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Exploiting natural antiviral immunity for the control of pandemics: Lessons from Covid-19

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A B S T R A C T

The outbreak of coronavirus disease 2019 (COVID-19), triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disruptive global consequences in terms of mortality and social and economic crises, have taught lessons that may help define strategies to better face future pandemics. Innate and intrinsic immunity form the front-line natural antiviral defense. They involve both tissue-resident and circulating cells, which can produce anti-viral molecules shortly after viral infection. Prototypes of these factors are type I interferons (IFN), antiviral cytokines with a long record of clinical use. During the last two years, there has been an impressive progress in understanding the mechanisms of both SARS-CoV-2 infection and the cellular and soluble antiviral responses occurring early after viral exposure. However, this information was not sufficiently translated into therapeutic approaches. Insufficient type I IFN activity probably accounts for disease progression in many patients. This results from both the multiple interfering mechanisms developed by SARS-CoV-2 to decrease type I IFN response and various pre-existing human deficits of type I IFN activity, inherited or auto-immune. Emerging data suggest that IFN-I-mediated boosting of patients' immunity, achieved directly through the exogenous administration of IFN-β early post viral infection, or indirectly following inoculation of heterologous vaccines (e.g., Bacillus Calmette Guerin), might play a role against SARS-CoV-2. We review how recent insights on the viral and human determinants of critical COVID-19 pneumonia can foster clinical studies of IFN therapy. We also discuss how early therapeutic use of IFN-β and prophylactic campaigns with live attenuated vaccines might prevent a first wave of new pandemic viruses.

1. Introduction

Viral pandemics represented major threats for mankind during the last century. The 1918 Spanish flu pandemic was indeed the most dramatic one, leading to approximately 50 million deaths [1]. At that time, virology was at its infancy and techniques to detect and culture viruses were not available. Viruses were only identified in the 1930s. The 1918 causative virus was isolated only in 2005 (variant H1N1) and a vaccine was subsequently developed. Over the last 50 years, there was a great progress in virology, which allowed to understand much more about the origin and biology of human viruses.

Looking back to recent viral outbreaks, including the Asian flu (1957), Hong Kong flu (1968) and swine flu (2009), and those caused by human coronaviruses (HCoV) such as SARS-CoV and MERS-CoV, several lessons can be learned. Among these lessons, the essential need of rapidly implementing effective prevention measures and early treatments capable of controlling the first wave of virus spread, before any specific vaccine can be available. Nevertheless, the outbreak of SARS-CoV-2 infection in late 2019 in China and the subsequent disruptive impact of the COVID-19 pandemic all over the world revealed that we were still poorly prepared to face the spread of a new and highly infectious virus.

During the first phase of the COVID-19 pandemic, there was a delay in fully implementing suitable prevention strategies by national prevention plans, starting from the initial shortage of personal protection equipment for healthcare workers, patients, and citizens at large. Very soon, the world witnessed a massive international effort to develop diagnostic tools and identify effective antiviral therapies. The research

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on antiviral drugs was, however, characterized by a poorly coordinated run to test almost any type of substance in patients, sometimes without a strong rationale and deep scientific debate. The lack of efficient prevention and treatment strategies contributed to the increase of infection rate world-wide, followed by a huge burden of deaths (more than 5 million at the present time), lock-down measures adopted by many governments with subsequent fatal effects at the social and economic levels. In parallel with the poor advancement in the identification of effective antiviral therapies, a great hope and international efforts were soon given to the development of anti-COVID-19 vaccines, which were very rapidly produced and distributed (early 2021 in Europe). The final implementation of the anti-COVID-19 vaccination campaigns in developed countries, together with adequate health prevention measures and diagnostic monitoring, may result in the control of the SARS-CoV-2-induced pandemic in these countries, even though uncertainty on long-term immunity and possible spread of new coronavirus variants remain open issues. In these countries, anti-SARS-CoV-2 monoclonal antibodies and recently developed antiviral drugs [2,3] are likely to represent a largely used antiviral therapy in the early stage of infection. Fig. 1 illustrates the timeline of SARS-COV-2 spread, vaccine development and distribution, COVID-19 treatment milestones and global deaths.

While we are now still facing a new wave of SARS-CoV-2 infection in developed countries with high percentages of vaccinated subjects, it is likely that COVID-19 pandemic will become an endemic infection disease here, with new vaccines to be produced for controlling the spread of emerging SARS-CoV-2 variants. However, as for the poorest countries in tropical regions of the world, high costs and practical difficulties in vaccine storage and administration and poor availability of monoclonal antibodies and recently developed antiviral drugs might hamper an effective control of COVID-19 pandemic.

Over the last two years, many data have been published on COVID-19 pathogenesis and the role of the immune response to SARS-CoV-2 infection. We can now take lessons from these studies for presenting and discussing new perspectives on how factors playing a first-line defense role in viral infection can be selectively exploited for preventing and/or controlling present and future viral pandemics.

2. The early cytokine and cellular response to Sars-Cov-2 infection

The early host response to SARS-CoV-2 infection is characterized by the rapid production of multiple cytokines released by virus-infected cells. Type I IFN, including 13 IFN-α and single IFN-β and IFN-ω, are cytokines discovered 65 years ago as antiviral factors produced by virus-infected cells. They deserve a special attention as they are first-line defensive responses to viruses, including SARS-CoV-2. Type I IFN bind to the same type I IFN receptor system (IFNAR1 and IFNAR2 subunits), but differ for the kinetics of production in response to viruses and for some downstream biological effects. Plasmacytoid dendritic cells (pDC) are the highly specialized cells for the production of large amounts of IFN-α in response to virus infection, while IFN-β is locally produced in response to viruses and other danger signals by virtually all host cells, including monocytes/macrophages, where it can restrict viral replication under physiological conditions [4,5]. Of note, IFN-β is the first IFN produced upon viral infection in most cells, kicking off the induction of the other type I IFN via the self-amplification loop. In addition to its evolutionary emergence as the first non-tissue specific antiviral factor, IFN-β is considered the “high affinity sentinel” of the IFN system, in light of its exceptionally high affinity for IFNAR1 and IFNAR2 subunits [6]. Because of its rapid and efficient binding to specific receptors and interaction with other membrane proteins, IFN-β is poorly detectable in

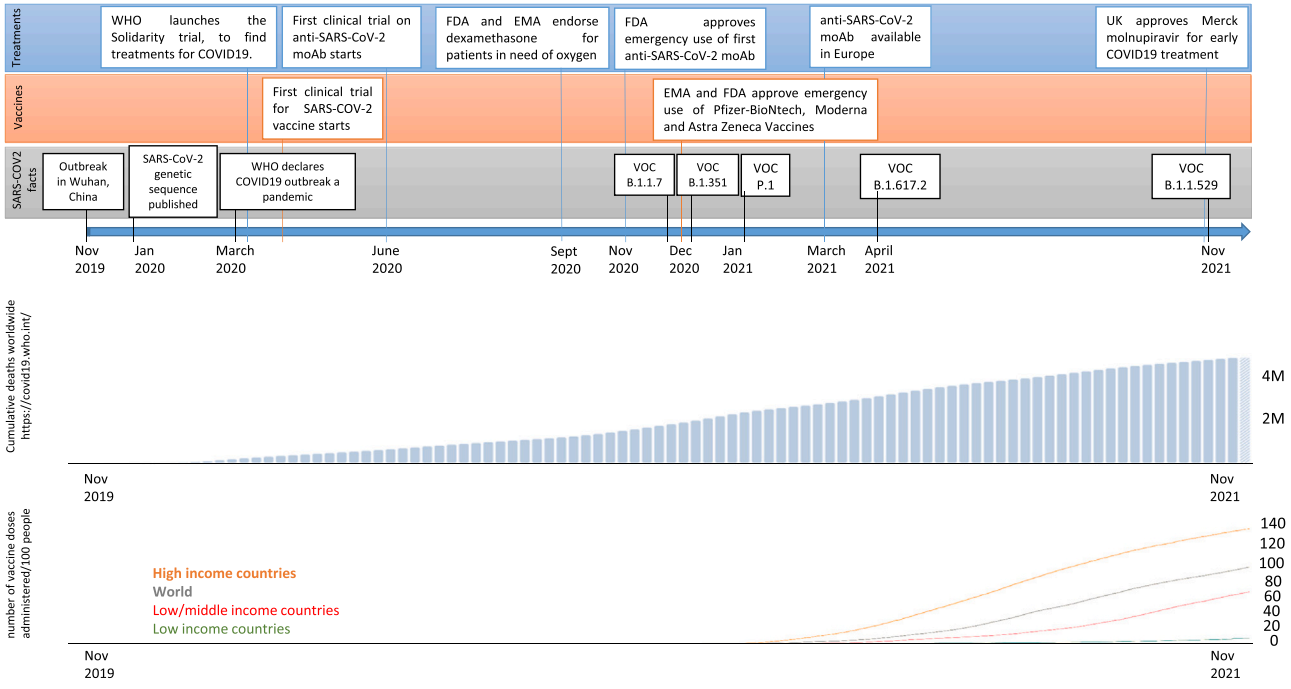

Fig. 1. Timeline of SARS-COV-2 spread, vaccine development and distribution, COVID-19 treatment milestones and global deaths. Upper panel: the gray bar shows the key events of COVID-19 pandemic in terms of SARS-CoV2 emergence and diffusion, genome sequencing and reporting of Variants of Concern (VOC); the orange bar illustrates the time frame occurring for anti-SARS-CoV2 vaccines development and approval by the competent authorities; the blue bar displays selected steps of the global clinical research on effective therapies against COVID-19. Middle panel: Cumulative number of deaths due to COVID-19 worldwide. Lower panel: Number of vaccine doses administered/100 people globally (world, gray line), in high income (orange line), low/middle income (red line) and low income (green line) countries.
(a) [Source: World Health Organization https://covid19.who.int/]. (b) [Source: Hannah Ritchie, Edouard Mathieu, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald, Diana Beltekian and Max Roser (2020) - "Coronavirus Pandemic (COVID-19)". (c) *Published online at OurWorldInData.org.* Retrieved from: ’https://ourworldindata.org/coronavirus’].

extracellular fluids and is rapidly catabolized when administered as an exogenous cytokine.

Most of current knowledge on the IFN system stems from several decades of studies on the production, mechanisms of action and clinical use of IFN-α2 and IFN-β. IFN-α2 exhibited a remarkable success in cancer and HCV-infected patients, while IFN-β found its major niche of use in patients with multiple sclerosis [7]. Both IFN-α2 and IFN-β were largely used in the past in clinical studies in patients with various viral infections, including respiratory viruses and coronaviruses [8]. Notably, in the history of cytokine research type I IFN represented a "moving target", since a variety of biological activities other than their antiviral action were progressively described [9]. Among the immunoregulatory effects, enhancement of the antibody response and T cell immunity by these cytokines were described in several preclinical and clinical settings, suggesting that they can play crucial roles in linking innate and adaptive immunity [10]. Of note, under certain conditions, both cytokines can act as potent immune adjuvants by enhancing the response to reference antigens as well as to vaccines ([11] and studies reviewed in [12]). Furthermore, they have a major role in the activation of key natural host cells, such as Natural Killer (NK) cells and dendritic cells (DC) (reviewed in [12]). Of interest, IFN-β exerts stronger anti-inflammatory effects with respect to IFN-α, inducing reduction of pathogenic Th17 $CD4^+$ T cells and increase in IL-10 producing Treg cells [13]. Moreover, IFN-β inhibits the production of TGF-β, thought to be involved in lung fibrosis and other inflammatory responses [14].

An increasing number of reports testifies that SARS-CoV-2, similarly to SARS-CoV and MERS [15], has evolved strategies to overcome antiviral immunity by blocking or delaying IFN production. These strategies have been recently reviewed with the aim of discussing their role in SARS-CoV-2 pathogenesis and suggesting perspectives for clinical treatment in COVID-19 patients [16].

Upon virus interaction with host cells, SARS-CoV-2 RNA genome is recognized by pattern recognition receptors (PRRs), such as the Toll-like receptors (TLR3, TLR7, and TLR8) and the cytosolic sensors retinoic acid-inducible gene 1 (RIG-1), melanoma differentiation-associated protein (MDA5) [17]. Activation of downstream signaling by these PRRs induces type I IFN through IRF3/IRF7 activation [17]. Upon binding to receptor, type I IFN trigger phosphorylation of STAT1 and STAT2 transcription factors, which activate the transcription of ISGs. DsRNA is also sensed by oligoadenylate synthetases (OASs), which induce the activation of RNase L and the consequent degradation of viral and host ssRNA, and PKR, which phosphorylates the translation initiation factor eIF2α, leading to protein synthesis shutdown and restriction of viral replication [18]. Of note, although RNase L and PKR antiviral activity is not dependent on IFN production, the genes encoding for OASs and PKR are ISGs and, therefore, these pathways are activated as a consequence of IFN production.

Some components of SARS-CoV-2, such as structural and nonstructural proteins [19,20] can antagonize the IFN response, thus evading innate immunity and enabling viral replication. Among these, nucleocapside (N) protein impedes type I IFN signaling by preventing the nuclear translocation of phosphorylated STAT1 and STAT2 [21]. A recent study identified six SARS-CoV-2 genes that block mitochondrial antiviral signaling protein (MAVS)-induced production of IFN-β, but not of IFN-α or IFN-γ [22]. Studies comparing peripheral immune responses in mild and severe COVID-19 patients report diminished type I IFN levels in severe cases versus mild cases, and restricted IFN-stimulated gene (ISG) expression among circulating immune cells [23–25]. Along these lines, single-cell analysis of epithelial cells from nasopharyngeal swabs of COVID-19 patients showed ISG upregulation in patients with mild or moderate disease, while severe COVID-19 patients were characterized by a dramatically blunted IFN response [26].

Type I IFN system downregulation by SARS-CoV-2 is strictly linked with the dysregulated innate immune response depicted in COVID-19 patients in terms of soluble factors released and immune cells recruited at both local and systemic level (Reviewed in [27]). Bronchoalveloar fluid lavages (BALF) and blood samples of SARS-CoV-2-infected patients have reduced levels of pDC. Notably, pDC have been described to be activated and functional during asymptomatic infection, but not in hospitalized patients [28]. This observation, together with the reduced count and activity of myeloid DC (mDC), involved in T lymphocyte priming, testifies a general impairment of the immunomodulatory functions of antigen presenting cells (APC) in patients with severe COVID-19. A significant reduction of NK count and cytotoxic phenotype was also observed in the peripheral blood and BALF of infected patients [29], thus indicating that SARS-CoV-2 also blunts NK-mediated spontaneous antiviral defense. It is tempting to speculate that the dysregulation of NK antiviral activity may be a consequence of an insufficient activation by type I IFN. A deficient IFN production during the early phase of the infection may result in uncontrolled viral replication that put the basis for the subsequent immune response hyperactivation, eventually leading to tissue damage and multiorgan failure. In fact, the exaggerated recruitment at the infection site of monocytes and macrophages, cells of the innate immune response capable of sensing and engulfing pathogens and responsible for regulating inflammation, may result in the hyperproduction of proinflammatory cytokines. Of note, high proportions of non-classical monocytes secreting inflammatory cytokines were reported in the blood of COVID-19 patients. At the local level, BALF of patients with severe COVID-19 were shown to be enriched in CCL2 and CCL7, chemokines involved in the recruitment of $CCR2^+$ monocytes and neutrophils [29]. Moreover, data suggest that neutrophils, generally deputed to virus clearance and antiviral cytokine production during viral infection, can also act in COVID-19 patients as hyperinflammation drivers contributing to the increased risk of thrombosis [30]. In summary, a balanced release of antiviral cytokines, chemokines and proinflammatory signals strongly influences the cells of the innate immune response, whose timely activation is essential for an early clearance of SARS-CoV-2 and disease resolution, while uncontrolled inflammatory response and subsequent "cytokine storm" can play a role in disease progression. Fig. 2 illustrates how an early production of IFN-β by virus infected cells, together with IFN-α secretion by pDCs, can result in viral clearance and immunity, while a virus-induced dysregulated expression of type I IFN can later lead to hyper inflammatory response, cytokine storm and subsequent severe COVID-19 disease.

3. Pre-existing deficits of type I IFN account for 20% of critical covid-19 cases

One of the main challenges of COVID-19 pandemic was the need to elucidate the reasons behind the great variability of the progression and outcome of SARS-CoV-2 infection among different individuals. During the first year of the COVID-19 pandemic, it became accepted that a general age-related impairment of immune response was somehow responsible for elderly patient increased COVID-19 mortality. Joint research efforts and international initiatives were then established in spring 2020 to elucidate the role of host genetic factors in SARS-CoV-2 susceptibility and COVID-19 severity in patients of all ages [31,32]. Notably, some of the genetic and immunological determinants of critical COVID-19 pneumonia (reviewed by Zhang et al, *Nature*, in press) turned out to be related to the individual ability to effectively activate IFN-I system in response to SARS-COV-2 infection.

The presence of inborn autosomal TLR3 and X-linked TLR7 errors, significantly impairing the production and amplification of type I IFN by respiratory epithelial cells and pDC, respectively, was shown to be responsible for the suboptimal or delayed antiviral responses occurring in some patients with increased susceptibility to life-threatening COVID-19 pneumonia [33,34]. Moreover, circulating autoantibodies neutralizing high concentrations of IFN-α and IFN-ω were detected in approximately 10% of patients with critical COVID-19 pneumonia and in 18% of COVID-19 deceased subjects, but not in asymptomatic individuals [35]. In contrast, a very low percentage (approximately 1%) of patients

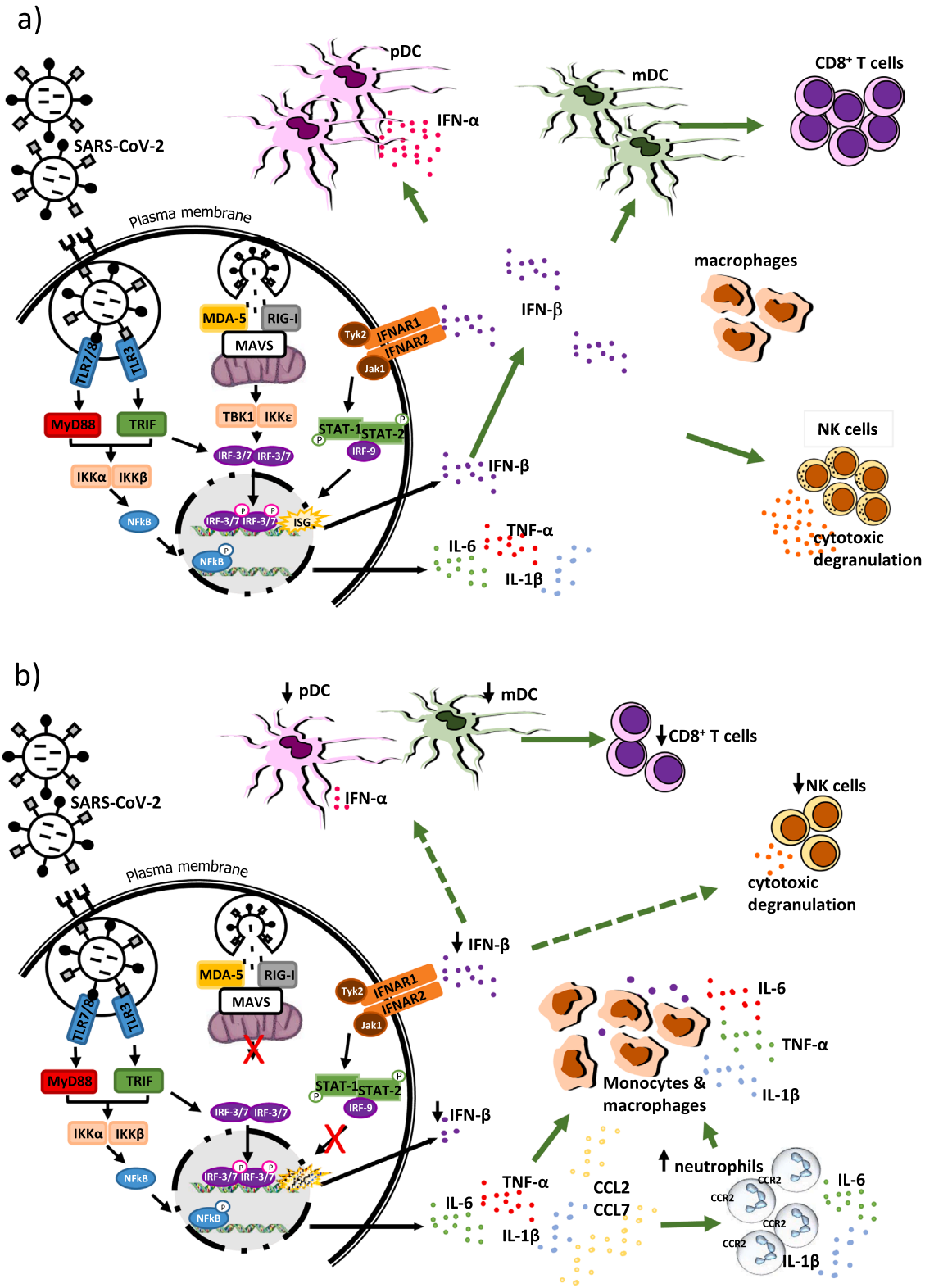

Fig. 2. Role of the type I IFN system in SARS-COV-2 clearance and immunity (panel a) versus its role in dysregulated immune response leading to severe COVID-19 (panel b). a) Signaling pathway and innate immune response during the functional response to SARS-CoV-2 infection. b) Virus-induced signaling alterations leading to reduced CD8 +T cells priming by DC and exaggerated recruitment of monocytes, macrophages, and of CCR2 + neutrophils, resulting in the hyperproduction of proinflammatory cytokines and disease exacerbation.

with critical COVID-19 symptoms have shown the presence of antibodies neutralizing IFN-β. Of note, the existence of autoantibodies deactivating the antiviral activity of IFN-I, firstly reported a long time ago in both mouse models [36] and humans [37], has been more recently proven to be a feature shared by a small proportion of the general young population, more frequently observed in men and elderly individuals [38]. Even in the absence of clinical manifestation under physiological conditions, the presence of anti-IFN-I autoantibodies can increase individual susceptibility to the dramatic effects of uncontrolled viral replication.

Since the outcome of viral infection occurs as a result of the delicate balance between spontaneous innate immunity and viral-induced suppression of type I IFN response, in ways that can depend on age and sex, insufficient type I IFN immunity in the respiratory tract during the first few days of infection accounts for the spread of the virus, leading to pulmonary and systemic inflammation.

On the whole, the ensemble of the studies published so far [33–35, 38] indicate that pre-existing genetic and auto-immune deficits of type I IFN account for approximately 20% of critical COVID-19 cases. It would not be surprising that additional inborn errors of type I IFN immunity will be identified in COVID-19 patients in future studies. Research in this field will be instrumental not only for a complete understanding the mechanisms of resistance and susceptibility to COVID-19 in individual patients, but also to determine whether the constitutive deficiency of type I IFN occurring in some patients may affect the efficacy of anti-SARS-COV-2 vaccination. In this light, particular attention should be focused on breakthrough cases occurring in fully vaccinated individuals.

4. Lessons from selected clinical trials with IFN

Since the beginning of COVID-19 pandemic, the use of broad antivirals was considered for treating patients infected with SARS-CoV-2, and both IFN-α and β were also used, administered by conventional injection schedules as well as by intranasal inhalation according to some of the national protocols for patients management [39], and in randomized clinical trials. Of note, the rationale behind most of these studies relied on the antiviral and not the immunomodulatory properties of type I IFN.

Here, we briefly focus on clinical studies based on the use of IFN-β, which can be considered a good IFN prototype for a clinical use in COVID-19 patients in view of its natural role as first-line antiviral sentinel in response to SARS-CoV-2 infection. The results of many of these studies have been published over the last two years [40–51] and recent reviews are now available [52,53]. Of note, at the doses and schedules used in COVID-19 studies, IFN-β was well tolerated: only a few adverse reactions, mostly local and temporary, were observed.

As shown in Table 1, the heterogeneity of cytokine administration schedule and route (inhaled, s.c., i.v.) and the confounding effects of the concurrent medications hamper a straightforward interpretation of the reported results. IFNβ-1a and IFNβ-1b were mostly given in combination with antivirals, either co-administered as experimental drugs or given to

Table 1
Summary of selected publications reporting the results of clinical trials testing IFNβ in COVID-19 patients.

Reference	IFNβ experimental arm	Standard of care (SOC)	Concomitant therapies	COVID19 status at enrollment	Days from symptoms onset to IFNβ treatment (average)	Results
Hung et al (2020)[40]	IFNβ-1b (s.c.) + ribavirin + SOC	Lopinavir/Ritonavir	Antibiotics, Corticosteroid, Respiratory support	mild and severe	5-Apr	IFN-base triple therapy alleviated symptoms and shorted the duration of viral shedding and hospital stay
Rahmani et al (2020)[41]	IFNβ-1b (s.c.)+ SOC	Hydroxychloroquine + Lopinavir/Ritonavir or Atazanavir/Ritonavir	Corticosteroids, antibiotics, Respiratory support	severe	7	IFN β-1b shortened TTCI, decreased admission in ICU and need for invasive mechanical ventilation
Khamis et al (2020)[42]	IFNβ-1b (inhaled)+ favipiravir	Hydroxychloroquine	Antibiotics, Steroids, Tocilizumab, Convalescent plasma	moderate/ severe	n.a.	No significant differences between groups
Dastan et al (2020)[43]	IFNβ-1a (s.c.)+ SOC	Hydroxychloroquine + Lopinavir/Ritonavir	Respiratory support	severe	6-May	No conclusion for lack of control group
Ader et al (2021) [44]	IFNβ-1a (s.c.)+ SOC	Lopinavir/Ritonavir	Corticosteroids, anticoagulants, immunomodulatory agents, Respiratory support	moderate/ severe	9	No clinical improvement; no reduction in viral shedding
Baghaei et al (2021)[45]	IFNβ-1a (s.c.)+ SOC	Lopinavir/Ritonavir	Antipyretic, antibiotics, serum therapy, Respiratory support	severe	7	IFNβ1-a reduced mortality rate and improved oxygenation
Darazam et al (2021)[46]	IFNβ-1a/IFNβ-1b (s.c.)+ SOC	Hydroxychloroquine + Lopinavir/Ritonavir	n.a.	moderate/ severe	5	IFNβ1-a reduced TTCI
Darazam et al (2021)[47]	IFNβ-1a (s.c.)+ SOC	Lopinavir/Ritonavir	n.a.	moderate/ severe	< 10	High dose IFNβ-1a did not improve TTCI or mortality vs low-dose IFNβ-1a
Davoudi-Monfared et al (2020)[48]	IFNβ-1a (s.c.)+ SOC	Hydroxychloroquine + Lopinavir/Ritonavir or Atazanavir/Ritonavir	n.a.	severe	11-Oct	IFNβ1-a increased the discharge rate on day 14 and decreased 28-day mortality.
Monk et al (2021)[49]	IFNβ-1a (inhaled) (SNG001)	n.a.	n.a.	moderate/ severe	10-Sep	SNG001 provided clinical improvement and faster recovery
WHO Solidarity Trial Consortium (2021)[50]	IFNβ-1a/IFNβ-1b (s.c. or i.v.)+ Lopinavir	n.a.	Antibiotics, Corticosteroids, Respiratory support	moderate/ severe	n.a.	No clinical improvement
Malhani et al (2021)[51]	IFNβ-1b (s.c.)+ Ribavirin + Lopinavir/ Ritonavir	n.a.	Corticosteroids, tocilizumab, Respiratory support	mild, moderate, or severe	6-May	IFN-based triple therapy was associated with: lower 28-day mortality, lower (NEWS2), less need for corticosteroids

all patients according to the national "standard of care" protocols, which in some cases also included hydroxychloroquine. Of note, glucocorticoids (GC) were sometimes used to prevent or mitigate the massive systemic inflammatory response leading to lung injury and multi-organ damage. As previously stated in a preclinical model [54] and recently demonstrated in the context of acute respiratory distress syndrome (ARDS) [55], GC interfere with IFN-I signaling, thus dampening both the immune-related and the direct antiviral effects of the cytokine.

Taking into account the limitations reported above, probably affecting the disappointing statistical significance of the results, IFN-β appears in some cases effective in accelerating the recovery from SARS-CoV-2 infection, in reducing the time to clinical improvement and the length of hospitalization. Notably, the effects of IFN-β seem to be more evident when the cytokine was administered shortly after symptoms onset [40,43,50]. This is somehow expected, considering the complex interplay between SARS-CoV-2 and the host immune system at the different stages of the disease (Fig. 2). In this light, it is worth underlying that, among the several studies performed in different settings, published data report the effects of IFN-β treatment administered to patients admitted to hospital with signs of moderate/severe COVID-19. At the time of writing, no data has been officially reported on IFN-β given to paucisymptomatic patients (i.e., not in need of immediate hospitalization). The lack of these data may be at least in part related to the difficulties, experienced by many research groups during the acute phase of COVID-19 pandemic, in intercepting patients at the early time following SARS-CoV-2 infection diagnosis. Our group designed and set up a phase II clinical study to test the efficacy of low dose IFN-β given s.c. to paucisymptomatic elderly patients with a recent diagnosis of SARS-CoV-2 infection during home isolation [56]. The study was aimed at exploiting the antiviral and immunomodulatory properties of low dose IFN-β in a time frame in which virus-induced impairment of endogenous IFN-I system activation can dramatically affect the course of the disease, especially in patients experiencing immunosenescence. The reduction of SARS-CoV-2 circulation among elderly people as a result of the vaccination campaign, and the difficulties experienced in conducting a randomized clinical trial in the home-setting during the COVID-19 pandemic, hindered patient recruitment, so that the study was very recently closed for lack of patients. We expect that the absence of information on the possible immunomodulatory effects of the early administration of low dose IFN-β to patients infected with SARS-CoV-2 will be partly resolved by an ongoing large clinical trial from NIH, testing the efficacy of several drugs, including nebulized IFN-β (SNG001), to outpatients not in need for hospitalization [ClinicalTrials.gov Identifier: NCT04518410].

5. Towards personalized therapies based on IFN biomarkers?

Today's medicine is aimed at treating patients, whenever possible, by a personalized targeted approach, which takes into consideration the individual genetic characteristics and potential biomarkers predictive of the clinical response to a given therapy in a given patient. While personalized/predictive medicine is certainly practicable in patients with genetic disorders or some chronic diseases, such as cancer, this is often much more difficult for infectious diseases, especially in the context of viral pandemics.

In some viral infections such as that caused by SARS-CoV-2, only some infected patients become symptomatic and may then develop a severe disease and eventually die. We had postulated [57] and it is now widely accepted [58–60] that the natural capability to cope with the virus without developing any disease is due to a strong natural antiviral response, mainly triggered by an early and adequate production of type I IFN, occurring in the majority of patients in spite of virus-induced down-modulation on endogenous IFN-I response. The important discovery of IFN-I-related genetic and immunologic determinants of COVID-19 susceptibility (see Section 3) opens new perspectives on the possibility to promptly identify patients that, by reasons of inherited or autoimmune defects in IFN-I system, are more likely to undergo uncontrolled viral replication and develop life-threatening disease. For these patients, the use of a personalized approach aimed at restoring a functional IFN-I response should be considered. Plasma exchange, reported to efficiently reduce blood auto-Abs in hospitalized patients with life-threatening pneumonia [61], can be considered a rescue strategy to treat hospitalized patients. Nevertheless, the subcutaneous administration of the exogenous cytokine may be an easier option to promptly treat patients with defective type I IFN response at earlier time post SARS-CoV-2 infection. Preliminary clinical evidence was reported in one patients with previously diagnosed genetic condition associated with anti-IFN-I auto-antibodies, and treated with IFN-β soon after SARS-CoV-2 infection [62]. In two cases of autosomal dominant disorders in TLR3 and IRF3, key genes of IFN-I immunity, the timely administration of peg-IFNα2b elicited the prompt resolution of COVID-19 symptoms [63]. Further studies are needed to confirm the feasibility and efficacy of this approach on a larger scale, but we prospect that future clinical studies with IFN could move towards the design of personalized therapy strategies, taking into consideration individual characteristics of patients, including defects in IFN-I response. Of note, according to the kinetic of SARS-CoV-2 pathogenesis (Fig. 2), exogenous administration of IFNα and IFNβ should be avoided during the inflammation phase of COVID-19, when they might exacerbate the deleterious effects of exaggerated leukocytes recruitment and activation. In this light, the identification and validation of accurate biomarkers of IFN-I activation state, based on circulating IFN-β levels [58,64] or on the expression of IFN and IFN-induced genes in different tissues [65], would be instrumental for the design of personalized therapies.

6. Fostering innate antiviral immunity for the control of pandemic viruses: Role of type I IFN

Epidemiological and biological data suggest that administration of live-attenuated vaccines (LAV) targeting tuberculosis, measles and polio as well as defined compounds such as β-glucan may enhance the ability to react against new pathogens (reviewed in [66]) including SARS-CoV-2 [66–69]. Thus, the finding that some old vaccines designed to induce adaptive immunity against a specific pathogen can also mitigate other infectious diseases may, in principle, open perspectives of their possible use in controlling the first dramatic wave of a newly emerging pandemic virus.

Bacillus Calmette Guerin (BCG), a weakened strain of *Mycobacterium bovis*, is a century old vaccine used in infant/childhood vaccination campaigns against tuberculosis (TB) in low to middle-income countries. It is also used in the current therapy of high-risk non-muscle invasive bladder cancer, even though the mechanisms of action are still elusive. It has been pointed out that countries with national vaccination programs for TB prevention (e.g, India, Korea, Japan), showed a much lower morbidity and mortality from severe COVID-19 compared with countries (e.g, Italy, USA, UK) that do not have such policies [70]. This is consistent with recent data reported by Rivas and coworkers [71] and discussed in detail elsewhere [72], indicating that history of BCG vaccination is associated with a decrease in the seroprevalence of anti-SARS-CoV-2 IgG and a lower number of subjects experiencing COVID-19-related clinical symptoms in a cohort of health-care workers. Notably, current studies are also based on the use of recombinant BCG activating the STING pathway to enhance the potency of the immune response [73]. While the interim results of the "ACTIVE" clinical trial aimed at evaluating the efficacy of BCG vaccination in protecting elderly patients against new infections seem to be encouraging [74], more data are needed to eventually confirm whether BCG vaccination, alone or in combination, can indeed exert a protective effect against SARS-CoV-2 infection. Among the possible mechanisms of action of BCG-induced immunity against new pathogens, the elicitation of type I IFN expression on monocytes and macrophages has been reported [75]. In particular, the cytosolic sensor nucleotide-binding oligomerization containing

protein 2 (NOD2), responsible for sensing *Mycobacterium tuberculosis* products, can stimulate the transcription of type I IFN in macrophages ([75] and references herein). NOD2-induced activation of type I IFN pathway can, in turn, downregulate the production of pro-inflammatory cytokines by means of epigenetic mechanisms [75]. Likewise, it has been recently hypothesized that BCG-induced immunity can restrain SARS-CoV-2 infection by ensuring the activation of type I IFN response and a proper control of proinflammatory cytokine production [76].

Of note, β-glucan is another agent capable of fostering innate immunity and its potential implications for controlling SARS-CoV-2 pandemic have also been discussed [77]. In this regard, it has recently been reported that innate immune training of granulopoiesis after injection of mice with β-glucan promotes a strong anti-tumor activity which is mediated by type I IFN [78]. In agreement with this, Hassankadeh-Kiabi and colleagues reported that autocrine type I IFN signaling in DC stimulated with fungal β-glucans promoted $CD8^+$ T cell activation [79]. This is not surprising since early studies revealed a crucial role of type I IFN in the generation of a protective humoral and cellular ($CD8^+$ T cells) adaptive immunity by acting on DC [11,80]. All this supports the hypothesis that BCG as well as β-glucan can impart non-specific protective effects against viral infections or their anticancer effect by the action of type I IFN, and in particular IFN-β, which is the cytokine constitutively expressed in resting cells such as macrophages [5] and soon induced at considerable levels after stimulation by viral proteins or other danger signals [4]. This issue deserves further research efforts.

7. Closing remarks

The research progress during the COVID-19 pandemic has shown how rapidly vaccines and specific drugs against emerging viruses can be developed thanks to international research efforts and innovative technologies. Nonetheless, it is worth mentioning that the distribution of new vaccines and treatments is not equal worldwide: while in developed

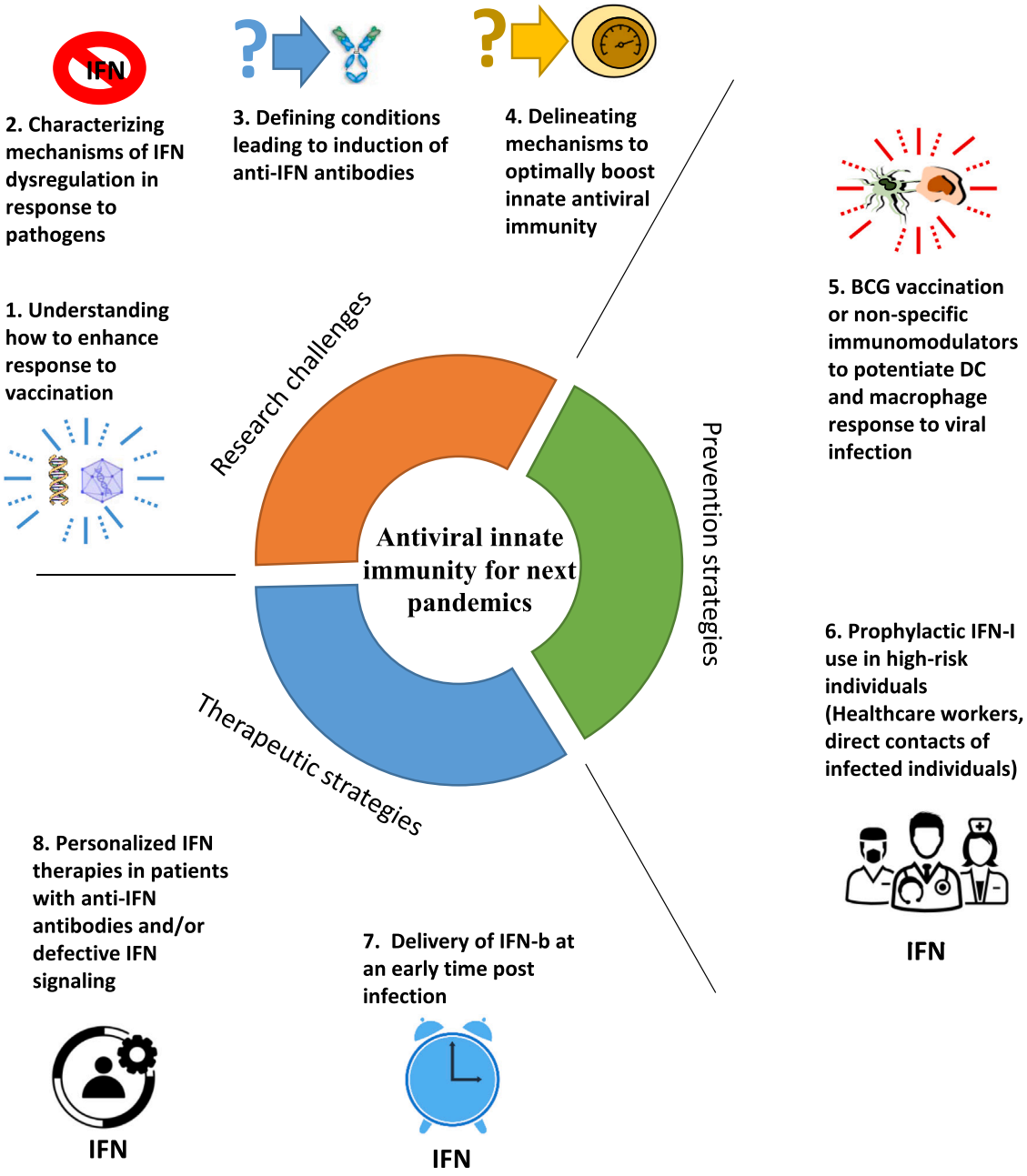

Fig. 3. Hypothetical scenario showing research challenges and possible strategies to boost antiviral innate immunity for the control of new viral pandemics.

countries there is an almost complete coverage in vaccination campaigns and booster doses are expected to be granted to the whole population soon, only 2–4% of the population in low- middle-income countries have so far got access to the anti-SARS-CoV-2 vaccines. Besides raising moral issues on health inequities, such uneven treatments and vaccination coverage increase the global risk of emergence of new variants resistant to the current vaccines. While scientists and global health management experts claim new ethical global politics to diminish the unfair health and socioeconomic consequences of the current pandemic on disadvantaged populations [81], some first-line interventions can be envisaged for future pandemics by taking lessons from the COVID-19 experience. Exploiting our current knowledge on the natural response to viruses and reconsidering the possible use of fully available drugs/vaccines should be highly encouraged at an international level by health policy makers in order to mitigate the disruptive consequences of a new pandemic. As discussed in this article and summarized in Fig. 3, some LAV, β-glucan, and IFN-β emerged during COVID-19 pandemic as potential boosters of the spontaneous and sometimes inefficient early antiviral immune response. Notably, here we mostly focused on IFN-β for its role as high affinity sentinel and regulator of inflammation, and for the promising preclinical and clinical evidence obtained in SARS-CoV-2 infection. Nevertheless, IFN-α and other IFN subtypes, including type III IFN and in particular IFN-λ1, can be considered, either directly or through the administration of drugs inducing IFN or IFN-induced genes. As discussed in detail elsewhere, among the strategies aimed at limiting pandemic viruses spread, the possible use of intranasally administered IFN-I as prophylactic measure for high-risk individuals should be also evaluated [82].

When looking at future directions of anti-SARS-CoV-2 therapeutic strategies, we can foresee that the increasing development and use of virus-specific monoclonal antibodies and very recently approved antiviral drugs could be paralleled by a selective use of IFN-β in patient-tailored approaches, based on individual genetic features and characterization of specific biomarkers of response (Fig. 3).

As for preparing to future pandemics, since personalized approaches, like the development of new variant-specific vaccines, require adequate resources and availability of diagnostic tools, an early use of IFN-β should be considered to face the first wave of emergency. Moreover, the employment of old LAV and substances capable of boosting cells of the innate immunity, such as DC and macrophages, rendering them reactive against new viral infections can represent another sustainable front-line public health measure particularly suitable for developing countries. Both approaches can be adopted to "bend the pandemic curve" before possible effective vaccines are available, thus preventing needless deaths and the social and economic consequences observed during the COVID-19 pandemic (Fig. 3). Fostering an early antiviral immune responses to react against new viruses could be also a useful strategy in subsequent phases of a viral pandemic, since it may also enhance the protection efficacy of specific vaccines (as discussed elsewhere [58,66]). It would be appropriate and timely to be prepared to react to future outbreaks with early actions grounded on the experience of COVID-19 and past pandemics. Implementing first-line immune-based strategies and fully understanding the mechanisms of natural antiviral immunity are major challenges with a potential great impact in terms of cost-effectiveness value for public health services.

CRedit authorship contribution statement

FB conceptualized the manuscript; EA led the review process, made substantial contributions to discussions of the content and drafted the initial manuscript together with FB; JLC critically reviewed the manuscript and substantially contributed to its finalization; LB, LC, FU contributed to discussions of the content and to the development, writing and revision of the manuscript. All authors reviewed, edited and approved the manuscript before submission.

Declaration of Competing Interest

The authors declare no competing interests.

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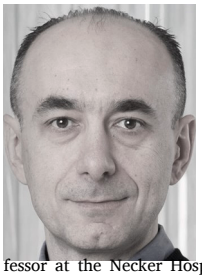

Jean-Laurent Casanova obtained his doctorate in medicine in 1987 from the medical faculty of the Paris-Descartes University. He carried out his internal training at the Institute Pasteur and at the Ludwig Institute for the research on cancer and received his doctorate in immunology at the Pierreet-Marie-Curie University in 1992. In 2008 he was appointed Professor at Rockefeller University in New York. In 2014 he joined the Howard Hughes Medical Institute. He is a member of the United States National Academy of Sciences and American Academy of Medicine, Senior Attending Physician, and Head of the St. Giles Laboratory of Human Genetics of Infectious Diseases at The Rockefeller University, as well as a visiting professor at the Necker Hospital for Sick Children, University of Paris. Prof. Casanova's laboratory is committed to study the genetic determinants of the clinical manifestations and outcome of primary infections by viruses, bacteria, fungi, and parasites, with particular focus on mutations that selectively compromise the immunity of otherwise healthy children and adults. In the course of COVID-19 pandemic, he was the co-leader of the "COVID Human Genetic Effort", an international consortium aiming to discover the human genetic and immunological bases of the various clinical forms of SARS-CoV-2 infection.

Filippo Belardelli received his degree in Biological Sciences in 1975 at the University "La Sapienza" in Rome, where he obtained the specialization degree in Microbiology in 1979. In 1980, he became staff investigator of the Laboratory of Virology at the Istituto Superiore di Sanità (ISS), where was appointed as Section Director in 1983. He was the Director of the Department of Cell Biology and Neurosciences (2006–2011) and of the Department of Hematology, Oncology and Molecular Medicine (2011–2016) at the ISS. Dr. Belardelli carried out important biomedical research activities as well as in several prestigious laboratories, including the Laboratory of Viral Oncology of the "Institut de Recherches Scientifiques sur le Cancer" in Villejuif and the Department of Immunology of the Scripps Research Institute in La Jolla. The research activity is documented by approximately 290 publications in international journals regarding the fields of interferon and cytokine research, infectious diseases, oncology and immunology. In 2017, he became Senior Research Associate of the Institute of Translational Pharmacology of the Italian National Research Council.