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Interferon-Lambda: New functions on intestinal symptoms in COVID-19

Role of IFN-λ on COVID-19 related intestinal symptoms

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Abstract

The tremendous public health and economic impact of COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a huge challenge globally. There is increasing evidence that SARS-CoV-2 induces intestinal infections. Type III interferon IFN (termed IFN-λ) has an antiviral role in intestinal infection, with focused, long-lasting, and non-inflammatory characteristics. This review presents a summary of the structure of SARS-CoV-2, including its invasion and immune escape mechanisms. Emphasis was placed on the gastrointestinal impact of SARS-CoV-2, including changes to the intestinal microbiome, activation of immune cells, and inflammatory responses. We also describe the comprehensive functions of IFN-λ in anti-enteric SARS-CoV-2 infection, and discuss the potential application of IFN-λ as a therapeutic agent for COVID-19 with intestinal symptoms.

Key Words: COVID-19; SARS-CoV-2; IFN-λ; gastrointestinal infection; mechanism; anti-viral response

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Core Tip: The tremendous public health and economic impact of the COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a huge challenge for countries across the whole world. Increased evidences have revealed that SARS-CoV-2 also induced intestinal infection. Type III interferon IFN, also called IFN-λ, plays an antiviral role in intestinal infection, and has focused, long-lasting, as well as non-inflammatory characteristics. In this review, we summarized the invasion and immune escape mechanisms of the SARS-CoV-2. Furthermore, we concerned about the gastrointestinal impact of the SARS-CoV-2 and the comprehensive role of interferon (IFN)-λ, also called type III IFN, in anti-enteric SARS-CoV-2 infection.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first documented in December 2019, as an outbreak of acute community-acquired atypical pneumonia occurred in Wuhan, China, with unknown etiology. At that time, COVID-19 represented a newly emerged respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which subsequently became a pandemic [1].

Similar to the flu virus, SARS-CoV-2 spreads in small liquid particles from the mouth or nose of an infected person when they cough, sneeze, speak, sing, or breath. These particles range from larger respiratory droplets to smaller aerosols [2]. It is widely reported that coronavirus has the largest non-segmented genome (close to 30 kb) of all RNA virus. This unique genome size enhances the plasticity of CoVs, which alter through mutations and recombination [3]. The first SARS-CoV-2 variant, Alpha B.1.1.7, was reported in the United Kingdom in September 2020 [4]. Increasing numbers of variants subsequently appeared, including Beta B.1.351, Gamma P.1, Delta B.1.617.2, and Omicron B.1.1.529 [5]. By November 2021, Omicron B.1.1529 had become the current major SARS-CoV-2 variant globally [6]. Because of this strong plasticity in CoV genes, generating high genetic diversity and a high risk of cross transmission, specific treatments remain elusive.

As a systemic disease, SARS-CoV-2 can infect multiple organs, resulting in multiorgan dysfunction in COVID-19 patients. Organs that are infected by SARS-CoV-2 include the lungs, small intestine, gallbladder, kidneys, testes, thyroid, adipose tissue, heart muscle, vagina, breasts, ovaries, and pancreas [7]. The symptoms of COVID-19 include pneumonia, fever, fatigue, intestinal ischemia, and diarrhea [8][9]. Many studies have reported gastrointestinal symptoms in COVID-19 patients, including diarrhea, nausea, vomiting, anorexia, abdominal pain, acid reflux, upper gastrointestinal bleeding, haematochezia, constipation, and melena [10]. Besides, angiotensin-converting enzyme 2 (ACE2), the receptor of SARS-CoV-2, is highly expressed in intestinal tissue. Moreover, fecal samples from COVID-19 patients have tested positive for SARS-CoV-2

RNA testing. Thus, there is potential for fecal-oral transmission, with SARS-CoV-2 Likely impacting the gastrointestinal tract [2].

As a part of the innate immune system, Type III interferon IFN (IFN-λ) mediates antiviral responses in the epithelial barrier. Moreover, IFN-λ receptor (IFN-λR)1 is preferentially expressed by the epithelial cells of the respiratory, intestinal, and reproductive tracts. The antiviral role of IFN-λ in intestinal infection has focused, long-lasting, and non-inflammatory characteristics. Consequently, many studies have explored the potential of applying IFN-λ in COVID-19 [11]. Continuing research on SARS-CoV-2 showed that it is also expressed in the intestinal tract. In particular, IFN-λ might have crucial roles in SARS-CoV-2 intestinal infection.

In this review, we summarize the invasion and escape mechanisms of SARS-CoV-2, and both the direct and indirect influence of SARS-CoV-2 on intestinal homeostasis. We also consider how IFN-λ impacts intestinal infections of SARS-CoV-2, and focus on the new functions of IFN-λ in COVID-19 with intestinal symptoms.

1. SARS-COV-2

Coronaviruses belong to the subfamily coronavirinae of the coronaviridae family, and have caused three pandemic outbreaks globally [12]. The subfamily coronavirinae consists of four genera; α, β, γ, and δ-coronaviruses. α and β-coronaviruses usually cause respiratory illness in humans and gastroenteritis in animals. In comparison, γ and δ-coronaviruses mostly infect birds, and, sometimes, mammals. According to genome sequence analysis, SARS-CoV-2, which was the third virus to create a pandemic, is classified in the β-coronavirus genome [12].

The four structural proteins of SARS-CoV-2 are essential for infections to occur. They consist of the spike (S) surface glycoprotein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein. The S protein is cleaved by host proteases, and allows SARS-CoV-2 to attach to host cells [13]. Both E and M proteins induce S protein to reside in the Golgi/ERGIC compartment, and subsequently, together, regulate N-glycosylation maturation of the S protein [14]. N structural proteins are responsible for

viral gene binding, compression, and packaging. In addition, they contribute to RNA transcription, and achieve the innate immune escape of the host through the N protein directly targeting and sequestering G3BP1 and host mRNA [15]. Once infected, SARS-CoV-2 mainly induces T cell responses; however, the generation of high-titer neutralizing antibodies by B-cell expansion and maturation might be limited [16, 17]. To explore potential treatment directions of SARS-CoV-2, it is important to learn its route of infection and mechanisms of immune evasion.

1.1 Infection mechanism of SARS-CoV-2

Zhou *et al* first confirmed that SARS-CoV-2 only infects HeLa cells that express ACE2, which is used as a SARS-CoV-2 receptor in patients [18]. Although there are two independent ways to mediate the infection of SARS-CoV [19, 20], the entry of SARS-CoV-2 involves ACE2-receptor-mediated transmembrane serine protease 2 (TMPRSS2)-dependent membrane fusion [21] (Figure 1).

SARS-CoV-2 is an enveloped virus containing a large nucleoprotein (N) encapsidated positive sense RNA genome. S trimers with closed and open prefusion structures usually protrude from the lipid bilayer of SARS-CoV-2. They are distributed randomly on the viral surface to bind to the receptor, ACE2, and, subsequently, mediate viral uptake and fusion. The receptor binding domain (RBD) site is occluded by three copies of the N-terminal domain (NTD) when in the closed prefusion. In the open prefusion, one or multiple RBDs lift up to expose the receptor binding site [22]. There are two main subunits, S1 and S2. S1 binds ACE2, while S2 triggers membrane fusion of the virus to the cell. In a typical SARS-CoV-2 infection process, S trimers must be activated by cellular protease-mediated cleavage at two distinct sites, S1/S2 and S2′. S2′ is responsible for triggering virus-cell membrane fusion. TMPRSS2 is expressed on the cell surface, and activates S trimers, which promote the virus to enter the plasma membrane in a pH-independent way [23]. Finally, the encapsidated genome buds into the ER Golgi intermediate compartment (ERGIC) to form virions, which are trafficked to the plasma membrane and released [22] (Figure 1).

1.2 Evasion mechanism of SARS-CoV-2

The first immune evasion of SARS-CoV-2 is related to the delayed occurrence of type-I interferon (IFN-I) [24]. As the first line of host defense against virus infections, IFN-I response is initiated by the recognition of pathogen-associated molecular patterns (PAMPs) *via* host pattern recognition receptors (PRRs). SARS-CoV-2 RNA is detected by various cytosolic sensors, including retinotic acid-inducible gene 1 (RIG-I/DExD/H-box helicase 58 [DDX58]) and melanoma differentiation-associated gene 5 (MDA5/IFN induced with helicase C domain 1 [IFIH1]). These sensors induce an antiviral signaling cascade to occur [25]. A subset of IFN-stimulated genes (ISG) is produced by the IFN-I response. These ISGs, along with other downstream molecules controlled by IFN-I, directly inhibit virus replication and recruitment, and activate diverse immune cells [26]. However, viral proteins (NSP3/papain-like protease) encoded by the SARS-CoV-2 genome selectively cleave IRF3 protein directly during SARS-CoV-2 infection, resulting in a blunted Type-I IFN response [27]. M proteins on SARS-CoV-2 also target mitochondrial antiviral signaling proteins (MAVS), and impair the aggregation and recruitment of downstream signaling components [28]. In parallel, stress granule analogues, formed by the N protein, competitively bind G3BP1 to inhibit the innate immune response [15]. Furthermore, SARS-CoV-2 nsp13 (helicase), nsp14 (exonuclease), nsp15 (endoribonuclease), and accessory protein orf6 block IFN-I production by antagonizing upstream signaling pathways [29, 30].

The second method of evasion is the upregulation of human inhibitory receptors, which modulate NK cell-mediated cytotoxicity. This process causes the exhaustion of NK cells, reducing their ability to clear viral infection [31].

1.3 Factors contributed to the severity of SARS-CoV-2

A recent meta-analysis of COVID-19 patients showed that physical activity could reduce the risk of COVID-19 infection. Physical activity strengthens the immune system, and allows cardiopulmonary and musculoskeletal adaptations [32]. Moreover,

adherence to a high-quality healthy diet has been linked to a reduced risk of COVID-19 infection and lower hospitalization rates. Mediterranean-style dietary patterns are associated with a lower risk of death from respiratory infections, including COVID-19, while plant-based diets have been associated with lower COVID-19 infection rates [33]. Age is also an important factor in severe COVID-19 illness and its adverse consequences. Statistically, the case fatality ratio for COVID-19 increases with age [34]. There has also been widespread concern about whether pregnant women are more susceptible to SARS-CoV-2. However, to date, there are no data supporting an increased susceptibility to SARS-CoV-2 due to pregnancy. Nevertheless, the risk of death in pregnant women with COVID-19 is significantly increased [35]. There is also a nonlinear association between ambient temperature and the risk of infection with SARS-CoV-2. Specifically, the risk of infection with SARS-CoV-2 increases significantly at temperatures between 0 and 10 °C[36].

2. INTESTINAL INFECTION OF SARS-COV-2

As a receptor of SARS-CoV-2, ACE2 is expressed in most organs. Consequently, COVID-19 is capable of infecting multiple organs, in addition to the respiratory tract [37]. It has been confirmed that ACE2 is abundantly expressed in gastrointestinal glandular epithelial cells [38]. There is also clinical evidence that the intestine is another target organ. When SARS-CoV-2 infects the gastrointestinal tract, it disrupts gut microbiota and induces other gastrointestinal (GI) symptoms. Current research on SARS-CoV-2 invasion of the gut is focused on (1) changes to the gut microbiome, and (2) whether gastrointestinal symptoms are caused by direct infection of SARS-CoV-2 or the consequence of a systemic immune activation.

2.1 Impact of SARS-CoV-2 on the gut microbiome

The gut microbiome consists of bacteria, fungi, viruses, and other microorganisms that dynamically interact with environmental factors to shape the intestinal mucosal immune system [39]. The intestinal bacteria of healthy individuals are mainly composed

of Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes. Intestinal microbiota is highly resilient to external disturbances, enabling the host to retain key species for a long time and maintain intestinal homeostasis. However, severe external influences cause microbial ecosystems to move from a stable state to an unhealthy stable state associated with disease [40]. A comparison of gut microbiota in COVID-19 patients and healthy people showed that the relative abundance of gut bacterial groups was higher in COVID-19 patients (including *Ruminococcus gnavus*, *Clostridium ramosum*, *Coprobacillus*, *Akkermansia muciniphila*, and *Eggerthella lenta*). Furthermore, the abundance of *Alistipes shahii* was comparatively lower in COVID-19 patients, along with several butyrate producers (including *Roseburia intestinalis*, *Eubacterium hallii*, *Ruminococcus bromii*, and *Faecalibacterium prausnitzii*) [41]. Gut microorganisms regulate mucosal sites in the distal part of the intestine *via* metabolites. These metabolites access other organs through the bloodstream, to induce immunomodulatory, immunoglobulin, and anti-inflammatory effects [42]. One cohort study showed that the lower abundance of *B. adolescentis*, *F. prausnitzii*, *E. rectale*, *R. (Blautia) obeum* and *D. formicigenerans* in the COVID-19 cohort might be associated with the decreased secretion of anti-inflammatory cytokines or increased secretion of inflammatory cytokines [43]. Another clinical study found that gastrointestinal infection with SARS-CoV-2 differed to that without infection. Significant dysbiosis of the microbiome was documented in COVID-19 patients, with high levels of pathogenic bacteria [44]. In general, the intestinal microbiota of active gastrointestinal infections with SARS-CoV-2 were mainly characterized by the enrichment of opportunistic pathogens and reduction of beneficial bacteria [45]. One study of COVID-19 patients showed that changes to the gut microbiome are correlated with the severity of COVID-19. In particular, the abundance of *Coprobacillus*, *Clostridium ramosum*, *and Clostridium hathewayi* is correlated with the severity of COVID-19. Furthermore, *Bacteroides dorei*, *Bacteroides thetaiotaomicron*, *Bacterodies massiliensis*, and *Bacteroides ovatus* downregulate the expression of ACE2 in the murine gut, correlating with SARS-CoV-2 Load in fecal samples [46].

In addition to SARS-CoV-2 directly infecting the gastrointestinal tract, it affects the functioning of the gastrointestinal tract through other organs. For instance, Keely *et al* showed that gut microbiota affected pulmonary health *via* vital cross-talk between the gut microbiome and lungs which is called the "gut-lung axis." However, the gut-lung axis is bidirectional; consequently, when SARS-CoV-2 infects the lungs, the gut microbiome might also be affected, including disruption [47].

2.2 Systemic immune activation

When infected by SARS-CoV-2, activated CD8+ IEL migrate to the intestinal mucosa [48]. The infected cells block IFN signaling, and exhibit strong pro-inflammatory responses by strongly activating the NF-κB/TNF pathway. In parallel, bystander cells not infected by SARS-CoV-2 mount an IFN-mediated response [49]. Although human plasmacytoid predendritic cells (pDCs) are not infected by SARS-CoV-2, pDCs may be activated by SARS-CoV-2 through IRAK4 and UNC93B1-dependent pathways, inducing high levels of type I and type III IFNS [50].

In healthy cells, CCL5, CXCL1, CXCL10, and CXCL11 recruit immune cells and pro-inflammatory chemokines. However, these four chemokines were significantly upregulated in SARS-CoV-2-infected epithelial cells in a trial of biomimetic human gut-on-chip system [51]. Interestingly, in a clinical cohort study, a subset of COVID-19 patients with gastrointestinal symptoms had small intestinal epithelial cells infected with SARS-CoV-2. Compared to patients without gastrointestinal symptoms, key inflammatory genes (including IFN-γ, CXCL8, CXCL2, and IL1B) were downregulated in these cells, and the frequency of pro-inflammatory dendritic cells was reduced in immune subsets [52]. The authors also recorded lower mortality among COVID-19 patients with gastrointestinal symptoms. Thus, a stronger immune response was induced in SARS-CoV-2 infected human intestinal tissue, reducing the efficiency of viral replication [53]. A recent study of rhesus monkeys infected with SARS-CoV-2 proposed that antiviral immunity was activated and the inflammatory response was enhanced at the early stage of intestinal infection. This response damages the intestinal barrier;

however, the intestine was repaired and inflammatory response decreased at the later stage, leading to mild intestinal pathological damage [54]. Intestinal IFN-related antiviral response and neutrophil related pathways are activated at the early stage. This process damages Paneth cells and the intestinal barrier, enhancing the inflammatory response. Nevertheless, the increasing number of Paneth cells and B cells that inhibit neutrophil-chemotactic cytokines CXCL8 and IL-1B at the later stage, repair the homeostasis of the intestinal barrier, inhibiting inflammation and tissue damage [54].

3. TYPE III INTERFERON

Interferons (IFNs) interfere with viral replication and induce inflammation, and are essential for mobilizing immune responses to SARS-CoV-2 infection [55]. There are three types of IFNs, and each has its own distinctive receptors. Type I IFN consists of at least 32 functional subtypes, including IFN-α subtypes (13 in humans and 14 in mice), IFN-β, IFN-ε , IFN-κ, IFN-ω, and IFN-ξ [56]. The type I IFN receptor (IFNR) is mainly expressed in immune cells. IFN-α/β responses to viral infections result in immunopathology. However, type I IFN also induces the infiltration of inflammation [57]. The mechanism of SARS-CoV-2 innate immune evasion depends on dysregulated IFN-I production, which contributes to robust early SARS-CoV-2 replication [31]. Type II IFN (IFN-γ) is a proinflammatory cytokine [58-60]. Type III IFN (IFN-λ) consists of four subtypes in humans (λ1, λ2, λ3, λ4), and its receptor is localized to epithelial cells and a subset of immune cells, including neutrophils. IFN-λ is widely believed to control pathologic microbes in the intestinal epithelium, and promotes the healing of the colonic epithelium without inducing an excessively strong inflammatory response [61].

Immune responses triggered by pathogen-associated molecular patterns (PAMPs) are key factors for pathogen defense. Differences in the location of PAMP recognized by some PRRs affect the type of IFN produced. PRRs in cytosol include RIG-I like receptors (RLRs), cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS), and Ku70, whereas PPRs in the endosome are toll-like receptors (TLRs) [62]. cGAS mainly induces the expression of pro-inflammatory cytokines and the IFN-I gene

through the STING-TBKI-IRF3/NF-κB signaling pathway. In comparison, RLRs, TLRs, and Ku70 induce the IFN-λ gene [63]. The downstream signaling pathways of IFN-λ is similar to IFN-I, which generates an antiviral response through the JAK-STAT pathway. In mitochondria or peroxisome, RLRs interacts with the mitochondrial antiviral signaling proteins (MAVS), resulting in interferon regulatory factors (IRF) 3 and 7 being recruited into the nucleus. IRF3/7 binds to the promotor of IFN-λ to initiate the gene expression of the IFN-λ family. Activated TLR7, 8 and 3 signal is transduced by Myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β (TRIF). This process results in the recruitment of IRFs and nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-κB) in the nucleus. Subsequently, the expression of IFN-λ gene is enhanced [64]. The cytoplasmic translocation of Ku70 is the first step in initiating IFN-λ1 secretion, which facilitates the interaction between stimulator of interferon genes (STING) and Ku70. Activated STING promotes TANK-binding kinase 1 (TBK1) phosphorylation, which activates IRF3. Since IRF3 is activated first, it produces the strong expression of IRF1 and IRF7, which are not endogenously expressed in cells. Subsequently IFN-λ1 is induced in the nucleus [65] (Figure 1).

In contrast to the type I IFN receptor, the type III IFN receptor (IFN-λR) is preferentially expressed by epithelial cells and neutrophils. The type III IFN receptor consists of IFN-λR1 (also called IL-28Rα) and IL-10R2. IFN-λR1 specifically binds IFN-λ, whereas IL-10R2 binds with cytokines in the IL-10 family. When type III IFN signaling is activated by IFN-λ, the receptor-associated kinases JAK1 and TYK2 phosphorylate STAT1 and STAT2. IFN-stimulated gene factor 3 (ISGF3) is activated by IFN-λ, and is a trimeric complex that is formed by phosphorylated STAT1, STAT2, and IRF9. ISGF3 binds IFN-stimulated response elements (ISREs) in the nucleus to promote the transcription of hundreds of antiviral effector IFN-stimulated genes (ISGs) [66]. In addition to the STAT1-dependent pathway, IFN-λ promotes tissue healing by the upregulation of collagens *via* the MAPK-dependent pathway [67] (Figure 2).

4. IMPACT OF THE TYPE III INTERFERON ON SARS-COV-2 INFECTION OF THE GUT

Diarrhea is the most common gastrointestinal symptom in COVID-19 patients. It is associated with changes to gut microbiota, malabsorption, and inflammation. It is also associated with the release of virulent proteins and toxins, and viral-induced intestinal fluid and electrolyte secretion. Of note, calprotectin, an inflammatory hallmark, was secreted by infiltrated neutrophils in COVID-19 patients with diarrhea [10].

The rapid initiation of the innate immune response after pathogen encounter is the result of infection and survival of the host. Highly expressed interferons induce the secretion of interferon stimulated genes (ISGs), which is a hallmark of the innate immune response. ISGs induce various cell-intrinsic antiviral responses, such as blocking the translation and induction of apoptosis, while recruiting of immune cells and stimulating effector functions [68]. Compared to IFN-I, the effects of IFN-λ are delayed but last longer. IFN-λ is transcribed and translated at higher rates in intestinal organoids. Furthermore, IFN-λ is preferentially induced on the mucosal surfaces of both the intestine and lung [69]. Furthermore, cells cultivated under polarizing conditions exhibit high IFN-λ responsiveness [70]. Pretreatment with IFN-λ in Vero E6 cells showed dose-dependent inhibition of SARS-CoV-2 [71]. IFN-λ promotes epithelial healing in patients infected with SARS-CoV-2 with acute colonic inflammation and tissue damage [72]. Moreover, IFN-λ treatment directly improves the proliferation and regeneration ability of differentiated gastrointestinal epithelial cells through Lgr5+ intestinal stem cells (ISC), leading to the recovery of intestinal barrier integrity [73]. Furthermore, IFN-λ protects epithelial cells from enteric viral infections, indicating that IFN-λ could be used to treat SARS-CoV-2 infection of the gastrointestinal tract.

4.1 IFN-λ-mediated anti-SARS-CoV-2 response

IFN has been confirmed to be the first line of innate immunity, producing an antiviral response when the virus infects the intestinal tract. SARS-CoV-2 infects, replicates, and implements de novo infectious virus production in human intestinal

epithelial cells (IECs). Furthermore, IFN-λ has huge potential for treating SARS-CoV-2. One study showed that the JAK-STAT1 dependent pathway of IFN-λ is more critical for anti-SARS-CoV-2 activity than IFN-I. Pretreatment IECs with IFN-λ resulted in a substantial decrease in the number of SARS-CoV-2 infected cells and viral replication [74]. Type I and II IFN upregulate antiviral ISGs when the virus infects cells, with ACE2 mRNA expression simultaneously increasing. Nevertheless, IFN-λ upregulates antiviral ISGs, whereas ACE2 mRNA is only marginally elevated [75]. Furthermore, one of the mechanisms by which interferons restrict viral replication is to inhibit the translation process, which inhibits the expression of structural proteins, with SARS-CoV-2 being more sensitive to IFN-λ. Compared to type I IFN, IFN-λ maintained a more consistent anti-SARS-CoV-2 infection state, with viral replication being inhibited for more than 72 h after drug withdrawal [76]. As for exogenous IFN-λ, pretreated IFN-λ significantly reduces the SARS-CoV-2 burden in the air-liquid interface of the lung model. The therapeutic administration of IFN-λ is also effective at restricting SARS-CoV-2 production in cultured human lung cells [77, 78]. Another vitro experiment showed that recombinant bovine IFN-λ produced in HEK-293 cells effectively prevents SARS-CoV-2 infection toward VERO cells [79].

4.2 Effect of IFN-λ mediated recruitment and activation on immune cells

It remains unclear whether IFN-λ directly or indirectly regulates the immune response after SARS-CoV-2 infection. To date, IFN-λ1-4 is considered to regulate the immune response, including the upregulation of IL-6, IL-8, and the downregulation of IL-10 in peripheral blood mononuclear cells (PBMCs) [79]. It also alters Th1/Th2 T-cell balance, reduces IL-13 production by T cells [80], and induces ISGs in B cells and plasmacytoid dendritic cells, as well as in CD8 T cells, especially effector memory cells (TEMRA) [81] (Figure 2). As an anti-inflammatory factor, IL-10 induction in macrophages provides a powerful pathogen immune escape mechanism, which causes chronic infection [82]. IFN-λ stimulates a stronger innate immune response by upregulating IL-6 and IL-8, and by reducing IL-10 secretion in PBMCs, which promote an antiviral

response [79]. In vivo, IFN-λ promotes the differentiation of initial T cells to Th1 cells, rather than Th2 cells, thus activating a stronger immune response, which combats the invasion of the gut by pathogens [80]. Furthermore, in the intestinal tract (unlike IFN-I), IFN-λ exhibits a compartmentalized response to virus infections because of the restricted expression of IFN-λR, which is preferentially expressed on IECs. IFN-λR expression has also been reported in NK cells, T cells, B cells, and pDCs [83]. Interestingly, IFN-λ induces the mTORC1 pathway, leading to the differentiation of naïve B cells in plasmablasts by activating PI3K *via* JAKs in an IRS-dependent, but STAT-independent, manner [84]. Thus, IFN-λ likely promotes the release of antibodies and increases the capability of antiviruses. These immune cells activate strong immune responses in the body to resist pathogen invasion and maintain intestinal homeostasis under IFN-λ regulation (Figure 2).

4.3 IFN-λ mediated regulation of intestinal inflammation

As a hallmark of intestinal inflammation in COVID-19 patients who have diarrhea, neutrophils are rapidly recruited from the blood after IEC infection. Neutrophils also restrict pathogen invasion through phagocytosis, reactive oxygen species (ROS), and the degranulation and release of cytotoxic antimicrobial molecules [85]. In contrast, excessive recruitment of neutrophils promotes inflammation. Thus, it is important to control the recruitment of neutrophils. Published studies show that IFN-λ provides a better balance of antiviral protection, with minimal inflammation and tissue damage. Specifically, IFN-λ in neutrophils inhibits the activation and phosphorylation of kinase AKT, which prevents the assembly of NADPH oxidase complex NOX2 and decrease ROS in a JAK2-dependent way [86]. The effects of IFN-λ in neutrophils are independent of protein synthesis and transcription, only depending on the activation of AKT being inhibited [87]. Another study showed that human neutrophils optimally respond to IFN-λ in vivo, potentially inducing ISG levels to rise during inflammatory conditions by up-regulating IFN-λR1 [88]. Mutual regulation between IFN-λ and neutrophils promotes

intestinal resistance to SARS-CoV-2 invasion, and reduces the damage of intestinal tissue caused by inflammation.

CONCLUSION

IFN-λ potentially has a protective role in COVID-19 patients with intestinal infections. However, there is increasing evidence that IFN-λ has a complex dual role in the intestinal tract. Exposure to IFN-λ might increase intestinal permeability, which is associated with the disruption of junctional proteins [89]. Elevated IFN-λ is also related to lower numbers of Paneth cells and increased apoptosis of epithelial cells in the small intestinal [90, 91]. In contrast, IFN-λ has been reported to exhibit an antiviral effect in the intestinal tract, and promotes the healing of intestinal epithelial cells [71-73]. Although IFN-λ has an anti-SARS-CoV-2 effect in the intestinal tract, the mechanism remains unclear. Furthermore, how IFN-λ affects other intestinal cells (Paneth cells, goblet cells, and intestinal stem cells) and tight junctions in the intestine of SARS-CoV-2 patients requires investigation. Although IFN-λ has strong potential for use in COVID-19 intervention strategies, the mechanisms need to be elucidated first.

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