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**EDITORIAL**

- 2251 Celiac Disease in Asia beyond the Middle East and Indian subcontinent: Epidemiological burden and diagnostic barriers  
*Poddighe D, Abdukhakimova D*

**FRONTIER**

- 2257 Biomarkers in autoimmune pancreatitis and immunoglobulin G4-related disease  
*Hara A, Watanabe T, Minaga K, Yoshikawa T, Kamata K, Kudo M*

**REVIEW**

- 2270 Receptor for advanced glycation end-products axis and coronavirus disease 2019 in inflammatory bowel diseases: A dangerous liaison?  
*Rojas A, Schneider I, Lindner C, González I, Morales MA*
- 2281 Individualized treatment options for patients with non-cirrhotic and cirrhotic liver disease  
*Hartl L, Elias J, Prager G, Reiberger T, Unger LW*

**MINIREVIEWS**

- 2299 Clinical characteristics and outcomes of patients with hepatic angiomyolipoma: A literature review  
*Calame P, Tyrode G, Weil Verhoeven D, Félix S, Klompenhouwer AJ, Di Martino V, Delabrousse E, Thévenot T*
- 2312 Risk of hepatitis B virus reactivation in patients with autoimmune diseases undergoing non-tumor necrosis factor-targeted biologics  
*Akiyama S, Cotter TG, Sakuraba A*
- 2325 Burden of venous thromboembolism in patients with pancreatic cancer  
*Frere C*
- 2341 Pathophysiological mechanisms underlying gastrointestinal symptoms in patients with COVID-19  
*Jin B, Singh R, Ha SE, Zogg H, Park PJ, Ro S*

**ORIGINAL ARTICLE****Retrospective Cohort Study**

- 2353 Risk factors and prognostic value of acute severe lower gastrointestinal bleeding in Crohn's disease  
*Yoon J, Kim DS, Kim YJ, Lee JW, Hong SW, Hwang HW, Hwang SW, Park SH, Yang DH, Ye BD, Byeon JS, Myung SJ, Yang SK*

**Retrospective Study**

- 2366 Changes in the nutritional status of nine vitamins in patients with esophageal cancer during chemotherapy  
*Liang LQ, Meng LL, Cai BN, Cui ZP, Ma N, Du LH, Yu W, Qu BL, Feng SQ, Liu F*

**Observational Study**

- 2376 Effects of sepsis and its treatment measures on intestinal flora structure in critical care patients  
*Yang XJ, Liu D, Ren HY, Zhang XY, Zhang J, Yang XJ*
- 2394 Gut microbiota dysbiosis in Chinese children with type 1 diabetes mellitus: An observational study  
*Liu X, Cheng YW, Shao L, Sun SH, Wu J, Song QH, Zou HS, Ling ZX*

**META-ANALYSIS**

- 2415 Selection of first-line systemic therapies for advanced hepatocellular carcinoma: A network meta-analysis of randomized controlled trials  
*Han Y, Zhi WH, Xu F, Zhang CB, Huang XQ, Luo JF*

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

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### 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

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**Core Tip:** Data raised during the pandemic suggest that inflammatory bowel diseases do not have an increased risk of contracting severe acute respiratory syndrome coronavirus 2 infection or develop a more severe course of infection. These findings are in some way unexpected considering that inflammatory bowel disease is a chronic inflammatory state of the gastrointestinal tract. We herein discuss how the receptor for advanced glycation end-products axis activation as well as the cross-talk with the renin-angiotensin system are dampened by the high expression of soluble forms of both receptor for advanced glycation end-products and angiotensin-converting enzyme 2.

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## 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-proteases, such matrix metalloproteinase-9 (MMP-9), a disintegrin metalloproteases (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 decrease the inflammatory responses driven by full-length RAGE activation [35,43,44]. Besides AGEs, RAGE can recognize many other ligands including the alarmin high-mobility group box 1 (HMGB1), members of the S100 protein family, glycosaminoglycans, and amyloid  $\beta$  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- $\kappa$ B), AP-1, and signal transducer and activator of transcription-3[35].

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- $\kappa$ B, which induces RAGE expression, following an enhanced and sustained inflammatory response[35,46-48].

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## RAGE AXIS ACTIVATION IN IBD

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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].

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## THE RENIN-ANGIOTENSIN SYSTEM

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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- $\kappa$ B[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- $\kappa$ B dependent expression of pro-inflammatory mediators[48].

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

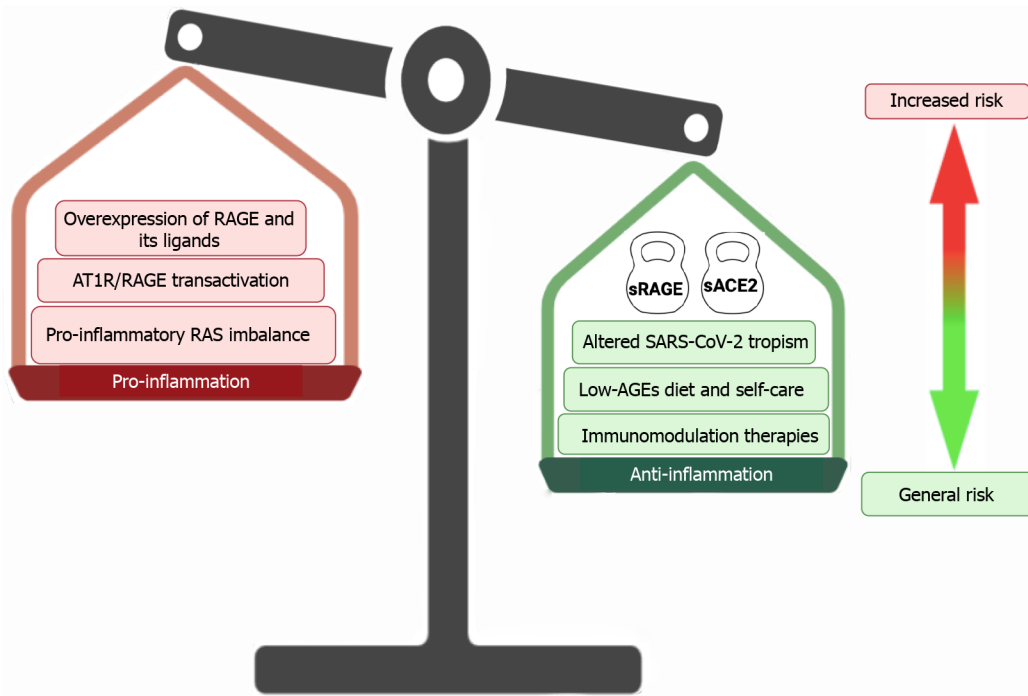
Contrary to what is expected, considering the pathophysiology of IBD, there is currently no evidence for an increased risk of worse clinical outcomes in patients with IBD in the context of COVID-19[21-25]. The role of the RAGE axis in the pathophysiology of IBD has been suggested by different reports[53-57]. 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.

A growing body of evidence demonstrates that in IBD patients the use of systemic immunosuppression is not associated with an increased risk of COVID-19 patients with IBD[96-100]. Furthermore, we must also keep in mind that the main objective of pharmacological treatments in IBD is to reduce inflammation levels. In this sense, in addition to interfering with signaling pathways, many drugs used in the current treatments also decrease the expression of RAGE and the bioavailability of some RAGE ligands, particularly the alarmins HMGB1 and S100 protein family members[96,97]. Indeed, several authors remark the possible protective role of IBD therapy against SARS-CoV-2 infection, especially through interfering with cytokine activity observed in the clinical course of COVID-19[98-100].

Additionally, the IBD patients have a high self-care standard and follow diets that help them to maintain good nutritional levels and the disease under control[101]. Some of these nutritional regimens are associated with a low-AGE diet, which may contribute to reducing the proinflammatory intestinal milieu mediated by RAGE activation[102] (Figure 1).

## 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 the transactivation of RAGE axis that can be produced by the virus-mediated imbalance of the ACE/Ang II/ AT1R pathway. Thus, RAGE axis activation in COVID-19 IBD patients does not seem to be a dangerous liaison.

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