EDITORIAL

Counter-regulatory 'Renin-Angiotensin' System-based Candidate Drugs to Treat COVID-19 Diseases in SARS-CoV-2-infected Patients

SARS-CoV-2 / COVID-19 and the 'Renin-Angiotensin' System

The ubiquitous 'Renin-Angiotensin' system (RAS), also referred to as 'Renin-Angiotensin-Aldosterone' system, plays a crucial physiological role in humans as being a key regulator of renal, cardiovascular and innate immune functions [1, 2]. It appears to work in tandem with vitamin D, a secosteroid pro-hormone which reportedly acts as a negative regulatory factor of the RAS [3-6]. A dysfunction (*e.g.* over-reactivity) of RAS, together with hypovitaminosis D, is likely associated with some of the various renal, cardiac, vascular and immune outcomes that might be observed in COVID-19 patients, including the cytokine storm (*i.e.* unopposed hyperactive immune reaction generating both pro-inflammatory and anti-inflammatory cytokines) and consequent lethal acute respiratory distress syndrome [1, 7]. Recently, SARS-CoV-2 [8, 9], the causative agent of COVID-19, has been described to interfere with the RAS [2] by interacting -*via* its spike (S) glycoprotein- with the metallopeptidase Angiotensin-Converting Enzyme 2 (ACE2) receptor [9, 10] that is expressed at the surface of epithelial cells from blood vessels, lung, kidney (renal tubules), intestine, and heart, as well as on cerebral neurons and immune monocytes/macrophages [11-13]. The main SARS-CoV-2-related COVID-19 symptoms/diseases reported hitherto are hypertension, atherosclerosis, thrombosis (coagulopathy), diarrhea, glaucoma, anosmia, ageusia, skin lesions (dermatitis), autoimmune inflammation of the central nervous system, and damages to various organs such as the lung, heart, kidney, and testicle [1, 2, 14]. All these diffuse COVID-19 disorders are likely linked to an over-reaction of RAS in SARS-CoV-2-infected persons. Such a RAS imbalance would be also favored by hypovitaminosis D [2-7, 11]. Since RAS appears to be central in COVID-19 symptoms/diseases, selective targeting of key component(s) of this system might be appropriate to treat RAS-dependent disorders.

COVID-19 Disorders: 'Renin-Angiotensin' System (RAS) & Counter-regulatory RAS

In the RAS pathway [1, 15], Renin (kidney) cleaves Angiotensinogen (liver) to give Angiotensin I (*i.e.* peptide DRVYIHPFHL). The latter is cleaved by the Angiotensin-Converting Enzyme (ACE) to produce Angiotensin II (*i.e.* peptide DRVYIHPF), which is the substrate of ACE2 (SARS-CoV-2 receptor) and key player of the RAS. The cellular targets of Angiotensin II are the vasoconstrictor type 1 (AT_1R) and vasodilatator type 2 (AT_2R) Angiotensin II receptors (AT_1R is expressed at the surface of monocytes/macrophages and T-cells indicating that RAS acts on innate immunity in host). When cleaved by ACE2, Angiotensin II gives Angiotensin 1-7 (*i.e.* peptide DRVYIHP), targeting the vasodilatator proto-oncogene Mas receptor (MasR). Angiotensin 1-7 can be further transformed to Alamandine (*i.e.* peptide ARVYIHP) by an aspartate decarboxylase. Alamandine would bind to the vasodilatator Mas-related G protein-coupled receptor member D (MRGD) thus promoting most of the Angiotensin 1-7-like effects. Angiotensin II can produce Angiotensin A (*i.e.* peptide ARVYIHPF) *via* an aspartate decarboxylase, and Alamandine *via* an additional ACE2 cleavage. ACE2 can also cleave Angiotensin I to form Angiotensin 1-9 (*i.e.* peptide DRVYIHPFH), which targets AT_2R. In the RAS pathway were finally evidenced the related Angiotensin III (*i.e.* peptide RVYIHPF) and Angiotensin IV (*i.e.* peptide VYIHPF) variants targeting the AT_1R and vasodilatator AT_4R, respectively. From the known molecular functioning of the RAS, Angiotensins I and II (aside Angiotensin III) are playing central roles in the activity of RAS and associated pathologies, including COVID-19 [2, 10]. Interestingly, it appears that a 'counter-regulatory' RAS does exist to modulate system homeostasis; it relies on Angiotensin 1-7, Angiotensin 1-9, Alamandine, Angiotensin A, and Angiotensin IV, which are targeting the MasR, AT_2R, MRGD, ACE2 and AT_4R vasodilatator receptors, respectively. These peptides were found to exhibit cardioprotective, vasoactive (anti-hypertensive), anti-hypertrophic and/or anti-inflammatory potentials [15]. Such naturally-produced molecules of the RAS are expected to counteract the SARS-CoV-2-induced over-activation of RAS and reverse, to some extent, the associated COVID-19 diseases.

CONCLUDING REMARKS

A recent report suggests that RAS inhibitors may act on the severity of viral infection and mortality of COVID-19 patients [14]. Whether or not RAS blockers would be beneficial to COVID-19 cases is still controversial. The RAS inhibitors likely prevent the cytokine storm as RAS is reported to control the release of pro-inflammatory cytokines [1, 7]. It appears that COVID-19 disorders of SARS-CoV-2-infected humans depend on the RAS over-reacted by the (ACE2-dependent) viral infection and vitamin D deficiency. The track for a possible COVID-19 treatment would be to target RAS using specific candidate chemotherapeutic drugs. The proposed molecules are (so far) ACE inhibitors (to prevent the production of Angiotensin II from Angiotensin I), and blockers/antagonists of AT_1R such as Losartan and derivatives. Recombinant ACE2 (under clinical trials) is also considered as a decoy for the recognition and competitive binding to the spike (S) glycoprotein of SARS-CoV-2 [9, 10]. We support the use of natural candidate peptide drugs that belong to the 'counter-regulatory' RAS, *i.e.* Angiotensin 1-7, Angiotensin 1-9, Alamandine, Angiotensin A and/or Angiotensin IV to treat COVID-19 disorders. The targeted receptors would thus be MasR, AT_2R, MRGD, ACE2 and AT_4R.

The authors wish to thank Bonabes De Rougé MD for fruitful discussions.

2212-3989/20

REFERENCES

[1] Perlot, T.; Penninger, J.M. ACE2 - from the renin-angiotensin system to gut microbiota and malnutrition. *Microbes Infect.,* **2013**, *15*(13), 866-873. http://dx.doi.org/10.1016/j.micinf.2013.08.003 PMID: 23962453

[2] Cao, Z.; Wu, Y.; Faucon, E.; Sabatier, J.M. SARS-CoV-2 & Covid-19: key-roles of the 'renin-angiotensin' system / vitamin D impacting drug and vaccine developments. *Infect. Disord. Drug Targets,* **2020**, *20*(3), 348-349. http://dx.doi.org/10.2174/1871526520999200505174704 PMID: 32370727

[3] Leung, P.S. The modulatory action of vitamin D on the renin-angiotensin system and the determination of hepatic insulin resistance. *Molecules,* **2019**, *24*(13), 2479-2482. http://dx.doi.org/10.3390/molecules24132479 PMID: 31284538

[4] Ajabshir, S.; Asif, A.; Nayer, A. The effects of vitamin D on the renin-angiotensin system. *J. Nephropathol.,* **2014**, *3*(2), 41-43. PMID: 24772394

[5] Aranow, C. Vitamin D and the immune system. *J. Investig. Med.,* **2011**, *59*(6), 881-886. http://dx.doi.org/10.2310/JIM.0b013e31821b8755 PMID: 21527855

[6] Ilie, P.C.; Stefanescu, S.; Smith, L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin. Exp. Res.,* **2020**, *32*(7), 1195-1198. http://dx.doi.org/10.1007/s40520-020-01570-8 PMID: 32377965

[7] Daneshkhah, A.; Eshein, A.; Subramanian, H.; Roy, H.K.; Backman, V. The role of vitamin D in suppressing cytokine storm in COVID-19 patients and associated mortality *medRxiv preprint,* **2020**.

[8] Wan, Y.; Shang, J.; Graham, R.; Baric, R.S.; Li, F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J. Virol.,* **2020**, *94*(7), 1-9. http://dx.doi.org/10.1128/JVI.00127-20 PMID: 31996437

[9] Lan, J.; Ge, J.; Yu, J.; Shan, S.; Zhou, H.; Fan, S.; Zhang, Q.; Shi, X.; Wang, Q.; Zhang, L.; Wang, X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature,* **2020**, *581*(7807), 215-220. http://dx.doi.org/10.1038/s41586-020-2180-5 PMID: 32225176

[10] Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.H.; Nitsche, A.; Müller, M.A.; Drosten, C.; Pöhlmann, S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically-proven protease inhibitor. *Cell,* **2020**, *181*(2), 271-280.e8. http://dx.doi.org/10.1016/j.cell.2020.02.052 PMID: 32142651

[11] Magrone, T.; Magrone, M.; Jirillo, E. Focus on receptors for coronaviruses with special reference to Angiotensin-converting Enzyme 2 as a potential drug target – A perspective. *Endocr. Metab. Immune Disord. Drug Targets,* **2020**, *20*(6), 807-811. http://dx.doi.org/10.2174/1871530320666200427112902 PMID: 32338224

[12] Rudemiller, N.P.; Crowley, S.D. Interactions between the immune and the renin-angiotensin systems in hypertension. *Hypertension,* **2016**, *68*(2), 289-296. http://dx.doi.org/10.1161/HYPERTENSIONAHA.116.06591 PMID: 27354427

[13] Crowley, S.D.; Rudemiller, N.P. Immunologic effects of the renin-angiotensin system. *J. Am. Soc. Nephrol.,* **2017**, *28*(5), 1350-1361. http://dx.doi.org/10.1681/ASN.2016101066 PMID: 28151411

[14] Vaduganathan, M.; Vardeny, O.; Michel, T.; McMurray, J.J.V.; Pfeffer, M.A.; Solomon, S.D. Renin-Angiotensin-Aldosterone system inhibitors in patients with Covid-19. *N. Engl. J. Med.,* **2020**, *382*(17), 1653-1659. http://dx.doi.org/10.1056/NEJMsr2005760 PMID: 32227760

[15] Paz Ocaranza, M.; Riquelme, J.A.; García, L.; Jalil, J.E.; Chiong, M.; Santos, R.A.S.; Lavandero, S. Counter-regulatory renin-angiotensin system in cardiovascular disease. *Nat. Rev. Cardiol.,* **2020**, *17*(2), 116-129. http://dx.doi.org/10.1038/s41569-019-0244-8 PMID: 31427727

Dr. Cédric ANNWEILER
(*Editor*)
Department of Geriatric Medicine and Memory Clinic, Research Center on Autonomy and Longevity, University Hospital, Angers, France; Laboratoire de Psychologie des Pays de la Loire, LPPL EA 4638, SFR Confluences, University Angers and University Nantes, France; Department of Medical Biophysics, Schulich School of Medicine and Dentistry, Robarts Research Institute, The University of Western Ontario, London, Ontario, Canada.

Dr. Zhijian CAO
(*Editor*)
State Key Laboratory of Virology, Modern Virology Research Center, College of Life Sciences, Wuhan University, Wuhan 430072, China

Dr. Yingliang WU
(*Editor*)
State Key Laboratory of Virology, Modern Virology Research Center, College of Life Sciences, Wuhan University, Wuhan 430072, China

Dr. Emmanuelle FAUCON
(*Editor*)
EFFE, 252 Bd Grignan, 83000 Toulon, France

Dr. Stéphanie MOUHAT
(*Editor*)
EFFE, 252 Bd Grignan, 83000 Toulon, France

Dr. Hervé KOVACIC
(*Editor*)
Université Aix-Marseille, Institut de Neuro-physiopathologie (INP), UMR 7051, Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille Cedex, France

Dr. Jean-Marc SABATIER
(*Editor-in-Chief*)
Université Aix-Marseille, Institut de Neuro-physiopathologie (INP), UMR 7051, Faculté de Pharmacie, 27 Bd Jean Moulin, 13385 Marseille Cedex, France