



Sociedade  
Brasileira de  
Infectologia

# The Brazilian Journal of INFECTIOUS DISEASES

[www.elsevier.com/locate/bjid](http://www.elsevier.com/locate/bjid)



## Review article

# Immune response in SARS-CoV-2 infection: the role of interferons type I and type III



Caciane Portela Sousa<sup>a,\*</sup>, Carlos Brites<sup>id b</sup>

<sup>a</sup> Universidade Federal do Piauí, Centro de Ciências da Saúde, Departamento de Parasitologia e Microbiologia, Teresina, PI, Brazil

<sup>b</sup> Universidade Federal da Bahia, Faculdade de Medicina, Laboratório de Pesquisa em Infectologia (LAPI), Salvador, BA, Brazil.

### ARTICLE INFO

#### Article history:

Received 4 June 2020

Accepted 31 July 2020

Available online 26 August 2020

#### Keywords:

IFN type I

IFN type III

SARS-CoV-2

Immune response

### ABSTRACT

**Background:** There is scarce information on the human immune response to the SARS-CoV-2 infection, and on the exacerbated inflammatory reaction observed in severe COVID-19 cases. **Objective:** To review the available evidence on the role of interferons type I and type III to SARS-CoV-2 infection.

**Methods:** We reviewed the available published evidence on the role of immune response to SARS-CoV-2 infection as well as recent publications on characteristics and outcomes of COVID-19, and their relationship with interferons type I and type III.

**Results:** The available data indicates that immune response plays an important role in controlling SARS-CoV-2 infection and the immune dysregulation can significantly modify the clinical outcomes of affected patients. In addition, the evidence suggests that IFN type I and III can play an important role in controlling viremia and modulating the immune response in COVID-19.

**Conclusions:** Due to their central role in immune response against SARS-CoV-2 infection, IFN type I and III could be considered for treatment of COVID-19.

© 2020 Sociedade Brasileira de Infectologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Coronaviruses (CoVs) are enveloped, single-stranded RNA viruses (ssRNA), that belong to the the Coronaviridae family, subfamily Orthocoronavirinae. Currently, they are considered as the main groups of viruses that cause acute respiratory infections, and one of them, SARS-CoV-2 is responsible for the pandemic that has affects public health worldwide.<sup>1-3</sup>

CoVs infect the respiratory tract and cause diseases varying from mild to moderate clinical manifestations to the most serious forms that can be fatal. In severe illness,

patients present with severe pneumonia associated with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), which are responsible for severe acute respiratory syndrome (SARS-CoV) and medium-eastern respiratory syndrome (MERS-CoV).<sup>4-8</sup>

The severity of the disease caused by SARS-CoV-2 (named COVID-19) can be modulated by several factors related to the

\* Corresponding author at: Universidade Federal do Piauí, Campus Universitário Ministro Petrônio Portella Bairro Ininga - Teresina - PI - CEP: 64049-550

E-mail address: [portelasousa@ufpi.edu.br](mailto:portelasousa@ufpi.edu.br) (C. Portela Sousa).

<https://doi.org/10.1016/j.bjid.2020.07.011>

1413-8670/© 2020 Sociedade Brasileira de Infectologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

virus-host interaction, such as viral load, immune response, age, and presence of comorbidities. The severe form of the disease has been described mainly in elderly individuals, while young adult individuals, when infected, usually have a mild to moderate clinical disease.<sup>5,9</sup> However, regardless of individual's age, the presence of comorbidities such as diabetes, obesity, heart and kidney failure, among others, is also associated with severe disease.<sup>10,11</sup> It is possible that the factors involved in virus-host interaction, such as viral load, viral evasion to host immune responses, and the exacerbated acute inflammatory response, can play an important role in defining the severity of the disease.

In addition, some studies demonstrate that socioeconomic inequalities and racial differences can also be considered as important risk factors for the severity of the disease, since poor sanitary conditions, low socioeconomic conditions and difficulties in accessing medical care can favor infection dissemination and cause clinical complications that increase mortality due to COVID-19.<sup>12,13</sup>

A characteristic of CoVs is their rapid viral replication. The virus can be detected in respiratory tract secretions (bronchoalveolar aspirate, tracheal aspirate and nasal secretions), feces, urine and blood (serum/plasma/whole blood).<sup>14,15</sup> The presence of viruses in the feces suggests oral-fecal transmission and infection of the digestive tract.<sup>15,16</sup> Viremia may contribute to disease severity, probably due to a failure of the innate immune mechanisms mediated by interferons (IFNs) in limiting viral spread to the respiratory airways.<sup>17-19</sup> In a study carried out with patients with MERS-CoV in South Korea, it was shown that patients with severe disease had a high viral load in respiratory secretions and with a longer duration of respiratory airway involvement when compared to those with mild to moderate disease.<sup>20</sup>

Although elevated viral load may contribute to disease severity,<sup>12,18</sup> a study conducted with patients with SARS-CoV-2 in Wuhan, China, demonstrated that patients hospitalized in intensive care units showed higher levels of pro-inflammatory cytokines, IL-2, IL-7, IL-10, G-CSF, IP-10, MCP1, MIP1A and TNF- $\alpha$  when compared to those who did not require intensive therapy, suggesting that increased secretion of pro-inflammatory cytokines is associated with disease severity.<sup>20</sup> However, authors did not evaluate the levels of type I and type III IFNs, both important cytokines that act in viral control.

In another study also conducted in Wuhan, China, in a retrospective cohort of 150 patients with SARS-CoV-2 infection, it was shown that respiratory failure and myocardial injury were the main clinical predictors of mortality in such patients, both associated with elevated levels of serum markers of acute inflammatory response, such as myoglobin, cardiac troponin, C-reactive protein, and IL-6.<sup>21</sup>

## Immune response in SARS-CoV-2 infection

Innate immune response is essential for the control and resolution of the disease. However, development of an exacerbated acute inflammatory response generates an imbalance of the innate immune system with the massive production of pro-inflammatory cytokines IL-1 $\beta$ , IL-6 and TNF- $\alpha$  and chemokines

CCL2 / MPC-1, CXCL8/IL-8 and CXCL10/IP-10 at a systemic pathological level that can contribute to the severity of the disease, increasing morbidity and mortality.<sup>22-25</sup>

CoVs mainly infect the epithelial cells of the respiratory airways. However, it is possible that alveolar macrophages<sup>26</sup> and dendritic cells can also be infected, although some studies have shown that these cells are not permissive to viral replication, but can act as viral reservoirs.<sup>27</sup>

Following CoVs entry into human host cells, viral RNAs are released and act as pathogen-associated molecular patterns (PAMPs), which are recognized by pattern receptors (PRRs) as toll-like receptors (TLR3, TLR7 and TLR9) and retinoic acid-inducible (RIG-I) type I receptors.<sup>28-31</sup> Signaling at these cell receptors induces cytosolic translocation of various nuclear transcription factors such as NF- $\kappa$ B and the activating protein (AP-1) to the cell nucleus, the transcription of genes and expression of acute inflammatory response proteins, such as C-reactive protein (CRP), pro-inflammatory cytokines and chemokines (like IL-1, IL-6, TNF- $\alpha$ , MPC-1, IL-8 and IP-10), as well as secretion of soluble factors associated with the interferon protein stimulator gene (ISGs) that encodes interferons (IFNs) acting in viral control, triggering an antiviral state.<sup>32,33</sup>

## Type I and type III- $\lambda$ interferons

Type I and type III IFNs are cytokines that act on innate immune response. The existing evidence shows that both IFNs share common functions in innate antiviral defenses, but with different intensity and kinetics of immune responses.

Type III IFNs have restricted expression, cell signaling and compartmentalized activity. They are involved in protection of epithelial surfaces barriers, where there is wide exposure to microorganisms and require a locally effective innate immune response, to maintain viral control and immunity without generating systemic activation of the immune system that could trigger an exacerbated acute inflammatory response. However, type I IFNs are widely expressed and involved in cellular signaling, which classify them as potent cytokines with systemic inflammatory effect. They are involved in antiviral defenses generated by the rupture of epithelial barriers and/or viral dissemination, as well as in serious and systemic infections.

Type I and type III IFNs are essential for maintaining viral control and limiting viral infections. However, it is still not clear how these IFNs share the ability to maintain viral control in infections. It is unclear whether they are secreted simultaneously in immune responses (even in different sites of action) or sequentially through immune system signaling, and what would be the real extents and kinetics of their responses in infectious and inflammatory diseases. In addition, it is also unclear if type I secreted IFNs could be involved in the exacerbation of the acute inflammatory response in SARS-CoVs-2.

Interferons (IFNs) are cytokines that can be divided into three families (type I, type II and type III), according to their gene homology sequences, cell receptors and functional activities. They exert effector functions in innate antiviral defenses, adaptive immune responses, antitumor responses, and autoimmunity.<sup>34-36</sup> Type I IFNs were originally identified due to their antiviral activities. The family of type I IFNs

(mainly IFN- $\alpha$  and IFN- $\beta$ ) in humans includes the subtypes IFN- $\alpha$ , IFN- $\beta$ , IFN- $\epsilon$ , IFN- $\kappa$  and IFN- $\omega$ . These IFNs signal through the IFNAR heterodimer receptor, shared with the IFNAR1 and IFNAR2 subunits.<sup>34</sup>

Type III IFNs (IFN- $\lambda$  lambda) include the subtypes IFN- $\lambda$ 1 (IL-29), IFN- $\lambda$ 2 (IL-28A), IFN- $\lambda$ 3 (IL-28B) and IFN- $\lambda$ 4. These type III IFNs signal through the IFNLR heterodimer receptor shared with the IFNLR1 (IFNLRA/IL-28R $\alpha$ ) and IL-10R $\beta$ <sup>34-36</sup> subunits.

Both, type I and type III IFNs, are genetically distinct and have different cell receptors. The signaling pathways are overlapping and several functional antiviral activities are shared with each other.<sup>35-37</sup> However, there are subtle differences in cytosolic signaling, mediated by several activation pathways, which can directly influence the magnitude and kinetics of its effector functions.<sup>38-40</sup>

After viral stimulation, IFNs are induced through the recognition of pathogen-associated molecular patterns (PAMPs) with pattern recognition (PRRs), endosomal (TLR3 and TLR7) and cytosolic (RIG-I) receptors inducing activation and phosphorylation of the JAK/STAT pathway and the formation of the heterotrimer complex STAT1-STAT2-IRF9 (ISGF3) which is involved in the induction of the genes responsible for the responses to IFNs in the promoter region of the IFN stimulating genes (ISG).<sup>41</sup>

Type I IFNs are secreted by almost all nucleated cells. However, depending on the cell type and immune-environmental status, there may be differences in immune responses. Type I IFNs are characterized as cytokines with a potent systemic and inflammatory antiviral effect and act through their receptors (IFNAR) present in almost all cells. However, when activated, cells can also trigger robust proinflammatory responses characterized by different secreted proinflammatory cytokines and chemokines, such as TNF, IL-1 $\beta$  and IL-6.<sup>42</sup> Thus, type I IFNs can be considered as one of the main initiators of pro-inflammatory cytokine and chemokine secretions associated with the immunopathology of viral infections.<sup>18</sup>

On the other hand, type III IFNs are secreted only by some cells of the immune system, such as dendritic cells, neutrophils, hepatocytes and mainly tissue epithelial cells (known as barrier cells), which also express their cellular receptors (IFNLR).<sup>35,36,43,44</sup> In COVID-19 it has been observed that the so-called "cytokine storm" is similar to the macrophage activation syndrome, which is characterized by increased production of IL-6, IL-17, TNF, and chemokine ligand 10 (CXCL10).<sup>45</sup>

Thus, type III IFNs effectively act in locations of epithelial barriers (respiratory airways, gastrointestinal tract, hepatocytes, female reproductive system and placenta). However, they are secreted in low magnitude and have an effective antiviral function limited to some barrier tissues.<sup>18,40,46</sup>

Although they provide an innate antiviral defense of lesser magnitude and lower potency than the antiviral response mediated by type I IFNs, they present less inflammatory damage, and are essential in the first innate defenses against microorganisms found on the epithelial surfaces of such barriers.<sup>42,47</sup> They are critically involved in controlling inflammation and maintaining epithelial barriers integrity without causing inflammatory tissue damage, whereas type I IFNs predominate when barrier surfaces are disrupted, or in systemic

infections.<sup>48,49</sup> However, there is a complex interplay between cytokines in immune response. For instance, mRNA expression of cytokines and chemokines (including type I IFNs) is negatively regulated by KH-type splicing regulatory protein (KSRP) at multiple levels.<sup>50</sup>

In infections with low viral loads, type III IFNs are sufficient to maintain viral control and immunity. However, in infections with high viral loads or in viral spread, the immune mechanisms mediated by type I IFNs are activated to improve host's antiviral defenses.<sup>48,49</sup>

In a study carried out on experimental models for influenza A virus (IAV) infection, Galani et al. suggest that viral load is the key factor that determines the different contributions of IFNs to antiviral defenses.<sup>18</sup> The viral load acts as the activation signal in the immune system to trigger IFN-mediated antiviral responses with different magnitudes for viral control. However, it is possible that viral SARS with high morbidity and mortality is due to the association between high viral load and acute exacerbated inflammatory response modulated by intrinsic factors of infected patients.<sup>51-53</sup>

Studies carried out in experimental models with the influenza A virus (IAV) demonstrated that epithelial cells of respiratory tract preferentially secrete type III IFNs, indicating an important effector role of these IFNs in viral control in the focus of infection.<sup>43</sup> Intranasal administration of type III IFNs in mice infected with IAV induced a reduction in respiratory infection and limited spread of viruses to the lungs, suggesting that type III IFNs could be used as a prophylactic medication during epidemics with respiratory viruses, as part of an effort to protect people who have not been vaccinated against IAV.<sup>19,55</sup> In addition, in rhinovirus infections IFN- $\gamma$  is predominantly secreted by bronchial epithelial cells, and the levels are inversely correlated with viral load and disease severity.<sup>54</sup>

Studies in experimental models in mouse and human hepatocytes have shown that IFN- $\lambda$ s and IFN- $\alpha$  were able to induce ISGF3 activity and ISG expression in hepatocytes, by inhibiting the replication of hepatitis B (HBV) and hepatitis C (HCV) viruses. However, the magnitude of ISGF3 activity and the expression of ISG induced by IFN- $\lambda$  were lower than that induced by IFN- $\alpha$ . Therefore, the available evidence suggests that this functional difference may provide a clinical advantage of IFN- $\alpha$  for the treatment of chronic HCV infection, since type III IFNs cause less adverse hematopoietic effects than IFN- $\alpha$ .<sup>56-58</sup>

The analysis of the viral genome of CoVs, SARS-CoV and MERS-CoV, demonstrated that these viruses express several structural and non-structural proteins that can antagonize innate immune responses mediated by type I IFNs, suppressing viral control<sup>59</sup> and stimulating secretion of pro-inflammatory cytokines with exacerbation of acute inflammatory response.<sup>60</sup> It is probably this imbalance in the innate immune system that contributes to disease severity.<sup>61,62</sup> In addition, ssRNA viruses are characterized by the ability to evade the mechanisms of the innate immune system, especially those mediated by signaling at RIG-I receptors.<sup>63,64</sup>

In cultures, it was observed that SARS-CoVs have the potential to inhibit the secretion of type I IFNs in productively infected cells. In studies carried out with Ebola virus and IAV,

viral proteins (VP35 and NS1, respectively) act on IFN signaling and inhibit the secretion of type I IFNs.<sup>65,66</sup>

### Dendritic cells

Dendritic cells (DCs) constitute a heterogeneous family of cells involved in the innate and adaptive immune response. They originate from hematopoietic precursors in the bone marrow. They are generally divided into distinct subpopulations, such as myeloid DCs (mDC), plasmacytoid DCs (pDC) monocyte derived dendritic cells (moDC), and Langerhans cells. Langerhans' cells were initially classified as DCs but according to their ontogeny these cells are currently being classified as macrophages.<sup>67,68</sup>

DCs are the main antigen presentation cells (APCs) involved in the capture, processing and presentation of viral peptides associated with class II and class I major histocompatibility complex (MHC) molecules for TCD4 + and TCD8 + cells (cross-priming), respectively.<sup>69</sup>

In CoV infection, DCs are essential in controlling viral infection, as they are the first cells of the immune system to detect the virus in tissues of respiratory tract and migrate to peripheral lymphoid tissues, to initiate adaptive immune responses. They play an important role that involves the innate and adaptive immune response, in eradication of viral infection.

DCs, especially pDCs, secrete high levels of both type I and type III IFNs.<sup>47,70</sup> These cells also express cellular PRR receptors (TLR7, TLR9 and RIG-1) that can detect CoV nucleic acids (ssRNA) and rapidly induce high-level secretion of type I IFNs, especially IFN- $\alpha$ , and high levels of type III IFNs. In addition, these cells also express receptors for type I and type III IFNs, and for the IFNs regulating factor (IRF-7) that directly stimulates the expression of these IFNs in an autocrine and paracrine manner.<sup>71,72</sup>

A study carried out with pDCs isolated from peripheral blood and infected with SARS-CoV demonstrated that these cells are probably the largest sources of type I IFNs in response to infection in SARS-CoV and suggested an important role of pDCs in SARS-CoV viral control.<sup>73</sup> However, the antiviral effect occurs mainly in systemic infections, when occurs rupture of local barriers defenses or when viruses reach circulation.<sup>46</sup> In such scenarios pDCs act as powerful viral sensors of the innate immune system that are essential for the control of systemic viral infections.

DCs, especially mDCs, are also capable of secreting pro-inflammatory cytokines, such as IL-6, which is a potent cytokine that stimulates the synthesis of acute phase inflammation proteins, acts in an autocrine manner to secrete pro-inflammatory cytokines, such as leukocyte chemotactic cytokines that stimulate leukocyte migration to the focus of infection. IL-6 also induces activation of the alternative macrophage (M2) pathway, inducing fibrosis in lung tissue.<sup>74,75</sup> It induces a cellular immune response mediated by CD4 + Th17 cells which generates an immune response rich in neutrophils and monocytes, through IL-17 secretion.<sup>76</sup> Thus, DCs through IL-6 secretion also contribute to exacerbating the acute inflammatory response and disease severity. In addition, a chemokine-like protein produced by plasmacytoid DC

is able to increase alpha-IFN production, but it also causes a delay in CD8 + T cell activation, impairing viral clearance.<sup>77</sup>

### Final considerations

There is no current effective treatment for COVID-19, and new therapeutic interventions are not expected in the short-term. A recent study demonstrates that SARS-CoV-2 did not significantly induce types I, II, or III interferons in ex-vivo infected human lung tissues compared to 2003 SARS-CoV.<sup>78</sup> A previous experiment with MERS-CoV provides evidence on benefits of the combination of Lopinavir/ritonavir plus interferon- $\beta$ 1b in an animal model.<sup>79</sup> In addition, a combination of oral ribavirin and pegylated interferon alpha-2 was also active against MERS-CoV.<sup>80</sup>

Recently, a work indicates that combining lopinavir/ritonavir plus ribavirin and interferon- $\beta$ 1b was able to maintain viral control without excessively activating the inflammatory response that could contribute to the severity of the disease in patients with SARS-CoVs-2.<sup>80</sup> Taken together, these data provides a rational for the potential role of IFNs use as a therapy for SARS-CoV2 infection.

### Conflict of interest

The authors declare no conflict of interest.

### REFERENCES

1. World Health Organization. Novel Coronavirus (2019-nCoV) situation report-2 [published online ahead of print January 21, 2020]. <https://www.who.int/docs/default-source/coronaviruse/situationreports/20200122-sitrep-2-2019-ncov.pdf>.
2. World Health Organization. Novel coronavirus – China. Jan 12, 2020. <http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/> (accessed Jan 19, 2020).
3. Note from the editors: World Health Organization declares novel coronavirus (2019-nCoV) sixth public health emergency of international concern. Eurosurveillance editorial team.
4. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med*. 2012;367:1814–20.
5. Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis*. 2014;29:301–6.
6. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology*. 2018;23(Feb (2)):130–7.
7. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020. Feb 24.
8. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579:270–3.
9. Li G, Fan Y, Lai Y, Han T, et al. Coronavirus infections and immune responses. *J Med Virol*. 2020;92:424–32.

10. Al-Tawfiq JA, Hinedi K, Ghandour J, et al. Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients. *Clin Infect Dis*. 2014;59:160–5.
11. Zhou F, Yu T, Du R, et al. Clinical Course and Risk Factors for Mortality of Adult Inpatients With COVID-19 in Wuhan, China: A Retrospective Cohort Study. *Lancet*. 2020;395:1054–62.
12. van Dorn A, Cooney RE, Sabin M. COVID-19 Exacerbating Inequalities in the US. 2020;395:1243–4.
13. Laster Pirtle WN. Racial Capitalism: A Fundamental Cause of Novel Coronavirus (COVID-19) Pandemic Inequities in the United States. *Health Educ Behav*. 2020:1090198120922942.
14. Ng EKO, Ng PC, Hon EKL, et al. Quantitation analysis and prognostic implication of SARS coronavirus RNA in the plasma and serum of patients with severe acute respiratory syndrome. *Clin. Chem*. 2003;49:1976–80.
15. Cheng PK, Wong DA, Tong LK, et al. Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. *Lancet*. 2004;363:1699–700.
16. Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. *Nat Med*. 2004;10:S88–97.
17. Poissy J, Goffard A, Parmentier-Decrucq E, et al. MERS-CoV Biology Group. Kinetics and Pattern of Viral Excretion in Biological Specimens of Two MERS-CoV Cases. *J Clin Virol*. 2014;61:275–8.
18. Galani IE, Triantafyllia V, Eleminiadou EE, et al. Interferon-lambda Mediates Non-redundant Front-Line Antiviral Protection against Influenza Virus Infection without Compromising Host Fitness. *Immunity*. 2017;46:875–90.
19. Kim S, Kim MJ, Kim CH, et al. The Superiority of IFN- $\lambda$  as a Therapeutic Candidate to Control Acute Influenza Viral Lung Infection. *Am J Respir Cell Mol Biol*. 2017;56:202–12.
20. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506.
21. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020:1–4.
22. Zhang Y, Li J, Zhan Y, et al. Analysis of serum cytokines in patients with severe acute respiratory syndrome. *Infect. Immun*. 2004;72:4410–5.
23. Jiang Y, Xu J, Zhou C, et al. Characterization of cytokine/chemokine profiles of severe acute respiratory syndrome. *Am J Respir Crit Care Med*. 2005;171:850–7.
24. Chien JY, Hsueh PR, Cheng WC, Yu CJ, Yang PC. Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome. *Respirology*. 2006;11:715–22.
25. Cheung CY, Poon LL, Ng IH, et al. Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis. *J Virol*. 2005;79:7819–26.
26. Tseng CT, Perrone LA, Zhu H, Makino S, Peters CJ. Severe acute respiratory syndrome and the innate immune responses: modulation of effector cell function without productive infection. *J Immunol*. 2005;174:7977–85.
27. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell*. 2006;124:783–801.
28. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell*. 2010;140:805–20.
29. Kell AM, Gale M Jr. RIG-I in RNA virus recognition. *Virology*. 2015;479–480:110–21.
30. Chow KT, Gale M Jr, Loo YM. RIG-I and Other RNA Sensors in Antiviral Immunity. *Annu Rev Immunol*. 2018;36:667–94.
31. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. *Nat Rev Immunol*. 2014;14:36–49.
32. Nelemans T, Kikkert M. Viral innate immune evasion and the pathogenesis of emerging RNA virus infections. *Viruses*. 2019;11:961.
33. Isaacs A, Lindenmann J. Virus interference. I. The interferon. By A. Isaacs and J. Lindenmann, 1957. *J Interferon Res*. 1987;7:429–38.
34. Kottenko SV, Gallagher G, Baurin VV, et al. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. *Nat Immunol*. 2003;4:69–77.
35. Sheppard P, Kindsvogel W, Xu W, et al. IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat Immunol*. 2003;4:63–8.
36. Lazear HM, Schoggins JW, Diamond MS. Shared and Distinct Functions of Type I and Type III Interferons. *Immunity*. 2019;50:907–23.
37. Odendall C, Dixit E, Stavru F, et al. Diverse intracellular pathogens activate Type III Interferon expression from peroxisomes. *Nat Immunol*. 2014;15:717–26.
38. Pervolaraki K, Stanifer ML, Münchau S, et al. Type I and Type III interferons Display Different Dependency on Mitogenactivated Protein Kinases to Mount an antiviral state in the human gut. *Front Immunol*. 2017;8:459.
39. Ye L, Schnepf D, Staeheli P. Interferon- $\lambda$  Orchestrates Innate and Adaptive Mucosal Immune Responses. *Nat Rev Immunol*. 2019;19:614–25.
40. Stark GR, Darnell JE Jr. The JAK-STAT pathway at twenty. *Immunity*. 2012;36:503–14.
41. Wells Aland Coyne CB. Type III interferons in antiviral defenses at barrier. *Trends Immunol*. 2018;39:848–58.
42. Jewell NA, Cline T, Mertz SE, et al. Lambda interferon is the predominant interferon induced by influenza A virus infection in vivo. *J Virol*. 2010;84:11515–22.
43. Lazear HM, Nice TJ, Diamond MS. Interferon- $\lambda$ : immune functions at barrier surfaces and beyond. *Immunity*. 2015;43:15–28.
44. Sommereyns C, Paul S, Staeheli P, Michiels T. IFN-lambda (IFN-lambda) is expressed in a tissue-dependent fashion and primarily acts on epithelial cells in vivo. *PLoS Pathogens*. 2008;4:e1000017.
45. Merad M, Martin J. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nature reviews. Immunology*. 2020;20:1–8.
46. Wack A, Terczyńska-Dyla E, Hartmann R. Guarding the frontiers: the biology of type III interferons. *Nat Immunol*. 2015;16:802–9.
47. Kumagai Y, Takeuchi O, Kato H, et al. Alveolar macrophages are the primary interferon-alpha producer in pulmonary infection with RNA viruses. *Immunity*. 2007;27:240–52.
48. Andreakos E, Ivan Zanoni I, Galani IE. Lambda interferons come to light: dual function cytokines mediating antiviral immunity and damage control. *Curr Opin Immunol*. 2019;56:67–75.
49. Lin M, Tseng HK, Trejaut JA, et al. Association of HLA class I with severe acute respiratory syndrome coronavirus infection. *BMC Med Genet*. 2003;4:9.
50. King PH, Chen CY. Role of KSRP in control of type I interferon and cytokine expression. *J Interferon Cytokine Res*. 2014;34:267–74, <http://dx.doi.org/10.1089/jir.2013.0143>.
51. Ng MH, Lau KM, Li L, et al. Association of human-leukocyte antigen Class I (B\*0703) and Class II (DRB1\*0301) genotypes with susceptibility and resistance to the development of severe acute respiratory syndrome. *J Infect Dis*. 2004;190:515–8.
52. To KKW, Hung IF, Li IW, et al. Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1N1 2009 influenza virus infection. *Clin Infect Dis*. 2010;50:850–9.

53. Klinkhammer J, Schnepf D, Ye L, et al. IFN- $\lambda$  prevents influenza virus spread from the upper airways to the lungs and limits virus transmission. *Elife*. 2018;7:e33354.
54. Message SD, Laza-Stanca V, Mallia P, et al. Rhinovirus-induced lower respiratory illness is increased in asthma and related to virus load and Th1/2 cytokine and IL-10 production. *Proc Natl Acad Sci U S A*. 2008;105:13562-7.
55. Oh MD, Park WB, Choe PG, et al. Viral load kinetics of MERS Coronavirus infection. *Engl J Med*. 2016;375:1303-5.
56. Robek MD, Boyd BS, Chisari FV. Lambda interferon inhibits hepatitis B and C virus replication. *J Virol*. 2005;79:3851-4.
57. Marcello T, Grakoui A, Barba-Spaeth G, et al. Interferons and inhibit hepatitis C virus replication with distinct signal transduction and gene regulation kinetics. *Gastroenterology*. 2006;131:1887-98.
58. Dickensheets H, Sheikh F, Park O, Gao B, Donnelly RP. Interferon-lambda (IFN- $\lambda$ ) induces signal transduction and gene expression in human hepatocytes, but not in lymphocytes or monocytes. *J Leukocyte Biol*. 2013;93:377-85.
59. Totura AL, Baric RS. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. *Curr Opin Virol*. 2012;2:264-75.
60. Channappanavar R, Fehr AR, Vijay R, et al. Dysregulated Type I Interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-Infected Mice. *Cell Host Microbe*. 2016;19:181-93.
61. Thiel V, Weber F. Interferon and cytokine responses to SARS-coronavirus infection. *Cytokine Growth Factor Rev*. 2008;19:121-32.
62. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin Immunopathol*. 2017;39:529-39.
63. Beachboard DC, Horner SM. Innate immune evasion strategies of DNA and RNA viruses. *Curr Opin Microbiol*. 2016;32:113-9.
64. García-Sastre A. Ten strategies of interferon evasion by viruses. *Cell Host Microbe*. 2017;22:176-84.
65. Basler CF, Mikulasova A, Martinez-Sobrido L, et al. The ebola virus VP35 protein inhibits activation of interferon regulatory factor 3. *J Virol*. 2003;77:7945-56.
66. Jia D, Rahbar R, Chan RWY, et al. Influenza virus non-structural protein 1 (NS1) disrupts interferon signaling. *PLoS One*. 2010;5:e13927.
67. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. *Nature*. 1998;392:245-52.
68. Collin M, Bigley V. Human dendritic cell subsets: an update. *Immunology*. 2018;154:3-20.
69. Le Bon A, Etchart N, Rossmann C, et al. Cross-priming of CD8+ T cells stimulated by virus-induced type I interferon. *Nat Immunol*. 2003;4:1009-15.
70. Colonna M, Trinchieri G, Liu YJ. Plasmacytoid dendritic cells in immunity. *Nat Immunol*. 2004;5:1219-26.
71. Megjugorac NJ, Gallagher GE, Gallagher GE. Modulation of human plasmacytoid DC function by IFN- $\lambda$ 1 (IL-29). *J Leukoc Biol*. 2009;86:1359-63.
72. Kelly A, Robinson MW, Roche G, Biron CA, O'Farrelly C, Ryan EJ. Immune cell profiling of IFN- $\lambda$  response shows pDCs express highest level of IFN- $\lambda$ 1 and are directly responsive via the JAK-STAT pathway. *J Interferon Cytokine Res*. 2016;36:671-80.
73. Cervantes-Barragan L, Züst R, Weber F, et al. Control of coronavirus infection through plasmacytoid dendritic-cell-derived type I interferon. *Blood*. 2007;109:1131-7.
74. Mora AL, Torres-González E, Rojas M, et al. Activation of alveolar macrophages via the alternative pathway in herpesvirus-induced lung fibrosis. *Am J Respir Cell Mol Biol*. 2006;35:466-73.
75. Page C, Goicochea L, Matthews K, et al. Induction of alternatively activated macrophages enhances pathogenesis during severe acute respiratory syndrome coronavirus infection. *J Virol*. 2012;86:13334-49.
76. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol*. 2015;16:448-57.
77. Wikstrom ME, Fleming P, Comerford I, McColl SR, Andoniou CE, Degli-Esposti MA. A chemokine-like viral protein enhances alpha interferon production by plasmacytoid dendritic cells but delays CD8+ T cell activation and impairs viral clearance. *J Virol*. 2013;87:7911-20.
78. Chu H, Chan JF-W, Wang Y, et al. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19. *Clin Infect Dis*. 2020, <http://dx.doi.org/10.1093/cid/ciaa410>, published online April 9.
79. Chan JF, Yao Y, Yeung ML, et al. Treatment with lopinavir/ritonavir or interferon- $\beta$ 1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *J Infect Dis*. 2015;212:1904-13.
80. Hung IF, Lung K-C, EY-S Tso, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet*. 2020, [http://dx.doi.org/10.1016/S0140-6736\(20\)31042-4](http://dx.doi.org/10.1016/S0140-6736(20)31042-4). May 8, 2020.