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SARS-CoV-2 infection causes intestinal cell damage: Role of interferon's imbalance

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ABSTRACT

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of the newly emerging lung disease pandemic COVID-19. This viral infection causes a series of respiratory disorders, and although this virus mainly infects respiratory cells, the small intestine can also be an important site of entry or interaction, as enterocytes highly express in angiotensin-2 converting enzyme (ACE) receptors. There are countless reports pointing to the importance of interferons (IFNs) with regard to the mediation of the immune system in viral infection by SARS-CoV-2. Thus, this review will focus on the main cells that make up the large intestine, their specific immunology, as well as the function of IFNs in the intestinal mucosa after the invasion of coronavirus-2.

1. Introduction

In March 2020, the outbreak of the severe acute respiratory syndrome of coronavirus 2 (SARS-CoV-2) suddenly evolved into a pandemic [1], and on October 2021, more than 239 million cases were reported worldwide [2]. Although SARS-CoV-2 targets mainly cells of the pulmonary epithelium, several studies have reported gastrointestinal symptoms, such as diarrhea, at the onset of the disease [3-6]. There is evidence that the viral infection by SARS-CoV-2 triggers a robust intrinsic immune response mediated by interferons (IFNs) [7,8], especially by IFNs type I and III [9,10].

This article discusses the role of interferons during SARS-CoV-2 infection, with special attention to what happens in the large intestine. In this review, consolidated data from the literature will be shown indicating that the interferon response contributes to the control of viral infections. On the other hand, it will also be shown that in COVID-19, the interferon response also contributes to the cytokine storm (equally well reported in scientific articles), which triggers a severe inflammatory process, in turn leading to the death of enterocytes in the intestinal mucosa.

2. Morphofunctionality of the large intestine

The large intestine (Fig. 1) is the segment of the gastrointestinal tract located between the ileum and the anal channel. This portion begins in the cecum that contains the ileocecal valve and the cecal appendix. The initial part of the large intestine progresses as an ascending colon towards the liver, angles medially to form the hepatic angle and moves to the left as a transverse colon to the location of the spleen and finally angles again in the caudal direction to form the descending colon and sigmoids. In the final portion of the sigmoid colon, there is a change in the muscle layer and a dilation of the large intestine to form the rectum. The latter ends in the anal channel [11].

Histologically, the large intestine does not differ much from the rest of the gastrointestinal tract. This segment is composed by two muscular layers, being a circular inner layer and a longitudinal outer layer. The longitudinal musculature presents a characteristic formation from the cecum, being arranged in three muscular aggregates that run throughout the large intestine, merging in the rectum, to again form a single longitudinal muscular layer. This muscle aggregate is called the tapeworm [12].

The mucous layer of large intestine possess glands and absence of villi, a submucosa with vessels [12]. Adding to this, that the simple

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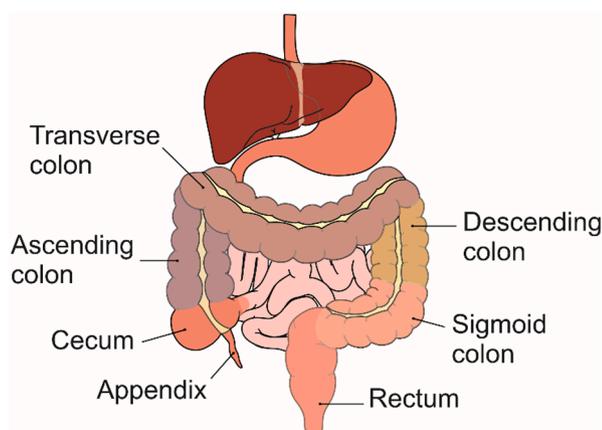


Fig. 1. Anatomical Parts of the Large Intestine. The large intestine is anatomically divided into appendix, cecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum.

cylindrical epithelium is responsible for the lining of intestinal crypts and they add that the number of goblet cells in relation to enterocytes is greater in the cervix than in the small intestine, with an increase in this proportion towards the cecum and rectum region [13] and, also, the crypts contain stem cells for the renewal of the epithelium, in addition to enteroendocrine cells [14].

Colonic mucosal epithelial cells include absorptive cells, goblet cells, undifferentiated columnar crypt cells, caveolated cells, Paneth cells and M-cells present in the colonic mucosa, almost identical to those cells present in the small intestine. The major functions of the colon are to reclaim luminal water and electrolytes [15].

The luminal surface of the human intestine is an environment where pathogens directly contact the gut mucosa. Thus, an important line of defense against invasion, the intestinal epithelial cells can express apical junction complexes forming a physical barrier through a tight junction complex, mucus, antimicrobial proteins and immunoglobulin A (IgA). Besides these cells, there are other specialized cells including goblet cells that can secrete a mucus inner layer to resist pathogen invasion, and Paneth cells that can secrete various proteins that hamper access and survival of pathogens adjacent to the epithelium [16,17].

The large intestine still has a layer of lymphocytes embedded in the middle of the epithelial cells. Beneath these cells, that is, in the basal layer, there is a population of dispersed immune T cells, the exclusive T cells that come into direct contact with the enterocytes, which are found to play an essential role in the maintenance of intestinal homeostasis. This population of dispersed immune T cells are a critical part of the intestinal immune system, simultaneously participating in the innate and adaptive immune regulation [18]. Another important lineage of T cells that make up the intestinal immune tissue are regulatory T cells (Tregs) [19]. These are a subset of CD4 T cells that play an important role in maintaining peripheral tolerance and are involved in the pathogenesis of various clinical disorders [20]. In the gut, cells (Tregs) have also been observed to be a primary mediator in maintaining the immune homeostasis [18]. In intestinal lamina propria, Tregs maintain intestine homeostasis through negative regulation of effector T cells and play a critical role in suppressing intestinal inflammation by producing IL-10 or TGF- β [21].

Among the morphological changes caused by infection by microorganisms (mainly viruses), we highlight the distortion of the mucosa architecture, the leukocyte infiltration of the lamina propria and the depletion of goblet cells [14,22,23]. These dysfunctions are due to the infiltration of inflammatory cells resulting in changes in the response of the intestinal immune system, triggering excessive release of pro-inflammatory cells such as TNF- α , IL-12, IL-13 and IL-17 and interferon-gamma mediated by type 1 (TH1) helper cells [24].

3. Gateway of SARS-CoV-2 at gastrointestinal tract

The prerequisite for SARS-CoV-2 infection is its entry into the host cell. In this process, the coronavirus expresses a spike glycoprotein that contains a receptor binding domain (RBD), a region that recognizes host cell receptors and induces the fusion of the virus with the cell membranes, and subsequently the entry of the virus into the cell [25,26]. SARS-CoV-2 invades the body's cells through the angiotensin-converting enzyme 2 (ACE2), which acts as a receptor for viral entry into target cells [26], and the transmembrane serine protease protein 2 (TMPRSS2), which has the function of cleaving the coronavirus spike protein in the cell membrane, allowing the virus to release the fusion peptide in the membrane [27,28]. Thus, ACE2 and TMPRSS2 are key proteins in the process of viral entry into the body during COVID-19 [29]. SARS-CoV-1 also shares this viral invasion mechanism [26,30].

A study using a single-cell transcriptomic analysis showed that the ACE2 and TMPRSS2 proteins were co-expressed in the upper esophageal epithelial cells and highly present in the absorptive enterocytes of the ileum and large intestine [29]. It is still interesting to note that of all the cells co-expressed in the digestive system and in the normal lung, the expression of ACE2 was relatively more pronounced in the ileum and colon, suggesting that intestinal epithelial cells are vulnerable to infection [29]. Another study showed biophysical and structural evidence that the SARS-CoV-2 spike protein binds with greater affinity to ACE2 compared to SARS-CoV-1 [31]. Given the above, these findings are relevant because the SARS-CoV-2 infection requires the co-expression of ACE2 and TMPRSS2 in the host cell, as well as the high affinity of this coronavirus for ACE2, thus, it is suggested that enterocytes are more susceptible to infection and the gastrointestinal tract, a potential route of infection by SARS-CoV-2.

The main biological process mediated by the specific co-expression network of SARS-CoV-2 in human intestinal enterocytes is distinct from SARS-CoV-1 regarding interferon signaling, regulation of the viral mechanism and the inflammatory response. The biological mechanism of SARS-CoV-1 has been associated with the transmembrane transporter and cell cycle control [32].

Fecal-oral transmission has been implicated as a possible route of contamination by SARS-CoV-2 [26]. Approximately 2% to 10% of patients with COVID-19 manifested enteric symptoms, including vomiting, diarrhea and abdominal pain [33,34]. A meta-analysis showed that these symptoms occurred in 17.6% of infected patients, being more common in patients with severe conditions [33]. Thus, the diarrhea reported by patients with COVID-19 may be related to the enterocytes that co-express ACE2 and TMPRSS2 [29].

A cohort study of 1,099 patients with COVID-19 demonstrated that 3.8% of patients had diarrhea and 5.0% had episodes of vomiting [35]. The prevalence of gastrointestinal symptoms in patients with COVID-19 can reach 50%, as about 50% of these patients have detectable virus in their stool till 27.9 days after the infection [36]. The frequency of enteric manifestations differ depending on the geographic region, population studied and time of evaluation of patients with COVID-19 [37]. The RNA SARS-CoV-2 was also identified in human biopsies of the esophagus, stomach, small and large intestine [38], in anal/rectal swabs [6,39] and stool specimens [40,41] from patients with Covid-19, even after virus clearance in the upper respiratory tract [6,39]. Thus, the possible fecal-oral route of SARS-CoV-2 contamination is suggested.

SARS-CoV-2 tropism by the gastrointestinal tract is attributed to ACE2 expression throughout the digestive system, with the greatest functional role in the small intestine and colon [32]. Furthermore, it has been shown that the increased expression of ACE2 in enterocytes in the proximal and distal portion of the small intestine makes the enterocytes more susceptible to infection [42]. Absorbent enterocytes can be infected with coronaviruses, although a large amount of coronaviruses can be killed by the strong acid in the stomach, but there is still the possibility that saliva and secretions can carry the virus into the digestive tract where the replication of this coronavirus can occur in

susceptible cells [33].

Coronaviruses can infect absorptive enterocytes, causing diarrhea by destroying them, reducing their absorption, altering intestinal secretion and activating the enteric nervous system [43]. Evidence in the literature indicates that SARS-CoV-2 can infect human intestinal enterocytes [44], in addition to the replication in intestinal epithelial cell lines, as well as in organoid models of the human intestine, contributing to the spread and increased SARS-CoV-2 viremia [10,44]. Another important factor refers to ACE2, which controls the intestinal microbiota indirectly through the secretion of antimicrobial peptides, and the intestinal microbiota stimulates the increase in the production of immune cells and interferons, thus triggering antiviral immunity [45].

4. Immune response against the virus

Viral infection in humans can cause variable tissue damage or can resolve without any tissue damage [46]. Normally, a viral infection happens as follows: the virus infects the organism, invading cells of its host in order to survive and replicate.

The immune system clearly plays a key role in the host defense during the viral infection. The host is able to set up immune responses upon infection by viruses and control the spread of these pathogens within the body. However, some viral strains are capable of evading the immune attack and proliferate in the body, as well as elicit severe inflammatory responses. More importantly, in susceptible individuals, viruses can cause strong systemic inflammatory responses, known as “cytokine storm”, resulting in a severe pathological consequence [47].

As a gateway, in the first contact the virus reaches mast cells and macrophages. Mast cells (MC) are strategically placed at sites that interface with our external environment such as the skin, lung and intestines. Within such tissues, they are predominately below the epithelial layer and closely associated with blood vessels [48]. This location allows them to act as sentinels for tissue damage and pathogen invasion. It also places them close to other sentinel cells, such as dendritic cells. The association between MC and blood vessels is optimal to enhance the rapid recruitment of effector cells out of the bloodstream and into neighboring tissues [49]. This process is facilitated by the MC rapid production of cytokine mediators such as TNF and IL-1 β (which activate endothelium) and lipid mediators (which facilitate vasodilatation), as well as a range of chemokines that promote the selective recruitment of specific subsets of effector cells [49]. In addition, there is the release of effector proteins such as interferons [50].

Macrophages are also cells that have a central role in detecting viral infections. They are found in all parts of the body and account for 5–15% of cells depending on the tissue [51]. They show great functional diversity and in addition to activating innate immune response, they have central roles in development, homeostasis and tissue repair [52]. Activation of macrophages by viral infection results in antiviral response and inflammation aiming to pathogen elimination. Upon activation, macrophages start to secrete cytokines to set up inflammatory response, chemokines to recruit other immune cells to the site of infection or inflammation and other proteins inducing antiviral defense and tissue regeneration [51].

Neutrophils are the first immune cell population recruited to the sites of the infection, including viral infections, and exhibit both protective and pathologic functions, together with macrophages, they constitute the professional phagocytes, and they exhibit potent phagocytic properties similar to those of macrophages. Phagocytosed virus are destroyed intracellularly by a plethora of preformed mediators stored in neutrophilic granules such as antimicrobial peptides, proteolytic enzymes, and ROS generated via the action of NADPH oxidase [53].

Once inside the cells, the virus cannot be fought by the cell itself. In order to overcome that, competent cells employ a system that allows them to show other cells what is inside them – they use molecules called class I major histocompatibility complex proteins (MHC class I) to display specific fragments of viruses from inside the cell upon the cell

surface [54]. This job is done with mastery by the dendritic cells. Dendritic cells (DC) are potent antigen-presenting cells that are critical in the initiation of immune responses to control and/or eliminate viral infections [55]. After the recognition of the antigen by the immune system, cytotoxic T cells and natural killer cells come into action, which recognize the patterns of proteins associated with pathogens and through them produce toxic compounds and antibodies that can neutralize the virus or cause the death of infected cells [56].

Activation of cytotoxic T lymphocytes (CTL) or natural killer (NK) cells are essential for a specific and effective antiviral immune response. Although multiple cytokines and chemokines are produced by several kinds of host cells in viral infection, type I IFNs are the main cytokines involved in the antiviral response. Type I IFNs include multiple IFN- α isoforms, a single IFN- β , and IFN- γ (type II) [57]. In contrast to type II IFN (IFN- γ), which is exclusively produced by T cells and NK cells, type I IFNs can be produced by all nucleated cells in response to virus infection. Type III IFNs, comprised of IFN-k1, k2 and k3, have also recently been identified [58]. These IFNs each have different receptors but share downstream signaling molecules and regulate the same genes. IFNs have pleiotropic functions. They increase the expression of intrinsic proteins and induce apoptosis of virus-infected cells [59]. In addition, they activate NK cells and dendritic cells (DC) and induce the activation of the adaptive immune system [60].

5. Immune response against the SARS-CoV-2 in the large intestine

The components of the innate immune system act as first responders for the detection and clearance of SARS-CoV-2 infections. Cells secrete proinflammatory cytokines that inhibit viral replication, stimulate the adaptive immune response and recruit other immune cells to the site of infection. Granulocytes degranulate in response to extracellular pathogens, releasing enzymes and toxic proteins. Monocytes traffic to tissues and differentiate into monocyte-derived macrophages and dendritic cells. Macrophages and neutrophils phagocytose and destroy pathogens as well as infected cells. Natural killer cells kill virally infected cells via degranulation, receptor-mediated apoptosis and antibody-dependent cell-mediated cytotoxicity. Finally, the complement system plays a role in immune cell recruitment, activation and destruction of pathogens [61].

Activated DCs present pathogen-derived antigens to naive helper T cells to initiate the adaptive immune response through signaling and activation of other cells. The signaling cascades are generally integrated with innate responses. This signaling happens via nuclear factor kappa B (NF- κ B)-dependent cytokine responses, interferon regulatory factor (IRF)-dependent IFN responses and inflammasome-dependent IL-1 β responses. IFNs are the major cytokines that limit viral replication, while other cytokines, including IL-6, TNF- α and IL-1 β , recruit immune cells to the site of infection and elicit inflammation [62]. These critical antiviral functions are an overactive innate immune response that can contribute to disease pathogenesis [61].

In the intestine, SARS-CoV-2 infects enterocytes; the virus interacts with the bowel, specifically with the angiotensin-converting enzyme 2 (ACE2) receptors located on the brush border of enterocytes [44]. The next steps after SARS-CoV-2 enters the enterocyte is viral proliferation and death of the enterocyte.

It is not known for sure how the specific immune response occurs in this situation, but based on what traditionally occurs with other viruses, fragments of enterocytes and exported viruses will be keys for activating an immune-inflammatory response causing activation of resident immunologic cells and stimulation of IFN-III production [10]. Apparently, the clinical manifestations of the intestine in the face of SARS CoV-2 infection are related both to the electrolyte imbalance caused by the death of enterocytes, as well as to a local inflammatory response caused by the death of infected intestinal cells [63,64].

6. Role of IFNs in viral infection

Interferons (IFNs) are a subset of cytokines that correspond to a central part of the innate immune response to viral infections [62], since viral genetic materials are the most potent inducers of IFN responses [65]. The cells detect viruses through pattern recognition receptors, leading to the transcription of molecules that act by means of autocrine and paracrine signaling to induce an antiviral state. This response includes the production and release of IFNs, which bind to cell surface receptors and conduct gene expression through the signaling pathways of the Janus kinase transducer and the transcription activator (JAK-STAT), resulting in the expression of hundreds of genes stimulated by interferon (ISGs) [66]. Taken altogether, these signals activate innate immunity against viral infections and prepare the adaptive immune response [67].

Humans have three classes of IFNs - types I, II and III - that signal through different receptor complexes. Type I IFNs include 13 subtypes of IFN- α in addition to IFN- β , IFN- ϵ , IFN- κ and IFN- ω , which bind to the heterodimeric IFN type I receptor (IFNAR) [68]. The type II IFN family consists of only IFN- γ [67], and type III IFNs consist of three to four IFN- λ s and signal through the IFNLR receptor [69].

As for the host's protective functions, IFNs can act by restricting viral replication [70], activating NK cell cytotoxicity, maturation of antigen-presenting cells (APCs), clonal expansion and survival of antigen-specific CD4 and CD8 T cells during viral infection, promotion of B cell responses and induction of apoptosis [71-75].

After a viral infection, most nucleated cells produce type I IFN targeting the innate antiviral innate immune response. Specialized immune cells, such as lymphocytes, produce IFN- γ , initiating the adaptive immune response to the virus. The cells respond to IFNs through a signaling process that involves specific recognition and activation of IFNs types I, II and III by specific receptor complexes expressed on the cell surface [67,76]. Conformational changes resulting from receptors create coupling sites for the main signaling molecules downstream, STAT-1 or 2, which are phosphorylated at specific sites (Y701, S708, S727 for STAT1 and Y690 for STAT2) [77].

The type I IFN receptor complex recruits and phosphorylates STAT1 and STAT2, which combine with the IFN regulatory factor (IRF) -9 to form the heterotrimeric ISG complex, translocating to the nucleus and activating stimulated response elements (ISRE) within the promoters of a set of ISGs. The ISG consists of a distinct panel of genes, usually with direct antiviral or regulatory functions responsible for the establishment of an antiviral state that blocks viral replication and limits the spread of the virus [78]. In the context of viral infections, type I IFNs are also critical for the clonal expansion of CD8 + T cells and the formation of memory [62].

On the other hand, the type II IFN receptor complex binds and phosphorylates exclusively STAT1, resulting in the formation of a homodimeric STAT1 / STAT1 complex that translocates to the nucleus and activates elements of the IFN-g (GAS) activation site in the genome, resulting in the induction of a set of genes specific to GAS [79].

Although type I and type III IFNs bind to different receptors, both activate the transcription factors STAT1, STAT2 and IRF9, leading to the positive regulation of a widely overlapping set of ISGs [80,81]. Type III IFN signaling acts more slowly and leads to a slightly weaker, but more sustained, induction of ISGs compared to type I IFN signaling [82,83]. In addition, both have different effects based on the location of their respective receptors. IFNAR is expressed in most nucleated cells, while IFNLR expression is restricted to distinct cell types, particularly epithelial cells [84-86]. IFNLR expression in epithelial barriers explains the critical role of type III IFNs in regulating viral infections in places such as the intestinal or respiratory epithelium [84,87,88].

In the intestine, intestinal epithelial cells (IECs) are the type of cell that responds to IFN [89]. IFN- α / β produced in the mucosa can increase the response of B cells to promote viral elimination and protection against reinfection [90]. Studies show that activated intraepithelial

lymphocytes (IELs) regulate the expression of IFN- α / β and IFN- λ positively to set up a rapid antiviral state for the protection of IECs [91]. The activation of IELs *in vivo* quickly causes the expression of ISGs through the IFN- α and IFN- λ receptors. Thus, the activation of IELs offers an evident means of promoting an innate antiviral potential of the intestinal epithelium [92].

Thus, virus-infected IECs are potent IFN- λ producers, suggesting that the intestinal mucosa has a compartmentalized IFN system in which epithelial cells respond predominantly to IFN- λ , while other intestinal cells depend on IFN- α / β for antiviral defense. The timely production of IFN- λ in IECs leads to the rapid elimination of intestinal viral infections and limits the elimination of viruses in the stool. The intestinal epithelium responds exclusively to IFN- λ in a non-redundant way to control epitheliotropic viruses [93].

7. Ifns in the gastrointestinal tract mucosa against the SARS-CoV-2 attack

As already mentioned, SARS-CoV-2 infects the gastrointestinal tract (GIT), mainly mature human enterocytes on the apical surface, and also triggers the fusion of epithelial cells [4,94], since there is a high co-expression of ACE-2 and TMPRSS2 in these cells [95]. It is known that infection of enterocytes by pathogens is linked to the induction of diarrhea; in addition, these infections can lead to the destruction of enterocytes [96]. Enterocytes produce an innate immune response to invaders, stimulating the secretion of a variety of cytokines and chemokines [97,98]. Following this perspective, SARS-CoV-2 infection has been associated with the generation of an intrinsic immune response mediated by IFNs [10].

Some studies prove that IFNs induce enterocyte resistance against infection by pathogens, such as IFN- γ against infection by *Cryptosporidium parvum*, INF- α and IFN- γ against rotavirus infection, by altering the intestinal epithelial cell phenotype [98,99] and IFN- λ in protecting epithelial cell infection during rotavirus gastroenteritis [3]. The role of IFNs in the immune response of GIT during infection by SARS-CoV-2 is still not very clear, especially due to the few data in the literature. Park and Iwasaki [100] point out that coronaviruses can alter the response of IFNs in the immune system, interfering in the production and signaling of IFNs and in the effective function of the ISG (Interferon stimulating gene). Lee et al. [101] also report the attenuation of the function of these molecules in organs infected with this coronavirus. Type I and type III IFNs induce hundreds of antiviral effectors, or ISGs, but even with this important host antiviral strategy, coronaviruses remain highly pathogenic, at least in part because of the various viral mechanisms to prevent and suppress IFNs responses [100].

However, it was seen that ACE2 is induced by IFNs in humans, but to a lesser extent in mice. In the study by Ziegler et al. [102], in monkeys infected with SHIV (Simian Human Immunodeficiency Virus), with high levels of chronic IFNs signaling, positive regulation of ACE2 was found in absorptive enterocytes. It is a fact that this positive regulation would provide more access to SARS-CoV-2 into the intestine, since this is the entrance receptor for these viruses [4], and may thus cause a greater immune system response and consequent inflammatory process. However, that diverges with the information that deficiency in the ACE2 enzyme results in highly increased susceptibility to intestinal inflammation induced by epithelial damage [103].

Thus, circumstances suggest that the amount of ACE-2 itself would not be related to intestinal inflammation and the consequent diarrhea in COVID-19. This would remove the IFNs response from having an influence on the diarrhea symptom in the course of the disease and to some degree on the risk of developing the severe form of COVID-19, as patients with gastrointestinal symptoms showed an increased risk of discomfort syndrome and acute respiratory disease in a recent study [104]. In addition to this conclusion, research with mouse models, in which changes in ACE2 were associated with colitis, suggests that the activity of SARS-CoV-2 can cause enzymatic changes, increasing the

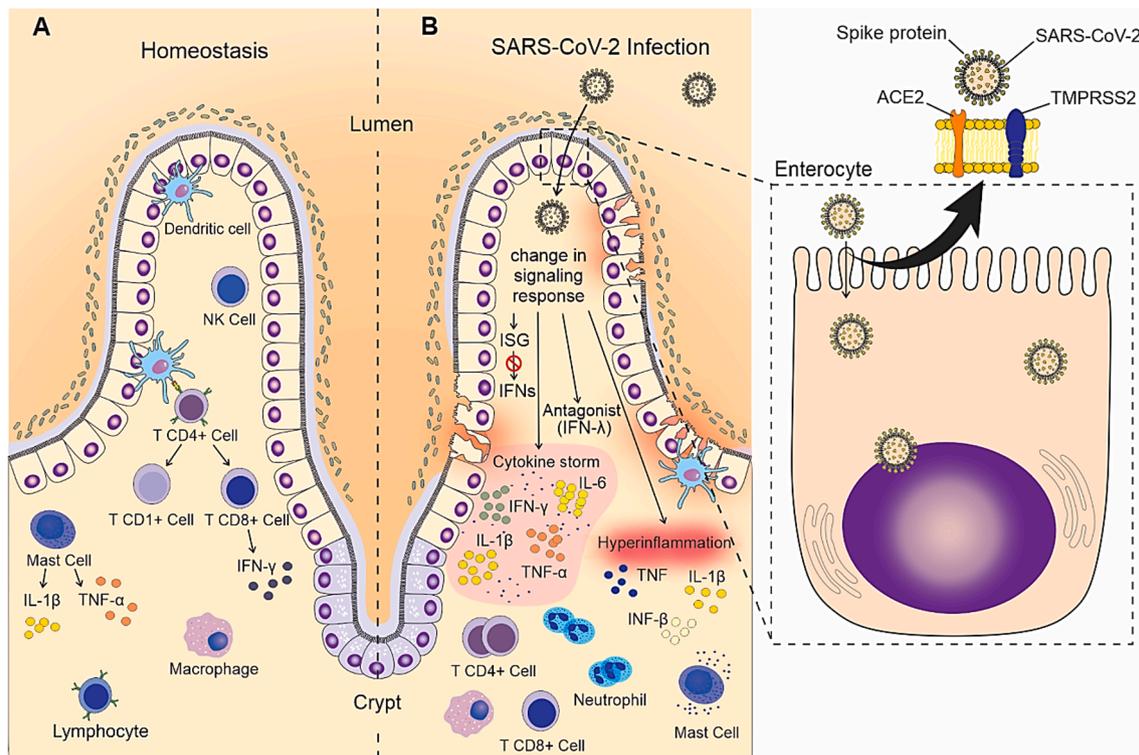


Fig. 2. Immune response of the intestinal mucosa after infection by SARS-CoV-2. Characteristics of the immunology of the intestinal mucosa under physiological conditions (A), in which there is a population of immune T cells dispersed, and these interact directly with the enterocytes, performing an essential function in local homeostasis. By invading the intestinal mucosa through ACE-2 (B), SARS-CoV-2 promotes a change in the response of immune signaling. This contributes to the hyperinflammatory process, with a “cytokine storm” profile, characterized by hyperactivation of T cells and a massive production of interleukin IL- β , IL-6, TNF- α and IFN- γ [122].

susceptibility to intestinal inflammation and diarrhea [105], thus decreasing the numerical importance of these ACE-2 enzymes in the diarrhea that occurs in COVID-19. Even though the amount is altered by the strong IFN activity in COVID-19, similarly to what happens in other viruses, it seems that the structural question of the enzyme would, in short, be more related.

In a comparison with Rotavirus, which effectively induces a strong IFN response, infection by wild-type SARS-CoV-2 similarly induced responses of IFN type I (IFN- β) and IFN- λ in intestinal epithelial cells for both apical and basolateral infections [94]. Positive regulation of IFN-I responsive genes was also seen in intestinal organoids infected with SARS-CoV-2 [44]. Thus, it is important to highlight that the severe COVID-19 shows that it is accompanied by the IFN-I response, in addition to the TNF / IL-1 β response, which indicates that the IFN-I response may contribute to the hyperinflammatory process during the potentiation of the inflammation caused by TNF / IL-1 β in the severe progression of COVID-19 [101]. However, this IFN- β response in the severity of SARS-CoV-2 infection does not seem to have relevance at the level of GIT, since the documented cytokine profile in patients with severe Covid-19 is similar to that seen in the inflamed intestine of patients with inflammatory bowel disease and during the “cytokine storm” syndrome, which is characterized by hyperactivation of T cells and a massive production of interleukin IL- β , IL-6, TNF- α and IFN- γ (not IFN- β) [87] (Fig. 2).

In another aspect, the role of IFN- λ is highlighted, which is predominant in the response of cells to invaders that reach TGI [10]. The effects of IFN- λ are more evident in epithelial cells, suggesting that it contributes to the specialized immune mechanisms that protect epithelial surfaces, which are constantly exposed to commensal and pathogenic microbes [106]. Research reveals that many of the non-structural proteins in coronaviruses play important roles in limiting the host’s response to virus infection, acting as antagonists to the responses of the

host’s type I IFNs and type III IFNs [107]. However, Stanifer et al. [10] saw that the response mediated by IFN type III was significantly more efficient in controlling the replication and spread of SARS-CoV-2 compared to IFN type I. In fact, IFN- λ exhibits antiviral activity against many viruses *in vitro*, but their activity *in vivo* has been more evident for viruses that infect epithelial cells of the respiratory, gastrointestinal and urogenital tracts and of the liver [105]. In fact, some other studies suggest that the immune response mediated by IFNs controls SARS-CoV-2 infection in intestinal epithelial cells, which can mitigate the pathogenesis of this virus [10,100,107].

8. Intestinal imbalance of IFNs in SARS-CoV-2 infection

The enteric commensal microbiota under normal conditions performs viral control [108] producing IFN III to maintain an antiviral and anti-inflammatory state [109]. After viral entry into the intestine, the nucleated cells of mammals can synthesize and secrete IFN I [110], to establish the viral response that can be initiated by epithelial cells, fibroblasts and dendritic cells [111]. However, SARS-CoV-1 can generate substantial amounts of IFN-inducing RNA [112]. That suggests that coronaviruses prevent or inhibit IFN production in a similar way to other viruses [93]. Studies with intestinal organoids infected with SARS-CoV-1 have not shown induction of IFN type I or type III genes [62].

Similarly, SARS-CoV-2 showed low expression of IFNs I and III with only small induction of type III IFN genes [62]. Studies demonstrate that intestinal epithelial cells do not respond to IFN I and imply a dominant role for IFN III signaling for inhibition of enteric RNA viruses [87,89,92,108]. IFN is produced in order to inhibit viral infection and establish an immunological response [112]. However, coronaviruses can use immunomodulatory strategies that cause IFN deregulation [113]. SARS-CoV-2 in intestinal organoids can cause IFNs imbalance by the low induction of types I and III [62], resulting in a slight increase in

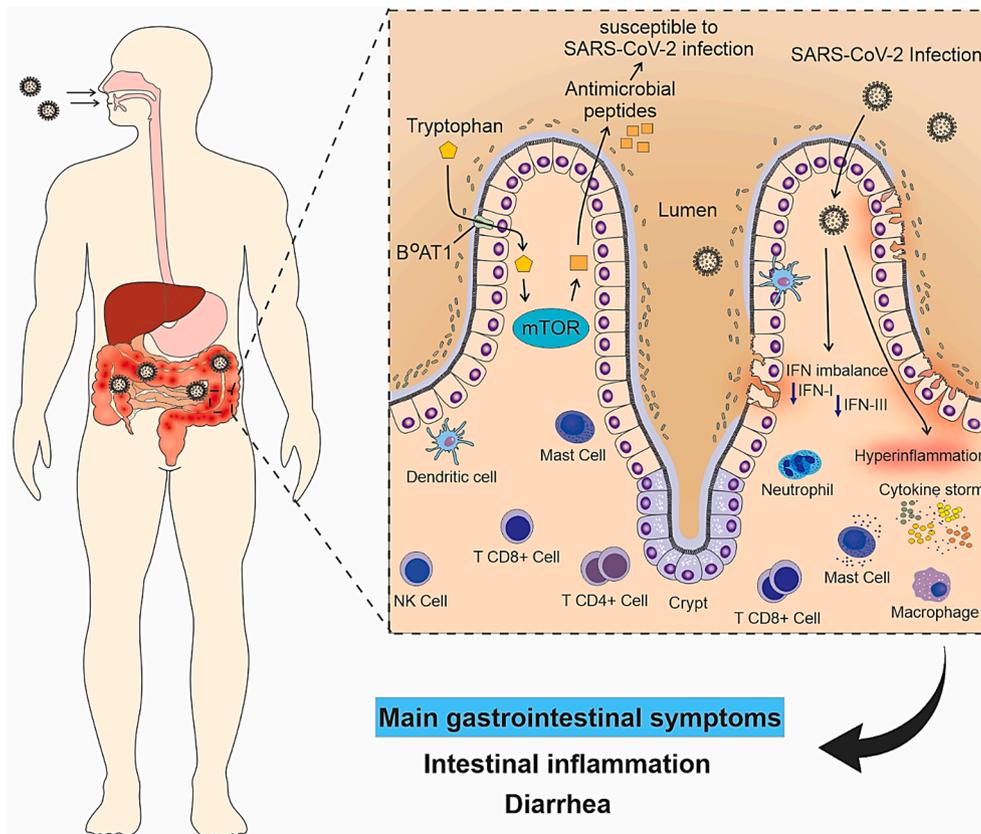


Fig. 3. IFNs imbalance and intestinal clinical repercussions in SARS-CoV-2 infection. From the moment that an imbalance in ECA2 occurs, the expression of the amino acid B⁰AT1 transporter is also unregulated, being responsible for controlling the uptake of tryptophan in the intestine. Therefore, there is a decrease in intestinal absorption of tryptophan and consequent deregulation of antimicrobial peptides and dysbiosis, justifying the occurrence of diarrhea in patients infected with SARS-CoV-2.

the number of infected cells and an increase in cellular infectivity respectively.

The damage caused on the gastrointestinal tract is also a result of the inflammatory response resulting from the SARS-CoV-2 infection as there is a decrease in ACE2 and an increase in the production of cytokines resulting from the viral infection that can cause a storm of cytokines leading to tissue damage, the disruption of the intestinal mucosa and infiltration of inflammatory cells [95].

The IFN I and III, when administered exogenously, cause an antiviral state in intestinal epithelial cells to fight infection caused by SARS-CoV-2, causing the restriction of viral replication [89]. In addition, the literature data showed that the administration of IFN- α , which is a type of IFN I, decreases hospitalization and disease severity leading to attenuation of systemic and local viral infestation, which can alleviate disease severity in patients with SARS-CoV-2 and even decrease mortality in critically ill patients. Treatment with IFN- α can also limit virus replication in the upper respiratory tract and decrease virus spread in the lungs [114].

The type I IFNs, and to a lesser extent, type II IFNs, increase the regulation of the ACE2 receptor [82]. However, SARS-CoV-1 promotes the coding of IFN antagonists and suppresses the JAK / STAT IFN signaling pathway [115,116]. In patients positive for SARS-CoV-1, the expression of ACE2 is deregulated [117]. The imbalance of ACE2 has relevance in the expression of the amino acid transporter B⁰AT1, which controls the uptake of tryptophan in the intestine [103]. This amino acid regulates the expression of mRNA of antimicrobial peptides through the mTOR pathway [103,117], peptides that play a fundamental role in intestinal homeostasis [118]. That can cause decreased intestinal absorption of tryptophan and lead to dysregulation of antimicrobial peptides and dysbiosis [119].

Dysbiosis can lead to an imbalance in IFN III production and facilitate viral infection in enterocytes and may explain the occurrence of diarrhea in SARS-CoV-2 infections [106] (Fig. 3), which is one of the

symptoms of patients infected with SARS-CoV-2, with a prevalence of gastrointestinal symptoms of 17.6%, of which 12.5% of those infected have diarrheal conditions [120]. Likewise, approximately 27% of those infected with SARS-CoV-1 [121] and MERS-CoV [122] had gastrointestinal symptoms.

9. Conclusions

SARS-CoV-2 primarily infects human enterocytes, triggering a fusion of epithelial cells, while stimulating the release of a variety of cytokines and chemokines. However, coronaviruses can alter the response of IFNs in the immune system, interfering with the production and signaling of IFNs and the effective function of the interferon-stimulating gene. In addition, this immune-mediated response dependent on the imbalance of interferons is the main factor involved in the damage of intestinal epithelial cells, resulting in the appearance of an important clinical characteristic for viral pathogenesis, such as diarrhea and other gastrointestinal symptoms resulting in inflammation from SARS-CoV-2 infection. It is a fact that COVID-19 shows a strong immunological aspect. The current treatment is based on the use of immunomodulatory drugs (such as corticosteroids, strong inhibitors of IFNs signaling and production of these mediators). This information is very important to propose other researches in an attempt to clarify the true benefit of these therapies at the level of the intestinal mucosa, as some types of IFNs appear to protect these epithelial cells during COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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