Receptor for advanced glycation end-products axis and coronavirus disease 2019 in inflammatory bowel diseases: A dangerous liaison?

Armando Rojas, Iván Schneider, Cristian Lindner, Ileana González, Miguel Angel Morales

ORCID number: Armando Rojas 0000-0001-9911-7142; Iván Schneider 0000-0001-5294-5995; Cristian Lindner 0000-0002-2642-4288; Ileana González 0000-0002-2488-9380; Miguel Angel Morales 0000-0001-7698-9669.

Author contributions: All authors contributed to the original ideas and writing of this paper; Rojas A designed the report and wrote the paper; Schneider I and Lindner C contributed to data collection and draft manuscript preparation and art-work, and both contributed equally; González I and Morales MA contributed to data acquisition and drafting and revising the manuscript.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Abstract

Compelling evidence supports the crucial role of the receptor for advanced glycation end-products (RAGE) axis activation in many clinical entities. Since the beginning of the coronavirus disease 2019 pandemic, there is an increasing concern about the risk and handling of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in inflammatory gastrointestinal disorders, such as inflammatory bowel diseases (IBD). However, clinical data raised during pandemic suggests that IBD patients do not have an increased risk of contracting SARS-CoV-2 infection or develop a more severe course of infection. In the present review, we intend to highlight how two potentially important contributors to the inflammatory response to SARS-CoV-2 infection in IBD patients, the RAGE axis activation as well as the cross-talk with the renin-angiotensin system, are dampened by the high expression of soluble forms of both RAGE and the angiotensin-converting enzyme (ACE) 2. The soluble form of RAGE functions as a decoy for its ligands, and soluble ACE2 seems to be an additionally attenuating contributor to RAGE axis activation, particularly by avoiding the transactivation of the RAGE axis that can be produced by the virus-mediated imbalance of the ACE/angiotensin II/angiotensin II receptor type 1 pathway.

Key Words: COVID-19; Inflammatory bowel diseases; Advanced glycation; Angiotensin-converting enzyme 2; Alarmins; Receptor for advanced glycation end-products; Receptor for advanced glycation end-products axis; Inflammation

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
INTRODUCTION

At the end of 2019, China reported several cases of severe pneumonia of unknown cause; the coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was subsequently identified as the etiological agent[1]. Due to its rapid spread all over the world, the World Health Organization defined coronavirus disease 2019 (COVID-19) as a pandemic on January 30, 2020.

The main symptoms of COVID-19 affect the lower respiratory tract, causing high mortality-rate complications such as acute distress respiratory syndrome[2-6]. However, recent reports reveal that gastrointestinal (GI) manifestations of SARS-CoV-2 infection are common clinical symptoms among patients who develop COVID-19[7-11].

The SARS-CoV-2 uses the cellular transmembrane angiotensin-converting enzyme 2 (ACE2) molecule as the receptor for viral cell entry. Under physiological conditions, epithelial ACE2 is widely expressed in several tissues. However, the expression of epithelial ACE2 in the terminal ileum and colon are amongst the highest in the body, which could explain why COVID-19 patients experience several GI symptoms[12-16].

Consequently, there is an increasing concern about the risk and handling of SARS-CoV-2 infection in inflammatory GI disorders, such as inflammatory bowel disease (IBD). The IBDs are chronic intestinal diseases that comprise Crohn’s disease (CD) and ulcerative colitis, which are characterized by chronic and relapsing intestinal inflammation[17,18]. Thus, since the beginning of the SARS-CoV-2 pandemic, IBD patients were considered a high-risk group for increased severity and adverse outcomes in SARS-CoV-2 infection[19,20].

However, clinical data raised during pandemic suggest that IBD patients do not have an increased risk of contracting SARS-CoV-2 infection or develop a more severe course of infection[21-25]. A compelling body of both clinical and experimental evidence has shed light on the crucial role of the receptor of advanced glycation end-products (RAGE) activation in many chronic inflammatory diseases[26-31]. More recently, the role of RAGE axis activation as a key contributor in the clinical course of SARS-CoV-2 infection has been documented[32].

In the present review, we intend to highlight the role of the RAGE axis activation in the context of SARS-CoV-2 infection and the clinical evolution of the IBD patient.

RAGE AXIS

Firstly described in 1992, the RAGE is a type I single-pass transmembrane protein that can bind advanced glycation-end products (AGEs). This molecule belongs to the immunoglobulin superfamily of cell surface receptors, which is now considered as a pattern recognition receptor and is regarded as a central mediator in chronic inflammatory and immune responses[33-35].

RAGE is usually expressed at low levels in many cell types and tissues, except for the lungs. However, this expression is noticeably increased under inflammatory conditions[36-38].
Besides the transmembrane form of RAGE, several soluble isoforms of this receptor (sRAGE) are generated either by alternative splicing or by the action of membrane associated-protexases, such matrix metalloproteinase-9 (MMP-9), a disintegrin metallo-protexases (ADAM)-10, and ADAM-17[39-42]. These soluble variants may function as a decoy receptor for ligands and thus prevent the interaction with the membrane-anchored full-length RAGE. In consequence, a high bioavailability of sRAGE will decreases the inflammatory responses driven by full-length RAGE activation [35,43,44]. Besides AGEs, RAGE can recognize many other ligands including the alarin high-mobility group box 1 (HMGB1), members of the S100 protein family, glycosaminoglycans, and amyloid β peptides, among many others[35,45].

As a consequence of RAGE engagement by its ligands, multiple signaling pathways are triggered, including reactive oxygen species, p21ras, extracellular signal-regulated protein kinase 1/2 (p44/p42) mitogen-activated protein (MAP) kinases, p38 and stress-activated protein kinases/c-Jun N-terminal kinase mitogen-activated protein kinases, rhoGTPases, phosphoinositol-3 kinase, and the janus kinase/signal transducer and activator of transcription pathway, having crucial downstream inflammatory consequences such as activation of nuclear factor-kappaB (NF-κB), AP-1, and signal transducer and activator of transcription-3[33].

Indeed, the RAGE axis signaling not only triggers pro-inflammatory gene expression but also a positive feed-forward loop, in which the inflammatory stimuli activate NF-κB, which induces RAGE expression, following an enhanced and sustained inflammatory response[35,46-48].

RAGE AXIS ACTIVATION IN IBD

Initially, RAGE axis activation was linked to the complications of diabetes such as macro- and microvascular complications[49,50]. However, a growing body of evidence indicates RAGE as a key molecule involved in many chronic inflammatory diseases[28-30,51].

Many underlying molecular mechanisms are involved in the onset and perpetuation of the disease, particularly those fueling the robust pro-inflammatory signals found in IBD patients[26,52]. Noteworthy, some pieces of evidence reveal an increased expression of RAGE and its ligands on intestinal cells in IBD patients, especially in inflamed areas[53-55]. In this context, it is important to highlight that the release of the RAGE ligand HMGB1 and members of the S100 protein family is increased under inflammation conditions[54-57]. Thus, the engagement of RAGE may play an important role in the maintenance of intestinal injury and inflammatory environment [53-57].

Strikingly, increased levels of both MMP-9 and ADAM17 have been reported in IBD patients[58,59], and both metalloproteases are involved in RAGE shedding, thus increasing the levels of sRAGE, which in turn can modulate the inflammatory responses driven by RAGE axis activation in IBD patients[58]. At present, a compelling body of evidence supports the fact that increased sRAGE levels correlate with a decrease in the RAGE activation-mediated inflammatory responses in many clinical entities[60-63]. In this context, it is important to highlight that CD147 significantly contributes to epithelial inflammation in many clinical entities including IBD[64,65], and it has been recently shown to act as a receptor for SARS-CoV-2[66]. Noteworthy, the inhibition of RAGE activation-mediated inflammatory response leads to a reduced expression of CD147[67].

THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAS) is a hormonal system regulated by two complementary pathways that mediate opposing effects on inflammation, fibrosis, and cell proliferation[68-70]. Thus, the balance of both pathways determines pro-inflammatory or anti-inflammatory conditions among several systems such as cardiovascular, renal, and respiratory systems[71-74].

The classical pathway mediated via ACE, angiotensin II (Ang II) and its receptor Ang II receptor type 1 (AT1R), triggers activation of pro-inflammatory signals such as oxidative and nitrosative stresses, the induction of cytokines and cell adhesion molecules, as well as the activation of transcription factors such NF-κB[75-78]. On the contrary, the alternative pathway predominantly mediated by ACE2, Ang (1-7) and its receptor Mas (MasR), induces the opposite effects of AT1R activation, being an anti-
inflammatory and anti-fibrotic counter regulator of the effects of ACE/Ang II/AT1R[71,75,79,80]. ACE and ACE2 are highly expressed in several tissues such as the lungs, kidneys, and blood vessels. However, the brush border of the ileum and the colon are among the tissues with the highest expression of both enzymes[13-16,81]. Both enzymes can cleave angiotensin, generating different sub-products and regulating the balance between both pathways of the RAS system[79,82,83].

**RAS IMBALANCE IN IBD**

Recent studies suggest high expression of the major components of both RAS pathways across the ileum and colon[81]. In this sense, the gut could be an especially susceptible organ for the imbalance of RAS pathways. Thus, the dysregulation of these components could have potential implications for inflammation and fibrosis for IBD patients[84,85]. Strikingly, several studies have revealed that the intestinal expression of ACE2 is inversely correlated with fibrosis in IBD patients[81,86].

Additionally, Ang (1-7) ameliorates colonic myofibroblast collagen secretion via MasR[81]. Furthermore, angiotensin receptor blockers and ACE inhibitors are reported to decrease mucosal pro-inflammatory cytokines, ameliorate colitis, and were associated with lower rates of complications, surgery, and hospitalization in patients with IBD[87-89].

Normally, ACE2 breaks down Ang II to Ang 1–7 peptide and thus avoiding the activation of the pro-inflammatory pathways of RAS. However, SARS-CoV-2 can hijack ACE2 and use it to gain entry into host cells[12,90]. Noteworthy, high bioavailability of soluble ACE2 has been reported in IBD patients[81,84], mainly ascribed to the increased level of ADAM17 observed in these patients[58,91-93], which in turn may function as a decoy receptor for SARS-CoV-2 and thus avoiding the hijacking of the counterbalancing enzyme.

This is particularly important considering that a novel ligand-independent mechanism for RAGE transactivation has been recently reported to occur following activation of the AT1R by Ang-II, thus leading to NF-κB dependent expression of pro-inflammatory mediators[48].

**RAGE AXIS ACTIVATION AND RAS IMBALANCE IN IBD PATIENTS INFECTED WITH SARS-COV-2**

Contrary to what is expected, considering the pathophysiology of IBD, there is currently no evidence for an increased risk of worse clinical outcomes in patients with IBD in the context of COVID-19[21-25]. The role of the RAGE axis in the pathophysiology of IBD has been suggested by different reports[53-57]. The colonic expression of RAGE and some RAGE ligands, such as HMGB1 and some members of the S100 protein family, are significantly higher in IBD patients[54-56]. Besides, this receptor has been also considered a key contributor to the dysregulated and misdirected COVID-19 inflammatory response[32,94].

However, a counterbalancing element must be added to this scenario: The soluble RAGE. This molecule is generated by alternative splicing or by cleavage of the ectodomain of the membrane-anchored RAGE by the action of both MMP-9 and ADAM17, which are highly expressed in IBD patients[58,59]. Therefore, the high bioavailability of soluble RAGE may dampen RAGE activation, despite the abundance of both receptor and ligands in the inflamed intestinal mucosa of IBD patients.

On the other hand, the high expression of ACE2 in GI tract, especially among IBD patients, makes this tissue a particularly trophic niche for infection with SARS-CoV-2. Furthermore, the ACE2 exhaustion mediated by the entry of SARS-CoV-2 may then induce a robust RAS imbalance in favor of the pro-inflammatory ACE/Ang II/AT1R pathway[95]. These observations suggest that the inflamed gut of IBD patients represents an optimal doorway for SARS-CoV-2 entry, driving poor clinical outcomes in IBD patients who develop COVID-19.

However, this hypothetical scenario also has an important counterbalancing actor, the soluble form of ACE2, which is also increased in patients with IBD due to the shedding of the membrane-anchored ACE2 by ADAM17[58-59]. This is particularly important considering the non-cognate transactivation mechanism described for RAGE because of AT1R activation by Ang II[48], which is dampened by the preservation of membrane-associated ACE2 exhaustion by its soluble form.
Figure 1 In inflammatory bowel diseases patients, different inflammation–prone mechanisms are known to be activated. Among them, the overexpression of receptor for advanced glycation end-products (RAGE) and the abundance of its ligands may produce a sustained activation of the axis, which can be also fueled by a non-cognate mechanism due to the pro-inflammatory rat sarcoma imbalance. These elements seem to be crucial contributors to the worsening course of inflammatory bowel diseases (IBD) patients with coronavirus disease 2019. However, other elements may dampen these inflammatory contributions, such as the high bioavailability of the soluble forms of both RAGE and angiotensin-converting enzyme 2. Soluble angiotensin-converting enzyme 2 may even interfere with severe acute respiratory syndrome coronavirus 2 entry to epithelial cells. Additionally, most if not all IBD patients are under pharmacological treatments directed to control inflammation. IBD patients deserve special attention to their diets, and as consequence, it is likely the ingestion of dietary advanced glycation-end products is also limited. RAGE: Receptor for advanced glycation end-products; RAS: Renin-angiotensin; ACE2: Angiotensin-converting enzyme 2; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; AT1R: Angiotensin II receptor type 1; AGES: Advanced glycation-end products; sRAGE: Several soluble isoforms of this receptor.

CONCLUSION

The COVID-19 pandemics represent the worst challenge for a century for health systems all over the world. Severity and mortality have been highest in people with underlying morbidities. Therefore, special efforts have been done to understand how SARS-CoV-2 may particularly fuel inflammation in many clinical entities where the chronicity of an inflammatory environment is a relevant part of the pathogenesis of diseases. Based on a particularly inflamed landscape depicted in IBD patients, the activation of the RAGE axis as well the RAS imbalance seem to be crucial contributors to worsen inflammation in the gut. However, data raised during the pandemic suggests that IBD patients have neither an increased risk of contracting SARS-CoV-2 infection nor developing a more severe course of infection.
RAGE axis activation seems to be dampened by the high bioavailability of soluble receptors functioning as a decoy for its ligands. Additionally, soluble ACE2 seems to be another attenuating contributor to RAGE axis activation, particularly by avoiding receptors functioning as a decoy for its ligands. Additionally, soluble ACE2 seems to dampen RAGE axis activation by the high bioavailability of soluble RAGE. Hence, soluble ACE2 and RAGE axis activation are another attenuating contributor to RAGE axis activation, particularly by avoiding receptors functioning as a decoy for its ligands. Additionally, soluble ACE2 seems to dampen RAGE axis activation by the high bioavailability of soluble RAGE.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020; 382: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

2. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion TR Jr, Nahid M, Ringel JB, Hoffman KL, Alishak MN, Li HA, Wehmeyer GT, Rajan M, Reshetynak E, Hupert N, Horn EM, Martinez FJ, Gulick RM, Safford MM. Clinical Characteristics of Covid-19 in New York City. N Engl J Med 2020; 382: 2372-2374 [PMID: 32302078 DOI: 10.1056/NEJMcv2010419]

3. Hui KPY, Cheung MC, Perera RPM, Ng KC, Bui CHT, Ho JCW, Ng MMT, Kuok DIT, Shih KC, Tsao SW, Poon LLM, Peiris M, Nicholls JM, Chan MCW. Tropism, replication competence, and innate immune responses of the coronavirus SARS-CoV-2 in human respiratory tract and conjunctiva: an analysis in ex vivo and in vitro cultures. Lancet Respir Med 2020; 8: 687-695 [PMID: 32386571 DOI: 10.1016/s2213-2600(20)30193-4]

4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Li XL, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen R, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZL, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708-1720 [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]

5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Zhang Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 496-503 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

6. Lai CC, Shih TP, Ko WC, Tang HJ, Hsupeh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020; 55: 105924 [PMID: 32081636 DOI: 10.1016/j.ijantimicag.2020.105924]

7. Zhou Z, Zhao N, Shu Y, Han S, Chen B, Shu X. Effect of Gastrointestinal Symptoms in Patients With Coronavirus. Gastroenterology 2020; 158: 2294-2297 [PMID: 32199880 DOI: 10.1053/j.gastro.2020.03.020]

8. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, Hao SR, Jia HY, Cai H, Zhang XL, Yu GD, Xu KJ, Wang XY, Gu Q, Zhang SY, Ye CY, Jin CL, Lu YF, Yu X, Yu XP, Huang JR, Xu KL, Ni Q, Yu CB, Zhu B, Li YT, Liu J, Zhao H, Zhang X, Yu L, Gao Y, Zou W, Zhao Y, Wu MM, Ye CY, Jin KL, Li SY, He JH, Wei Y, Wu W, Xie X, Wei X, Wang Y, Li X, Zhang L, Fan G, Xu J, Gu X, Zhang Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 496-503 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

9. Xiao F, Tang M, Zhang X, Liu Y, Li X, Shan H. Evidences for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology 2020; 158: 1831-1833. e3 [PMID: 32142773 DOI: 10.1053/j.gastro.2020.02.055]

10. Garg M, Christensen B, Lubel JS. Gastrointestinal ACE2, COVID-19 and IBD: Opportunity in the Face of Tragedy? Gastroenterology 2020; 159: 1623-1624.e3 [PMID: 32353370 DOI: 10.1053/j.gastro.2020.04.051]

11. Grassia R, Testa S, Pan A, Conti CB. SARS-CoV-2 and gastrointestinal tract: The dark side of the pandemic. Dig Liver Dis 2020; 52: 700-701 [PMID: 32423849 DOI: 10.1016/j.dld.2020.04.023]

12. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, 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: 271-280. e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

13. GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. Nat Genet 2013; 45: 580-585 [PMID: 23715323 DOI: 10.1038/ng.2653]

14. Hamming I, Timens W, Bulhuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004; 203: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]

15. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA profiling of ACE2, a novel homologue of angiotensin converting enzyme. FEBS Lett 2002; 532: 107-110 [PMID: 12459472 DOI: 10.1016/s0014-5793(02)03640-2]

16. Sibony M, Gasc JM, Soubrier F, Alhenc-Gelas F, Corvol P. Gene expression and tissue localization of the two isoforms of angiotensin I converting enzyme. Hypertension 1993; 21: 827-835 [PMID: 8072887]
mediates neutrophil migration across intestinal epithelium.

González I, Pérez-Castro R, Rojas A. The immunobiology of the receptor of advanced glycation end-products: a complex signaling scenario for a promiscuous receptor. Cell Signal 2013; 25: 609-614 [PMID: 23200851 DOI: 10.1016/j.cellsig.2012.11.022]

Zen K, Chen CX, Chen YT, Wilton R, Liu Y. Receptor for advanced glycation endproducts mediates neutrophil migration across intestinal epithelium. J Immunol 2007; 178: 2483-2490 [PMID: 17277156 DOI: 10.4049/jimmunol.178.4.2483]

González I, Romero J, Rodríguez BL, Pérez-Castro R, Rojas A. The immunobiology of the receptor of advanced glycation end-products: trends and challenges. Immunobiology 2013; 218: 790-797
Manolakis AC, Cugusi S, Antonelli A, Barabino SM, Monti L, Bierhaus A, Reiss K, SafiP, Bianchi ME. A soluble form of the receptor for advanced glycation endproducts (RAGE) is produced by proteolytic cleavage of the membrane-bound form by the sheddase a disintegrin and metalloprotease 10 (ADAM10). JASEB J 2008; 22: 3716-3727 [PMID: 18603587 DOI: 10.1065/jf.08-109032]

Zhang L, Bukulin M, Kojro E, Roth A, Metz VV, Frauenholz F, Nawroth PP, Bierhaus A, Postina R. Receptor for advanced glycation end products is subjected to protein ectodomain shedding by metalloproteinases. J Biol Chem 2008; 283: 35507-35516 [PMID: 18952609 DOI: 10.1074/jbc.M806948200]

Deuss M, Reiss K, Hartmann D. Part-time alpha-secretases: the functional biology of ADAM 9, 10 and 17. Curr Alzheimer Res 2008; 5: 187-201 [PMID: 18393804 DOI: 10.2174/156720508783954686]

Metz VV, Kojro E, Rat D, Postina R. Induction of RAGE shedding by activation of G protein-coupled receptors. PLoS One 2012; 7: e41823 [PMID: 22860017 DOI: 10.1371/journal.pone.0041823]

Grauen Larsen H, Marinovic G, Nilsson PM, Nilsson J, Engstrom G, Melander O, Orho-Melander M, Schiopu A. High Plasma sRAGE (Soluble Receptor for Advanced Glycation End Products) Is Associated With Slower Carotid Intima-Media Thickness Progression and Lower Risk for First-Time Coronary Events and Mortality. Arterioscler Thromb Vasc Biol 2019; 39: 925-933 [PMID: 30917679 DOI: 10.1161/ATVBAHA.118.312319]

Geroldi D, Falcone C, Emanuele E. Soluble receptor for advanced glycation end products: from disease marker to potential therapeutic target. Curr Med Chem 2006; 13: 1971-1978 [PMID: 16842191 DOI: 10.2174/092986706777585013]

Bucciarelli LG, Wendt T, Rong L, Lalla E, Hofmann MA, Goova MT, Taguchi A, Yan SF, Yan SD, Stern DM, Schmidt AM. RAGE is a multiligand receptor of the immunoglobulin superfamily: implications for homeostasis and chronic disease. Cell Mol Life Sci 2002; 59: 1117-1128 [PMID: 12222959 DOI: 10.1007/s00018-002-8491-x]

Bierhaus A, Schieker S, Schwaninger M, Andrassy M, Humphet PM, Chen J, Hong M, Luther T, Henle T, Klöting I, Morcos M, Hofmann M, Tritschler H, Weigle B, Kasper M, Smith M, Perry G, Schmidt AM, Stern DM, Häring HU, Schleicher E, Nawroth PP. Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. Schmid AM, Stern DM, Schmidt AM. RAGE is a multiligand receptor of the immunoglobulin superfamily: implications for homeostasis and chronic disease. Cell Mol Life Sci 2002; 59: 1117-1128 [PMID: 12222959 DOI: 10.1007/s00018-002-8491-x]

Manigrasso MB, Sanna C, Pavia E, Pennacchio I, Nicastri G, Forsi G, Marchesini G, Angelico M, Ianzini G, Belloni C, Monti L, Bierhaus A, Schiopu A. High Plasma sRAGE (Soluble Receptor for Advanced Glycation End Products) Is Associated With Slower Carotid Intima-Media Thickness Progression and Lower Risk for First-Time Coronary Events and Mortality. Arterioscler Thromb Vasc Biol 2019; 39: 925-933 [PMID: 30917679 DOI: 10.1161/ATVBAHA.118.312319]

Manigrasso MB, Sanna C, Pavia E, Pennacchio I, Nicastri G, Forsi G, Marchesini G, Angelico M, Ianzini G, Belloni C, Monti L, Bierhaus A, Schiopu A. High Plasma sRAGE (Soluble Receptor for Advanced Glycation End Products) Is Associated With Slower Carotid Intima-Media Thickness Progression and Lower Risk for First-Time Coronary Events and Mortality. Arterioscler Thromb Vasc Biol 2019; 39: 925-933 [PMID: 30917679 DOI: 10.1161/ATVBAHA.118.312319]

Ramosamy R, Yan SF, Schmidt AM. The RAGE axis and endothelial dysfunction: maladaptive roles in the diabetic vasculature and beyond. Trends Cardiovasc Med 2005; 15: 237-243 [PMID: 16226677 DOI: 10.1016/j.tcm.2005.08.003]

Manigrasso MB, Jurank J, Ramosamy R, Schmidt AM. Unlocking the biology of RAGE in diabetic microvascular complications. Trends Endocrinol Metab 2014; 25: 15-22 [PMID: 24011512 DOI: 10.1016/j.tem.2013.08.002]

Sims GP, Rowe DC, Rietdijk ST, Herbst R, Coyle AJ. HMGB1 and RAGE in inflammation and cancer. Ann Rev Immunol 2010; 28: 367-388 [PMID: 20192808 DOI: 10.1146/annurev.immunol.021908.132603]

Yadav V, Varum F, Bravo R, Furrer E, Bojic A, Basit AW. Inflammatory bowel disease: exploring gut pathophysiology for novel therapeutic targets. Transl Res 2016; 176: 38-68 [PMID: 27220087 DOI: 10.1016/j.trsl.2016.04.009]

Ciccoceppio R, Vanoli A, Klersy C, Imbesi V, Bocccaccio V, Manca R, Betti E, Cangemi GC, Strada E, Besio R, Rossi A, Falcone C, Ardizzone S, Fociani P, Danelli P, Corazza GR. Role of the advanced glycation end products receptor in Crohn's disease inflammation. World J Gastroenterol 2013; 19: 8269-8281 [PMID: 24363518 DOI: 10.3748/wjg.v19.i15.8269]

Hu Z, Wang X, Gong L, Wu G, Peng X, Tang X. Role of high-mobility group box 1 protein in inflammatory bowel disease. Inflamm Res 2015; 64: 557-563 [PMID: 26077468 DOI: 10.1007/s00011-015-0841-x]

Foeld D, Kucharzik T, Kraft M, Vogl T, Sorg C, Domschke W, Roth J. Neutrophil derived human S100A12 (EN-RAGE) is strongly expressed during chronic active inflammatory bowel disease. Gut 2003; 52: 847-853 [PMID: 12740341 DOI: 10.1136/gut.52.6.847]

Yamasaki H, Mitsuayuma K, Masuda J, Kuvwaki K, Takedatsu H, Sugiyama G, Yamada S, Sata M. Roles of high-mobility group box 1 in murine experimental colitis. Mol Med Rep 2009; 2: 23-27 [PMID: 21475785 DOI: 10.3892/mmr_00000056]

Manolakis AC, Kapsoritakis AN, Tiaka EK, Potamianos SP. Calprotectin, calgranulin C, and other members of the s100 protein family in inflammatory bowel disease. Dig Dis Sci 2011; 56: 1601-1611 [PMID: 21203903 DOI: 10.1007/s10620-010-1494-9]
Rojas A et al. IBD, RAGE axis and COVID-19

58 Cesaro A, Abakar-Mahamat A, Brest P, Lassalle S, Selva E, Filippi J, Hébuterne X, Hugot JP, Doglio A, Galland F, Naquet P, Vouret-Craviari V, Mograbi B, Hofman PM. Differential expression and regulation of ADAM17 and TIMP3 in acute inflamed intestinal epithelia. *Am J Physiol Gastrointest Liver Physiol* 2009; 296: G1352-G1343 [PMID: 19299578 DOI: 10.1152/ajpgi.90641.2008]

59 Meijer MJ, Mieremet-Ooms MA, van der Zom AM, van Duijn W, van Hogezaand RA, Sier CF, Hommes DW, Lammers CB, Verspaget HW. Increased mucosal matrix metalloproteinase-1, -2, -3 and -9 activity in patients with inflammatory bowel disease and the relation with Crohn's disease phenotype. *Dig Liver Dis* 2007; 39: 733-739 [PMID: 17602907 DOI: 10.1016/j.dld.2007.05.010]

60 Park L, Raman KG, Lee KJ, Lu Y, Ferran LJ Jr, Chow WS, Stern D, Schmidt AM. Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation end products. *Nat Med* 1998; 4: 1025-1031 [PMID: 9734395 DOI: 10.1038/2012]

61 Lalla E, Lamster IB, Feit M, Huang L, Spessot A, Qu W, Kislinger T, Lu Y, Stern DM, Schmidt AM. Blockade of RAGE suppresses periodontitis-associated bone loss in diabetic mice. *J Clin Invest* 2000; 105: 1117-1124 [DOI: 10.1172/JCI8942]

62 Wendt T, Harja E, Bucciarelli L, Qu W, Lu Y, Rong LL, Jenkins DG, Stein G, Schmidt AM, Yan SF. RAGE modulates vascular inflammation and atherosclerosis in a murine model of type 2 diabetes. *Atherosclerosis* 2006; 185: 70-77 [PMID: 16076470 DOI: 10.1016/j.atherosclerosis.2005.06.013]

63 Bucciarelli LG, Wendt T, Qu W, Lu Y, Lalla E, Rong LL, Goova MT, Moser B, Kislinger T, Lee DC, Kashyap Y, Stern DM, Schmidt AM. RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice. *Circulation* 2002; 106: 2827-2835 [PMID: 12451010 DOI: 10.1161/01.CIR.0000019325.03698.36]

64 Wang H, Ye J, Liu R, Chen G, Zhao J, Huang L, Yang F, Li M, Zhang S, Jinxie, Xiong L, Chen H, Xu Y, Su M, Xie Y, Zheng F, Geng L, Xu W, Gong S. Clinical Significance of CD147 in Children with Inflammatory Bowel Disease. *Biomed Res Int* 2020; 2020: 7647181 [PMID: 33015178 DOI: 10.1155/2020/7647181]

65 Xu Z, Liu R, Huang L, Xu Y, Su M, Chen J, Geng L, Xu W, Gong S. CD147 Aggravated Inflammatory Bowel Disease by Triggering NF-kB-Mediated Pyroptosis. *Biomed Res Int* 2020; 2020: 5341247 [PMID: 32714980 DOI: 10.1155/2020/5341247]

66 Wang K, Chen W, Zhang Z, Deng Y, Lian JQ, Du P, Wei D, Zhang Y, Sun XX, Gong L, Yang X, He L, Zhang L, Yang Z, Geng JJ, Chen R, Zhang H, Wang B, Zhu YM, Nan G, Jiang JL, Li L, Wu J, Lin P, Huang W, Xie L, Zheng ZH, Zhang K, Miao JL, Cui HY, Huang M, Zhang J, Fu L, Yang XM, Zhao Z, Sun S, Gu H, Wang Z, Wang CF, Lu Y, Liu YY, Wang QY, Bao W, Chen ZN. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Signal Transduct Target Ther* 2020; 5: 283 [PMID: 33277466 DOI: 10.1038/s41392-020-00426-x]

67 Bao W, Min D, Twigg SM, Shackel NA, Warner FJ, Yue DK, McLennan SV. Monocyte CD147 is induced by advanced glycation end products and high glucose concentration: possible role in diabetic complications. *Am J Physiol Cell Physiol* 2010; 299: C1212-C1219 [PMID: 20810913 DOI: 10.1152/ajpcell.00228.2010]

68 Garg M, Angus PW, Burrell LM, Herath C, Gibson PR, Lubel JS. Review article: the pathophysiological roles of the renin-angiotensin system in the gastrointestinal tract. *Aliment Pharmacol Ther* 2012; 35: 414-428 [PMID: 22221317 DOI: 10.1111/j.1365-2036.2011.04971.x]

69 Khajah MA, Fateel MM, Ananthalakshmi KV, Luqmani YA. Anti-Inflammatory Action of Angiotensin 1-7 in Experimental Colitis. *PLoS One* 2016; 11: e0150861 [PMID: 26963721 DOI: 10.1371/journal.pone.0150861]

70 Santos RAS, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigm. *Am J Physiol Heart Circ Physiol* 2019; 316: H958-H970 [PMID: 30707614 DOI: 10.1152/ajpheart.00723.2018]

71 Gaddam RR, Chambers S, Bhatia M. ACE and ACE2 in inflammation: a tale of two enzymes. *Inflamm Allergy Drug Targets* 2014; 13: 224-234 [PMID: 25019157 DOI: 10.2174/18715281136661407131364596]

72 Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. *Am J Physiol Cell Physiol* 2007; 292: C82-C97 [PMID: 16870827 DOI: 10.1152/ajpcell.00287.2006]

73 Simões E Silva AC, Teixeira MM. ACE inhibition, ACE and angiotensin-(1-7) axis in kidney and cardiac inflammation and fibrosis. *Pharmacol Res* 2016; 107: 154-162 [PMID: 26995300 DOI: 10.1016/j.phrs.2016.03.018]

74 Tan WSD, Liao W, Zhou S, Mei D, Wong WF. Targeting the renin-angiotensin system as novel therapeutic strategy for pulmonary diseases. *Curr Opin Pharmacol* 2018; 40: 9-17 [PMID: 29288933 DOI: 10.1016/j.coph.2017.12.002]

75 Fyhriquist F, Saajonnaa O. Renin-angiotensin system revisited. *J Intern Med* 2008; 264: 224-236 [PMID: 18793332 DOI: 10.1111/j.1365-2796.2008.01981.x]

76 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 [PMID: 12676714 DOI: 10.1016/s1357-2725(02)00271-6]

77 Husain K, Hernandez W, Ansari RA, Ferder L. Inflammation, oxidative stress and renin angiotensin system in atherosclerosis. *World J Biol Chem* 2015; 6: 209-217 [PMID: 26322175 DOI: 10.4331/wjbc.v6.i3.209]
Burke KE, Kohcar B, Allegretti JR, Winter RW, Lochhead P, Khalili H, Colizzo FP, Hamilton MJ, Rojas A et al. IBD, RAGE axis and COVID-19

Capettini LS, Montecucco F, Mach F, Stergiopoulos N, Santos RA, da Silva RF. Role of renin-angiotensin system in inflammation, immunity and aging. Curr Pharm Des 2012; 18: 963-970 [PMID: 22283774 DOI: 10.2174/138161212799436593]

Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Action S. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res 2000; 87: E1-E9 [PMID: 10960042 DOI: 10.1161/01.RES.87.5.e1]

Ruiz-Ortega M, Ruperez M, Estevez V, Rodriguez-Vita J, Sanchez-Lopez E, Egidio J. Modulation of angiotensin II effects, A potential novel approach to inflammatory and immune diseases. Curr Med Chem 2003; 2: 379-394 [DOI: 10.2174/1381612033483626]

Garg M, Royce SG, Tikelis C, Shallue C, Bata D, Velkoska E, Burrell LM, Patel SK, Beswick L, Jackson A, Britto K, Lukies M, Shuka P, Wardan H, Hirokawa Y, Tan CW, Faux M, Burgess AW, Hosking P, Monagle S, Thomas M, Gibson PR, Lubel J. Imbalance of the renin-angiotensin system may contribute to inflammation and fibrosis in IBD: a novel therapeutic target? Gut 2020; 69: 841-851 [PMID: 31409604 DOI: 10.1136/gutjnl-2019-318512]

Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, Campagnole-Santos MJ. The ACE2/Angiotensin-(1-7)/MAS Axis of the Renin-Angiotensin System: Focus on Angiotensin-(1-7). Physiol Rev 2018; 98: 505-553 [PMID: 29351514 DOI: 10.1152/physrev.00025.2016]

Patel S, Rauf A, Khan H, Abu-Irneid T. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. Biomed Pharmacother 2017; 94: 317-325 [PMID: 28772209 DOI: 10.1016/j.biopharm.2017.07.091]

Garg M, Burrell LM, Velkoska E, Griggs K, Angus PW, Gibson PR, Lubel JS. Upregulation of circulating components of the alternative renin-angiotensin system in inflammatory bowel disease: A pilot study. J Renin Angiotensin Aldosterone Syst 2015; 16: 559-569 [PMID: 24505094 DOI: 10.1177/1470320314521086]

Hirasawa K, Sato Y, Hosoda Y, Yamamoto T, Hanai H. Immunohistochemical localization of angiotensin II receptor and local renin-angiotensin system in human colonic mucosa. J Histochem Cytochem 2002; 50: 275-282 [PMID: 11799146 DOI: 10.1177/002215540205000215]

Ferreira-Duarte M, Estevinho MM, Duarte-Araújo M, Magro F, Morato M. Unraveling the Role of ACE2, the Binding Receptor for SARS-CoV-2, in Inflammatory Bowel Disease. Inflamm Bowel Dis 2020; 26: 1787-1795 [PMID: 33064417 DOI: 10.1093/ibd/izu2a49]

Jacobs JD, Wagner T, Gullotta G, Liao C, Li YC, Bissonnette M, Pekow J. Impact of Angiotensin II Signaling Blockade on Clinical Outcomes in Patients with Inflammatory Bowel Disease. Dig Dis Sci 2019; 64: 1938-1944 [PMID: 30725290 DOI: 10.1007/s10620-019-5474-4]

Wengrower D, Zanninelli G, Pappo O, Latella G, Sestieri M, Villanova A, Faitelson Y, Pines M, Goldin E. Prevention of fibrosis in experimental colitis by copsitol: the role of tgf-beta1. Inflamm Bowel Dis 2004; 10: 536-545 [PMID: 15472513 DOI: 10.1097/00054725-200409000-00007]

Mantaka A, Tsokakli E, Fragkaki M, Karmiris K, Viazis N, Mantzaris GJ, Kontourbakis IE. Is there any role of renin-angiotensin system inhibitors in modulating inflammatory bowel disease outcome? Eur J Gastroenterol Hepatol 2021; 33: 364-371 [PMID: 32925506 DOI: 10.1097/MEG.0000000000001912]

Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen KY, Wang Q, Zhou H, Yan J, Qi J. Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. Cell 2020; 181: 894-904.e9 [PMID: 32275855 DOI: 10.1016/j.cell.2020.03.045]

Colón AL, Menchén LA, Hurtado O, de Cristóbal J, Lizasoain I, Leza JC, Lorenzo P, Moro MA. Implication of TNF-alpha convertase (TACE/ADAM17) in inducible nitric oxide synthase expression and inflammation in an experimental model of colitis. Cytokine 2001; 16: 220-226 [PMID: 11884025 DOI: 10.1016/cyto.2001.0969]

Brynskov J, Foegh P, Pedersen G, Ellervik C, Kirkegaard T, Bingham A, Saermark T. Tumour necrosis factor alpha converting enzyme (TACE) activity in the colonic mucosa of patients with inflammatory bowel disease. Gut 2002; 51: 37-43 [PMID: 12077089 DOI: 10.1136/gut.51.1.37]

He L, Du J, Chen Y, Liu C, Zhou M, Adhikari S, Rubin DT, Pekow J, Li YC. Renin-angiotensin system promotes colonic inflammation by inducing Tgα17 activation via JAK2/STAT pathway. Am J Physiol Gastrointest Liver Physiol 2019; 316: G774-G784 [PMID: 30995068 DOI: 10.1152/ajpgi.00053.2019]

De Francesco EM, Vella V, Belfiore A. COVID-19 and Diabetes: The Importance of Controlling RAGE. Front Endocrinol (Lausanne) 2020; 11: 526 [PMID: 32760352 DOI: 10.3389/fendo.2020.00526]

Rojas A, Gonzalez I, Morales MA. SARS-CoV-2-mediated inflammatory response in lungs: should we look at RAGE? Inflamm Res 2020; 69: 641-643 [PMID: 32372149 DOI: 10.1007/s00011-020-01353-x]

Bezio C, Saibeni S, Variola A, Allocca M, Massari A, Gerardi V, Casini V, Ricci C, Zingone F, Amato A, Caprioli F, Lenti MV, Viganò C, Ascolani M, Bossa F, Castiglione F, Cortelezzi C, Grossi L, Mildia M, Morganti D, Pastorelli L, Ribaldone DG, Sartini A, Soriano A, Manes G, Danese S, Fantini MC, Armuzzi A, Daperno M, Fiorino G; Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. Gut 2020; 69: 1213-1217 [PMID: 32354990 DOI: 10.1136/gutjnl-2020-321411]
Chan WW, Ananthakrishnan AN. Immunosuppressive Therapy and Risk of COVID-19 Infection in Patients With Inflammatory Bowel Diseases. *Inflamm Bowel Dis* 2021; 27: 155-161 [PMID: 33089863 DOI: 10.1093/ibd/izaa278]

Occhipinti V, Pastorelli L. Challenges in the Care of IBD Patients During the CoViD-19 Pandemic: Report From a “Red Zone” Area in Northern Italy. *Inflamm Bowel Dis* 2020; 26: 793-796 [PMID: 32314792 DOI: 10.1093/ibd/izaa084]

Tursi A, Angarano G, Monno L, Saracino A, Signorile F, Ricciardi A, Papa A. COVID-19 infection in Crohn’s disease under treatment with adalimumab. *Gut* 2020; 69: 1364-1365 [PMID: 32312788 DOI: 10.1136/gutjnl-2020-321240]

Bezzio C, Pellegrini L, Manes G, Arena I, Picascia D, Della Corte C, Devani M, Schettino M, Saibeni S. Biologic Therapies May Reduce the Risk of COVID-19 in Patients With Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2020; 26: e107-e109 [PMID: 32869831 DOI: 10.1093/ibd/izaa242]

Sigall-Boneh R, Levine A, Lomer M, Wierdsm N, Allan P, Fiorino G, Gatti S, Jonkers D, Kierkus J, Katsanos KH, Melgar S, Yuksel ES, Whelan K, Wine E, Gerasimidis K. Research Gaps in Diet and Nutrition in Inflammatory Bowel Disease. A Topical Review by D-ECCO Working Group [Dietitians of ECCO]. *J Crohns Colitis* 2017; 11: 1407-1419 [PMID: 28961811 DOI: 10.1093/ecco-jcc/jjx109]

Uribarri J, del Castillo MD, de la Maza MP, Filip R, Gugliucci A, Luevano-Contreras C, Macias-Cervantes MH, Markowicz Bastos DH, Medrano A, Menni T, Portero-Otin M, Rojas A, Sampaio GR, Wrobel K, Garay-Sevilla ME. Dietary advanced glycation end products and their role in health and disease. *Adv Nutr* 2015; 6: 461-473 [PMID: 26178030 DOI: 10.3945/anj.115.008433]
