Intestinal SARS-CoV-2 infection and the importance of breastfeeding

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June 11, 2020

Abstract

The novel coronavirus (SARS-CoV-2) binds to Angiotensin II- Converting-Enzyme (ACE2) on cell membrane, allowing the virus entrance, replication and host commitment. ACE2 is expressed by different cell types, which include the enterocytes in the gut. Such cells are highly active in metabolism, as they internalize molecules to be processed and used by the organism. ACE2 disruption leads to intestinal inflammation and impairs tryptophan absorption by enterocytes. Low tryptophan levels are also associated with intestinal inflammation and decreased synthesis of serotonin, affecting motility. During postnatal development, breastfeeding is the first source of nutrition, and tryptophan is milk component, together with mucin1, growth factors and secretory immunoglobulin A (sIgA). By reviewing the pathways and effects of SARS-CoV-2 and the gut responses to early weaning, we suggest that it is important to evaluate the benefits of maintaining breastfeeding during SARS-CoV-2 infection, as it might be essential to protect newborns from gastrointestinal-associated disorders.

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The novel coronavirus (SARS-CoV-2) binds to Angiotensin II- Converting-Enzyme (ACE2) on cell membrane, allowing the virus entrance, replication and host commitment. ACE2 is expressed by different cell types, which include the enterocytes in the gut. Such cells are highly active in metabolism, as they internalize molecules to be processed and used by the organism. ACE2 disruption leads to intestinal inflammation and impairs tryptophan absorption by enterocytes. Low tryptophan levels are also associated with intestinal inflammation and decreased synthesis of serotonin, affecting motility. During postnatal development, breastfeeding is the first source of nutrition, and tryptophan is milk component, together with mucin1, growth factors and secretory immunoglobulin A (sIgA). By reviewing the pathways and effects of SARS-CoV-2 and the gut responses to early weaning, we suggest that it is important to evaluate the benefits of maintaining breastfeeding during SARS-CoV-2 infection, as it might be essential to protect newborns from gastrointestinal-associated disorders.

Introduction

The novel coronavirus (SARS-CoV-2) infection can cause severe pneumonia, multi-organ failure and death. The mechanism used by the virus to enter human cells is the binding of spike glycoprotein (S protein), located on the virus nucleocapsid surface, to the receptor Angiotensin II-Converting Enzyme (ACE2) on cell membrane (Guo et al., 2020; Neurath, 2020), which consequently allows the virus replication and host commitment.

The identification of ACE2 led to the investigation of its main role in the catalytic cleavage of Angiotensin I to Angiotensin 1-9, being a key regulator of the renin-angiotensin system (RAS). This mechanism is part of renal and cardiovascular physiology and pathophysiology, in addition to be related to diabetes development, and lung diseases (Tipnis et al., 2000). Although ACE2 acts through a canonical pathway, ACE2 has also a RAS-independent function, regulating intestinal inflammation via its downregulation in response to epithelial

damage (Hashimoto et al., 2012). Accordingly, besides ACE2 expression in the lung, liver, testis, heart, brain and kidney, studies also showed a widespread distribution of ACE2 in the small intestine and colon (Perlot and Penninger, 2013).

The role of ACE2 in the gastrointestinal epithelium is still under investigation, but when ACE2 knockout mice are challenged by dextran sodium sulphate (DSS) they have increased inflammatory reaction, disruption of intestinal epithelial barrier, enhanced infiltration of inflammatory cells and severe diarrhea, resulting in colitis and other enteric diseases (Hashimoto et al., 2012). Interestingly, ACE2 deficiency leads to critical impairment of local tryptophan homeostasis and to intestinal inflammation (Wu, 2009). Tryptophan controls the expression of small intestinal antimicrobial peptides, maintaining microbial diversity (Hashimoto et al., 2012). Previous reports showed that amino acids activate mTOR signaling and regulate intestinal cell proliferation, differentiation, migration, and cytoskeletal reorganization (Wu, 2009). In addition, nicotinamide and dietary tryptophan appear to exert effects on intestinal antimicrobial peptides and colitis via mTOR pathway, indicating that its activation may be involved in peptide expression and microbiota homeostasis in the gastrointestinal tract.

In this brief review, we discuss the role of ACE2 in the intestine and the possible mechanisms associated with COVID-19 symptoms and the importance of breastfeeding in gastrointestinal protection.

SARS-CoV-2 and enterocytes infection

In the human body, SARS-CoV-2 binds to ACE2 receptor, which is highly expressed in the plasma membrane of differentiated enterocytes, mainly in the brush border, causing gastrointestinal symptoms in part of the patients (Cholankeril et al., 2020) The virus fuses into the host cell membrane and releases its RNA into the cytoplasm, incorporating its genetic material into cell machinery to translate accessory and structural proteins (Guo et al., 2020).

Recent studies used scRNA-seq to demonstrate the co-expression of ACE2 and transmembrane serine protease (TMPRSS2) in the enterocytes in the ileum and colon of human and primates (Hoffmann et al., 2020; Zhang et al., 2020; Ziegler et al., 2020). TMPRSS2 acts on the cleavage of S protein from the virus in the cell membrane, allowing the release of a viral peptide that is necessary for membrane fusion (Hoffmann et al., 2020). Thus, the co-expression of ACE2 and TMPRSS2 is critical for the entry of SARS-CoV-2 into the host cell, suggesting that the enteric symptoms of COVID-19 may be associated with the invasion of SARS-CoV-2 into enterocytes. Lamers et al. (2020) demonstrated in human small intestinal organoids (hSIOs) that the virus targets progenitors cells and a large number of enterocytes, leading to their apoptosis. However, this condition seems to be independent of ACE2 expression, as low levels of ACE2 mRNA were detected in the infected enterocytes (Lamers et al., 2020). Moreover, despite the high viral replication, SARS-CoV-2 infection does not induce cell death in Caco2 cells (Chu et al., 2020).

In addition to its essential role in viral infection, ACE2 endogenously plays a non-catalytic role via non-RAS-related pathway in the transport of neutral amino acids. This mechanism is essential to increase the transport of amino acids by ACE2 interaction with SLC6A19/B^0AT1 that is responsible for carrying tryptophan in the intestinal brush border (Kowalczuk et al., 2008; Cole-Jeffrey et al., 2015). It was demonstrated that both KO rats and mice for ACE2 have impaired tryptophan absorption and reduced expression of antimicrobial peptides (Hashimoto et al., 2012; Singer et al., 2012; Borges et al., 2017). Tryptophan is an essential amino acid precursor to various metabolites, such as serotonin and niacin (O'Mahony et al., 2015). Accordingly, in the intestine, tryptophan is converted into serotonin, acting in the regulation of motility of the gastrointestinal tract, in the microbiota homeostasis and as anti-inflammatory agent through AHR receptors (Metidji et al., 2018). The tryptophan absence, due to reduced absorption or to low protein diets, is related to diseases such as inflammatory bowel disease, irritable bowel syndrome, and Hartnup disorder (Taleb, 2019).

In addition to balanced diets, an important source of tryptophan and proteins during early life development is the breast milk, which is widely known for its immunological role in early development (Liu and Newburg, 2013). The most common milk-borne proteins are caseins and whey proteins, such as lactoferrin, mucin and secretory immunoglobulin A (sIgA) (Goldman, 1993; Roager and Licht, 2018). sIgA is important for

immunity and protection against respiratory and intestinal infections during the postnatal period. Moreover, it is also involved in the development of the immune system in children, being especially relevant against both bacterial (*S. pneumoniaie*) and viral pathogens (rotavirus, influenza and respiratory syncytial virus) (Goldman, 1993; Lönnerdal, 2003; Pribylova et al., 2012; Santos et al., 2013; Walker and Meng, 2020). In newborn pigs, a protein-deficient diet reduces the amount of sIgA generated in response to a viral agent. This is due to the low protein intake and, consequently, the low absorption of tryptophan via ACE2, causing the impaired immune response, deregulation of microbial homeostasis and intestinal inflammation (Fischer et al., 2017). Additionally, early weaning induces changes in the morphology of the small intestine in pigs, showing a reduction in villus height and an increase crypt depth, which are followed by a decrease in body weight (Hampson, 1986; Pluske et al., 1997; Boudry et al., 2004; McLamb et al., 2013). Immunologically, early-weaned animals show high expression of pro-inflammatory molecules, such as TNF-a, IL-6 and IL1-b, immediately in the first days after weaning (Pie et al., 2004; McLamb et al., 2013). Similarly, our group demonstrated that early weaning induced a reduction of intestinal villus height and alteration of proliferative index in the small intestine of rats, and the effects were maintained until adulthood (da Costa et al., 2019).

In summary, because ACE2 is expressed in enterocytes and it is essential for amino acids transport, a plethora of factors as the modulation of the immune system and the composition of the microbiota, infection by viruses or other microorganisms can altogether prevent the correct functioning of this receptor protein, and trigger diarrhea, and inflammation (Perlot and Penninger, 2013).

Diarrhea is a frequent symptom in coronavirus-induced diseases (SARS and MERS), with up to 73% of incidence (reviewed in Wong et al., 2020). However, SARS-CoV virus can replicate better in intestinal cells when compared to SARS-CoV-2, indicating the reason why diarrhea is more usual in CoV infections (Chu et al., 2020). Several cohorts reported frequencies of diarrhea in adults infected with CoV-2 ranging from 2 to 10% (Chen et al., 2020; Wang et al., 2020; Wong et al., 2020). A report with almost 2000 patients and another with 1099 adult patients with COVID-19 described diarrhea in 4.8% and 3.8% of the cases, respectively (Guan et al., 2020; Li et al., 2020). Interestingly, the number of children affected and presenting the symptom was lower than in adults. A Chinese epidemiologic study with 2135 children with COVID-19 analyzed 379 that were under 1- year-old. From them, 54% presented mild symptoms and 9% reported severe sickness (Dong et al., 2020). Some of the mild and severe cases developed digestive symptoms, such as nausea, vomiting, and diarrhea, suggesting that it is less frequent during early life in infected children.

Breastfeeding and weaning for maturation of epithelial cells and protection from virus

Before birth, the gastrointestinal tract exposure to commensal bacteria from the maternal gut/blood has an important contribution to the development and maturity of intestinal cells, which is enhanced in newborn early life and later on (Martin et al., 2016). During the postnatal period, breastfeeding is the first source of infant nutrition with bioactive agents, which are important to establish gastrointestinal function and immune ontogeny (Goldman, 1993).

Weaning and early transition to solid food affect the development of intestinal tract and interfere in the proliferation of stem cells and differentiation of progenitor cells. In the gastric mucosa, early weaning changes cell proliferation through MAPK signaling (Osaki et al., 2011) and interferes in cell differentiation (Zulian et al., 2017; Teles Silva et al., 2019). In the small intestine, early weaning decreases proliferative indices, causing reduction of crypt depth and enterocytes number (da Costa et al., 2019). Interestingly, some studies demonstrated the antiviral action of milk-born molecules (Yolken et al., 1992; Santos et al., 2013). Specifically, mucin 1 (MUC1) makes up 70% of the fat globule membrane in milk, and it can inhibit 100% of poxvirus replication and 97% of HIV in cell culture (Habte et al., 2007; Habte et al., 2008). KO mice for MUC1 present intestinal damage, increase of infection and more apoptotic cells, confirming MUC1 protective function in mucosal barrier (McAuley et al., 2007). Other intestinal mucins (Reis et al., 1999) are associated with the modulation of inflammatory response (Rokhsefat et al., 2016), which contributes to a lower risk of morbidity and, consequently, infant mortality. Intestinal mucins are produced by goblet cells, which are reduced in early-weaned rats (da Costa et al., 2019), and this feeding condition could be more prominent to pathogenic infections (Lidell et al., 2006). Thus, the production of mucins becomes indispensable for the

development, maturation, and intestinal protection.

As mentioned above, sIgA is another milk component, and it is in the secretion of 80% of mothers after recovery from SARS-CoV-2 infection (Fox et al., 2020). We consider that the low frequency of hampering intestinal response observed in babies with COVID-19 may be due to breastfeeding through the activity of sIgA through intestinal immune system modulation, and/or cross regulation of effects from sIgAs with other microorganisms, reducing the symptoms of COVID-19. Since these secretory antibodies are resistant to proteolysis and are acquired through breastfeeding in early life (Hurley and Theil, 2011), breast milk might have a therapeutic potential in relieving gastrointestinal symptoms and, possibly, other systemic responses. Although the virus has already been detected in breast milk samples (Groß et al., 2020), the evens and odds of breastfeeding interruption should be carefully evaluated in cases of infected mothers. Whereas Jing et al., (2020) suggest that breastfeeding should be suspended for 14 days and babies fed with artificial milk, Davanzo (2020) highlights the importance of considering the beneficial effects of it. Therefore, the decisions on breastfeeding maintenance during infection should be balanced, bearing in mind the short and long terms effects.

In summary, since breastfeeding is associated with low incidence of diarrhea and respiratory syndromes such as SARS-CoV and SARS-CoV-2, the reviewed data suggest that breast milk is essential to deliver the necessary elements for prevention of frequent intestinal inflammation, decrease of diseases during postnatal period and to support infant immune development (Figure 1 summarizes the information). Although the presence of SARS-CoV-2 in breast milk has been demonstrated, breastfeeding is still essential. In the presence of viral infections, breastfeeding in the first postnatal days and its maintenance during the first year of life may contribute to the attenuation of gastrointestinal symptoms caused by different pathogens, as well as providing proteins and antibodies that can act on the mucosa as the first defense barrier.

Declaration of interest

No conflict of interest to declare

Acknowledgements

The authors thank the Foundation for the Support of Research in the State of São Paulo (FAPESP; fellowship grants 2018/07409-5 and 2020/02888-2 and project grant 2018/07782-8) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES: Finance Code 001) for the financial support.

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Legend

Figure 1. Protective effects of breastfeeding in the intestine: milk-born molecules and their metabolites reach the intestinal epithelium and tryptophan (Trp) uses ACE2 in the brush border. During SARS-Covid-2, stem cells and enterocytes are affected and can be infected by the virus through ACE2 receptor, which disturbs homeostasis and contributes to intestinal malfunction, diarrhea and inflammation.