoV-2, the strain implicated in the current COVID-19 epidemic, similarly to strain SARS-CoV (23). All this discussed information evaluates the idea of treating AT1R blockers as a temporary treatment for SARS-CoV-2 infections. It will also guide future research.

Conflict of Interests

The authors of this paper have no conflict of interests, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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