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Mini review

Type I IFN-dependent antibody response at the basis of sex dimorphism in the outcome of COVID-19

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the ongoing coronavirus disease 2019 (COVID-19) pandemic, induces severe pneumonia mainly in elderly males. Epidemiological data clearly indicate sex-based differences in disease outcomes, with men accounting for about 70 % of deaths, despite similar susceptibility to infection. It is well known that females are endowed with higher capacity to produce antibodies, which correlates with viral clearance and disease resolution in the context of SARS-Cov-2 infection. Many X-linked immune genes escape X inactivation showing biallelic expression in female immune cells, particularly in plasmacytoid dendritic cells (pDCs). PDCs are more active in females and endowed with high capability to induce IFN-α-mediated B cell activation and differentiation into antibody-producing plasma cells throughout epigenetic mechanisms linked to trained immunity. Thus, we hypothesize that following SARS-CoV-2 infection, epigenetic modifications of X-linked genes involved in pDC-mediated type I IFN (IFN-I) signaling occurs more effectively in females, for inducing neutralizing antibody response as an immune correlate driving sex-biased disease outcome.

1. Introduction

In December 2019, Chinese health authorities reported an outbreak of pneumonia cases of unknown etiology in Wuhan city. A new highly infectious coronavirus (CoV), officially called SARS-CoV-2, was later identified as the cause of this outbreak [1,2]. SARS-CoV-2, whose disease was named COVID-19 by WHO, spread rapidly worldwide causing a serious pandemic with more than 30 million confirmed cases and one million of deaths by September 2020. SARS-CoV-2 disease occurs and continues asymptomatically or mildly in approximately 80 % of patients, but in about 15–20 % of cases the disease develops into severe pneumonia [3], especially in elderly with comorbidities which are characterized by immunosenescence with increased rate of inflammation [4]. Evidence gathered to date, clearly indicates sex-based differences in the outcomes of disease, despite similar or sometimes female-biased rate of infection. In 37 out of 38 countries reporting sex-disaggregated data, males display 1.7 times higher case fatality rate (CFR) than females [5]. Despite CFR increases for both sexes with advancing age, males have a significantly higher rate at all ages from 30 years than females [5]. Therefore, the success of SARS-CoV-2 prevention and therapy will depend on the quantity and quality of knowledge on gender differences in the response to the virus. The question is as relevant as complex, and there are several possible explanations of this disparity, involving both innate and adaptive immunity as well as non-immune factors [6]. While both B and T cells participate in immune-mediated protection to viral infection, neutralizing antibody response is essential in containing viral spreading and resolving most acute infection [7]. However, the dysregulation of antibodies production may lead to pathogenic conditions. Patients surviving SARS-CoV infection were previously reported to have antibody responses [8]. Similarly, neutralizing IgG antibodies induced during acute COVID-19 correlate with viral clearance and are detected in convalescent patients [9,10]. Importantly, the crucial role of neutralizing antibodies in infection resolution is underlined by the success of plasma therapy from

Abbreviations: PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; TLRs, toll-lLike receptors; Xi, X chromosome inactivation; SLE, systemic lupus erythematosus; ASCs, antibody-secreting plasma cells.

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convalescent patients, uncovered as a powerful approach to treat severe disease [11–13]. Likewise, pathogenic antibodies have been reported in life-threatening COVID-19 patients, preferentially in males [14]. In this scenario, following SARS-CoV-2 infection, an appropriate humoral response in females can account for their better outcome with respect to males. We describe the molecular events driving this response, mainly based on a greater aptitude of females to rapidly activate, through specific epigenetic mechanisms, IFN-I-mediated innate immunity that, in turn, drives adaptive humoral response.

2. Sexual dimorphism in antibody response

Common viruses invading respiratory tracts, such as CoVs, rhinoviruses, respiratory syncytial virus (RSV) and influenza, have an RNA genome. The first line of defense following viral infection are different cell types, such as alveolar macrophages, airway epithelial cells, innate lymphoid cells and dendritic cells (DCs), that express innate sensors recognizing different forms of viral genome for triggering innate antiviral response [15]. The innate immune response signaling cascade starts with the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs), that include the endosomal Toll-like receptors (TLRs) 3, 7 and 8 and the cytosolic MDA5 and RIG-I shown to be relevant for respiratory RNA viruses [16]. Once the innate immune system senses pathogen-derived molecules activates downstream signaling leading to the induction of IFN-I, IFN-III and other pro-inflammatory cytokines. Subsequently, an autocrine and paracrine IFN signaling induce a large set of IFN-stimulated genes (ISGs) in infected as well as surrounding uninfected cells, establishing an antiviral state. This state inhibits the productive infection and viral spread, and at the same time triggers adaptive immune response responses that definitively eradicate the infection [17]. Thus, the dynamics between the host's innate and adaptive immunity and the capability of virus to evade this response ultimately dictates the evolution of infection and the disease outcome. It is well known that females are less susceptible to infections than males [18], as confirmed by their higher capability to mount stronger humoral as well as cell-mediated immunity [19]. However, due to the complexity of the network of cells and mediators linking innate and adaptive immunity, it is quite difficult to set in a defined paradigm the sex dimorphism in immunity. Nevertheless, it was hypothesized that sex differences in the onset and outcome of respiratory virus infection may depend on the strength of the host immune responses upon infection and the capability to recover tissue damage that the same response induces [20]. Of interest, protective antibody responses after vaccination against several viruses are twice as high in females as compared with males [21]. This was confirmed during pandemic H1N1 vaccination in 2009, when females displayed enhanced antibody responses with respect to males, with slightly reduced differences among elderly individuals [22]. Accordingly, the majority of genes differentially expressed between sexes are significantly upregulated in B cells from adult females compared with males [22].

3. TLR7/IFN-α axis in plasmacytoid dendritic cells at the basis of dimorphic antibody response: lesson from IFN-α-related autoimmunity

The female immunological gain in their high capacity to produce antibodies is corroborate by the striking sexual dimorphism observed in human autoimmune disease, where females represent more than 80 % of subjects [23]. In addition to sex hormones and associated factors, X chromosome inactivation (Xi) mechanisms of immune X-linked genes are at the basis of this difference. Xi is a dosage-compensation mechanism that balances the expression of X-linked genes between sexes [24]. However, up to 30 % of X-linked genes display some variable degree of escape from Xi, while about 23 % of X-linked genes show constitutive variable expression among individuals and cell types [25]. Mechanistically, Xi is driven mainly by long non-coding RNA Xist, whose dynamic regulation on the inactive X chromosome in female immune cells results in biallelic expression of some X-linked genes (Fig. 1) [26]. This evidence contributes to the hypothesis that genetic predisposition to autoimmunity is an evolutionary consequence of positive selection for a greater resistance to infections [18]. Many X-linked genes are involved in the innate and adaptive immune system, including PRRs genes (TLR7, TLR8, DDX3X), key regulators of TLR signaling (IRAK1, NEMO), and diverse immune-related genes (IL3RA, CD40 L, CXCR3, FOXP3, TMEM187, CXorf21). Interestingly, four out of six genes (TLR7, TMEM187, IRAK1, and CXorf21), identified as susceptibility loci in systemic lupus erythematosus (SLE), are located on X chromosome region undergoing robust Xi escape in female immune and somatic cell populations [24,27]. SLE is a chronic autoimmune disorder characterized by the production of auto-antibodies and has a strong gender bias, being 70–90 % of SLE patients female [28]. IFN-α has been identified as

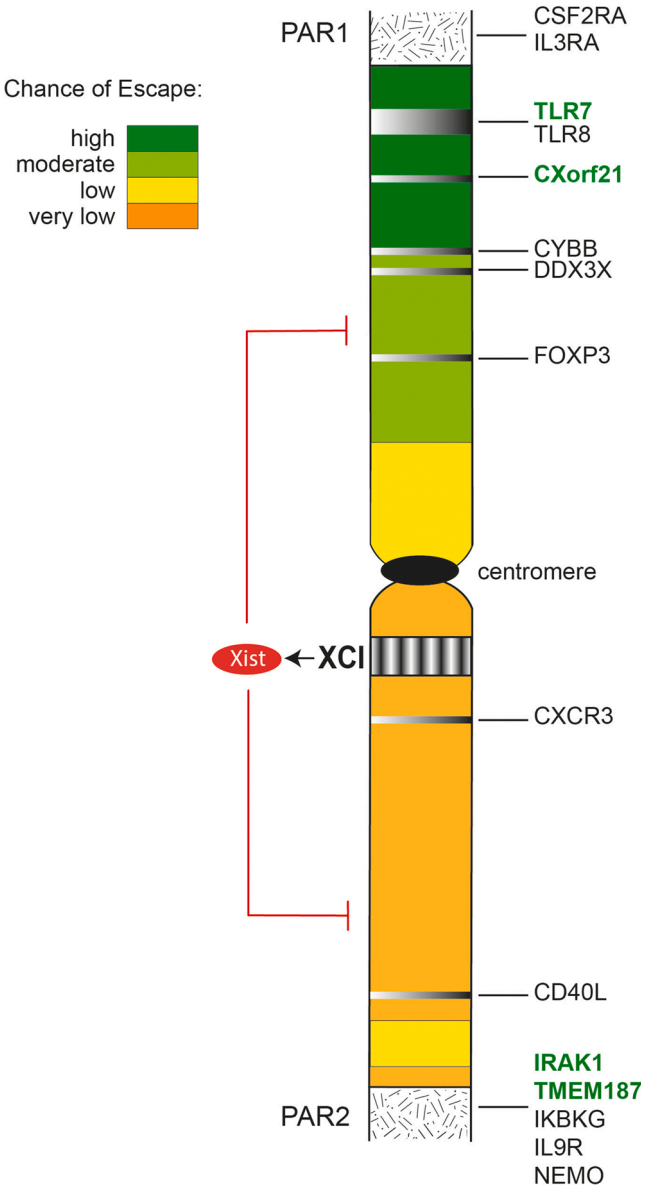

Fig. 1. X inactivation escape of immune genes. Regions of X chromosome with high vs low chances of inactivation are highlighted in different colors while the main genes discussed in this article are indicated in green. TLR7 and CXorf21, displaying the highest chance of escaping X inactivation, are expressed two-three-fold higher in female cells compared to male cells, and along with TMEM187 and IRAK1 are associated with SLE. XIC: X chromosome inactivation center containing the long-non coding RNA Xist, responsible for X inactivation.

the pivotal factor in SLE pathogenesis. SLE patients show elevated IFN-α levels in their sera that are able to trigger dendritic cell differentiation [29] and their peripheral blood cells overexpress IFN-α-regulated genes [30]. Of note, rIFN-α therapy of viral hepatitis or certain malignancies was found to induce SLE-associated auto-antibodies and symptoms [31]. In a SLE mouse model the disruption of IFN signaling diminished significantly the disease burden [32]. In the same model, the deletion of TLR7 reduced both the titers of auto-antibodies and kidney disease [33]. Intriguingly, TLR7, TMEM187, IRAK1 and CXorf21 genes, identified as susceptibility loci for SLE, are in the pathway that upon recognition of RNA viral genome leads to IRF7-mediated IFN-α production [34]. TLR7 and IRAK1 are critical to IFN-α-mediated antiviral immune responses and antibody-mediated immunosurveillance against endogenous retroviruses reactivation [35]. CXorf21, a protein co-localizing with endosomal resident TLR7, is a binding partner of the SLE-associated gene SLC15A4 in the regulation of endosomal pH [36,37], and is particularly active in pDCs, representing the main source of IFN-α in the immune system [38]. Sex-based differences in the innate function of human pDCs have been reported. The enhanced activation of female pDCs with respect to male ones correlates with biallelic expression of X-linked immune genes escaping Xi [39]. Female pDCs exhibit improved TLR7-mediated IFN-α production [40,41], a process to which X chromosome complement [42], estrogens [43], and IRF5 [44] can contribute. Since differences between female and male pDCs were not observed for TLR9 stimulation or TLR7-mediated TNF-α induction, IFN-α production in female pDCs via TLR7 is a sex-specific phenomenon [27]. From a mechanistic point of view, unlike other somatic cells, Xist RNA is not concentrated on X chromosome in the nucleus of many immune cell types, and it is virtually absent in pDCs displaying biallelic expression of TLR7 [45]. Upon infection, pDCs rapidly activate multiple pathways leading to the production of IFN-I and pro-inflammatory cytokines. Activation of TLR7 by microbial nucleic acid triggers a signaling cascade, that through MyD88 and IRAK1/4 leads to IFN-α production via IRF7, as confirmed by severe susceptibility to influenza in a IRF7-mutated patient associated to lack of IFN-α production by pDCs [46]. In recent studies, the impaired production of IFN-I during the course of SARS-CoV-2 infection has also been reported. Severe COVID-19 patients exhibit an insufficient IFN-I transcriptional response despite high viral replication, while simultaneously inducing high levels of chemokines recruiting effector cells [47]. Moreover, 3.5 % of COVID-19 patients with life-threatening disease harbor genetic mutations in key genes involved in IRF7- dependent induction of IFN-I [48]. In this study, circulating pDCs from a patient with autosomal recessive mutation in IRF-7 gene were shown to be unable to produce IFN-α2 and IFN-λ1 in response to SARS-CoV-2 infection. In addition, about half of these patients had low levels of serum IFN-α [48]. Noteworthy, in the context of viral infection other proinflammatory cytokines, such as TNF-α and IL-6, are produced by pDCs through the activation of MyD88/IRAK4 signaling and NFκB. In these intertwined signals, IRF5 and IRF7 are master regulators. While IRF5 activated from early endosomes drives pro-inflammatory gene expression, IRF7 activated from late endosomes triggers IFN production [49]. Moreover, upon viral infection pDCs can activate the NLRP3 inflammasome pathway leading to IL-1β production, that in turn inhibits IFN-α by SOCS1-mediated negative regulation of MyD88-IRF7 signaling [50]. In this regard, a strong activation of the IL-1β pathway was found in COVID-19 patients [51]. Ultimately, in this complex array of signals, timing and magnitude of IFN production is under an intertwined control of IFN itself and inflammatory cytokines. Viral infection triggers TLR signaling leading to the production of the IRF7-dependent first wave of IFN-β and IFN-α4, that in turn amplifies IFN response by a positive feedback loop with a IRF-8-dependent second wave of enlarged production of an array of IFN-α subtypes [52]. Therefore, a cytokine-induced SOCS1 dynamic system controls IFN production while continuous viral TLR7 activation may sustain IFN secretion [53]. These signals are tightly associated to antibody production, since TNFα-mediated inflammation determines impaired antibody response to influenza vaccine in aging women [54]. Thus, upon SARS-CoV-2 infection females might benefit of a more prompt activation of TLR7-mediated pathway leading to IFN-α prevalence over inflammatory cytokines, thus sustaining viral clearance and limiting COVID-19 clinical inflammatory pathology, which conversely is observed mostly in elderly men.

4. pDC-mediated B-cell activation for antibody production

SARS-CoV-2 elicits an effective B-cell response, with defined virus-specific IgM, IgG and IgA kinetics [9]. MyD88 signaling of B cells is required for antibody response to retroviral infection [55]. Likewise, TLR7 is critical for the antibody-dependent control of endogenous retroviruses, and associated tumors [56]. In a mouse model of LCMV infection, B cell-intrinsic TLR7 signaling was required for optimal B-cell responses and germinal center (GC) formation [57]. Nanoparticle-based vaccine containing TLR7 agonists induces neutralizing antibody responses that persist for a lifetime and are protective against lethal influenza virus infection in mice [58]. Biallelic female B lymphocytes displayed greater TLR7 and CD40L transcriptional expression than male monoallelic cells resulting in a TLR7-driven preferential enrichment of plasma cells [27,59]. In addition, biallelic cells showed a more than twofold increase over monoallelic cells in the propensity to IgG class switch during TLR7-driven, T cell–dependent differentiation of naive B lymphocytes into Ig-secreting cells [27]. Together, these results indicate that TLR7 signaling is crucial for enhancing GC selection of antigen-specific B cells and promote B-cell maturation into ASCs cells and that this process is more effective in biallelic TLR7-expressing cells. PDCs play an essential role in activating B cells and driving their maturation in plasma cells, a process mediated by IFN-α. Upon viral infection, pDCs control the differentiation of activated B cells into plasma cells through IFN-α and IL-6 secretion [60]. Moreover, pDCs are required for T cell-independent polyclonal B cell expansion and differentiation toward ASCs via IFN-α-mediated TLR7 up-modulation of B cells [61]. Of interest, in response to TLR7 engagement, pDCs display and shed soluble B cell maturation antigen (sBCMA) [62], whose elevated high levels correlate with local IgG production in multiple sclerosis patients [63]. SBCMA is also detected at high levels in serum of SLE patients [64]. Importantly, the pathogenic antibody production in SLE patients was correlated to a dysfunctional regulatory feedback mechanism of B-cell activation, in which pDCs retain capability to drive plasmablast differentiation but fail to activate IL-10-producing B regulatory (reg) cells, thus missing the feedback control on IFN-α production [65]. These findings highlight the complex network and the crucial role played by pDCs in controlling antibody production via a time-dependent and balanced production of IFN-α, that in turn triggers protective humoral immunity and concomitantly avoiding pathological effects (Fig. 2). As a consequence, appropriated B cell activation and virus-specific antibody secretion are a direct result of optimal IFN-mediated pDC function. This assumption is supported by the evidence that diverse viral infections were found significantly amplified in pDC-deficient mice, confirming that pDC-dependent antibody production is critical for viral clearance [66,67]. Conversely, an unbalanced spatio-temporal production of IFN-α associated with a lack of activation of the feedback inhibition can lead to an altered induction of the antibody response. Indeed, in a recent study 13.7 % of COVID-19 patients with severe disease have anto-antibodies against IFN-α or IFN-ω or both, while a very small fraction of those have auto-antibodies against IFN-β [14]. In contrast, patients with mild or moderate disease do not have antibodies to IFN-I. Interestingly, 94 % of patients with severe disease and with auto-antibodies against IFN-I were males, which drops to 28 % in patients with asymptomatic or mild disease without antibodies against IFN-I [14]. According to the authors, this marked bias in favor of men suggests that the production of auto-antibodies against IFN-I may be due to recessive mutations at X-linked loci susceptible to autoimmunity and therefore pre-existing to infection. Indeed, auto-antibodies

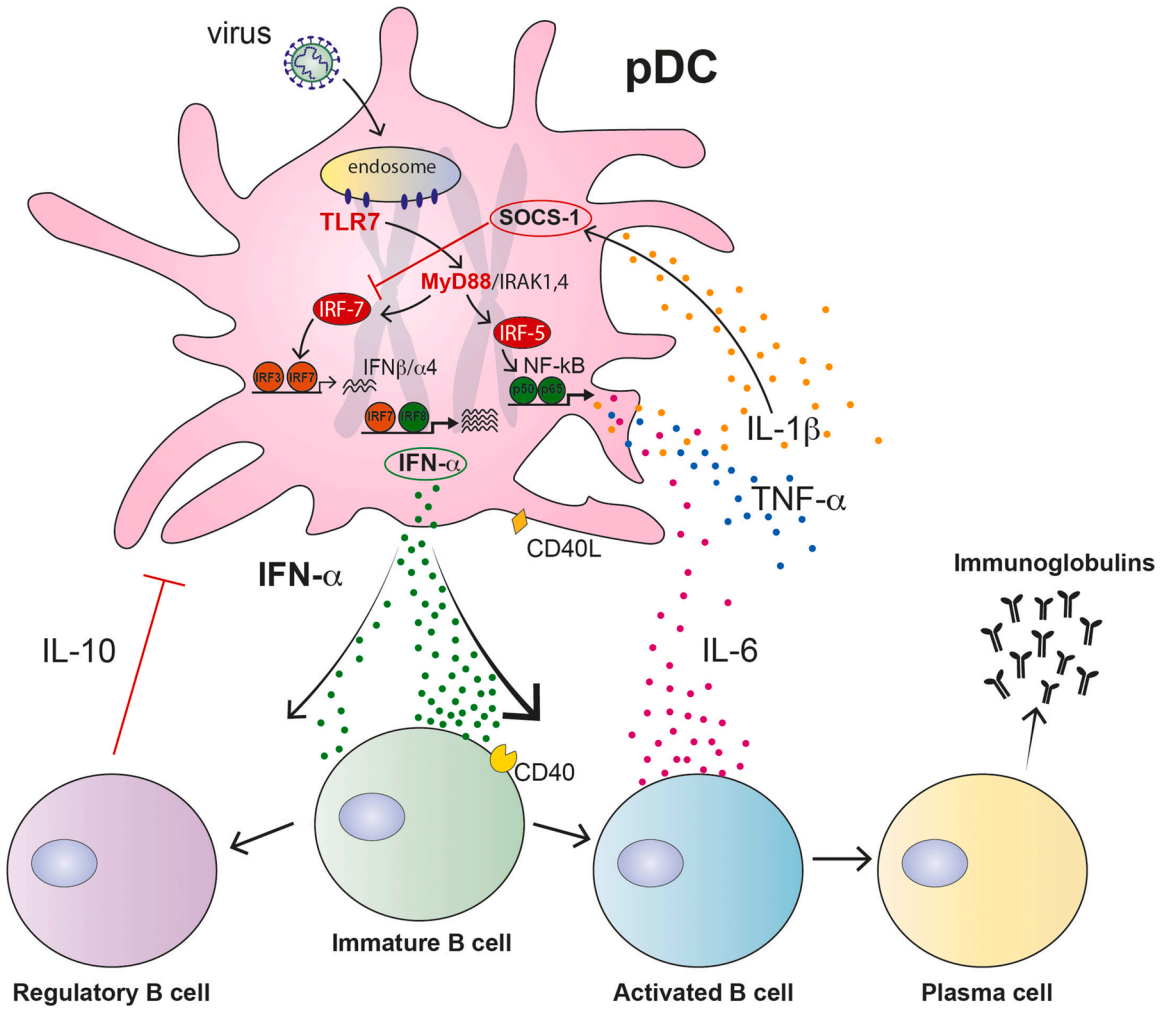

Fig. 2. IFN-α-driven pDC-B cells crosstalk leading to antibody production in response to viral infection. Upon virus encounter, pDCs activate TLR7/MyD88 pathway that leads to IRF7-mediated first wave of IFN-I production (mainly IFN-β/IFN-α4) and IRF-5-dependent secretion of inflammatory cytokines (i.e. IL-1β, TNF-α, IL-6), respectively. IFN-I early response activates an IFN-mediated feedback amplification signaling leading to a second massive production of IFN-α. In the context of a direct CD40 stimulation, IFN-α induces activation of B cells that in the presence of IL-6 differentiate into Ig producing plasma cells. Two negative feedback signals limit the production of IFN-α. One is triggered by IL-1b-mediated SOCS1 activation targeting IRF-7; the other is mediated by IFN-α itself, that induce immature B cells to differentiate into IL-10 producing regulatory B-cells capable to turn off pDCs. In the context of female cells the biallelic expression of TLR7 may determine a more rapid and considerable production of IFN-α, thus preferentially leading to plasma cell differentiation and antibody secretion.

against IFN-α have already been detected in some autoimmunity diseases like SLE [68]. Hence, the preponderance of males with autoantibodies in the context of COVID-19 was unexpected, given that women have higher rates of autoimmune disease. Thus, an alternative explanation may be that the auto-antibodies against IFN-I could be the consequence rather than the cause of severe COVID-19, due to the absence of the negative feedback regulation of IFN-α production by impaired pDC function. This perspective, is also strongly supported by recent results showing that among severe to critical COVID-19 patients, early treatment with IFN-α was associated with reduced in-hospital mortality, while late treatment increased mortality and delayed recovery [69], sustaining that timely and regulated IFN-I activation is crucial for a suitable response to SARS-CoV-2 infection and favorable disease outcome.

5. IFN-driven control of trained immunity

Trained immunity, the innate immune memory process resulting in enhanced responsiveness of innate immune system to stimuli recalling unrelated previous ones, has been hypothesized to play a role in susceptibility and outcome of SARS-CoV-2 infection. Timing and strong activation of innate immune response, occurring more frequently in women, keeps viral infection under control. On the contrary, week and defective early immune response, characterizing aged and people with co-morbidities, allows viral replication with the potential to trigger hyperinflammation [70]. Trained immunity has been largely described to be induced by BCG vaccine, showing protective effects against non-related viral infections via increased activation of TLR-mediated epigenetic-reprogrammed monocytes with enhanced IL-1β production [71]. Noteworthy, longer-term effects of BCG vaccination on overall mortality and reduced incidence of respiratory infections was reported higher in girls with respect to boys [72].

From a mechanistic point of view, trained immunity shapes enhanced innate immune response by ensuring a long-lasting state of activation in certain cells of the innate immune system via epigenetic modifications. This process ensures a durable epigenetic shaping of innate immune cells, characterized by the persistence of transcriptional memory allowing faster and greater gene expression upon restimulation [73]. The chromatin acquisition of stable specific marks, such as the histone H3K4 trimethylation (H3K4me3), is a hallmark of trained immunity. In this landscape, IFN-I plays a crucial role in regulating chromatin accessibility ensuring reprogrammed cellular states. The

epigenetic memory established by IFN-I, via the incorporation of the long-lasting chromatin marks histone variant H3.3 and histone modification H3K36me3 [74,75] leads to a prompt expression of at least half of all ISGs and inflammatory non-ISGs, suggesting a multiple layer contribution to training immunity [76]. Reprogrammed epigenetic transcriptional activation of IFN and immune signaling pathways is also a trait of immune memory responses of DCs [77]. Accordingly, aged DCs were reported to exhibit a severe reduction in IFN production in response to influenza virus as result of decreased presence of the activator histone H3K4me3 [78]. Noteworthy, TLR7-induced IFN response in pDCs was reported to be regulated by the zinc finger CXXC5 protein, which licenses antiviral defense via active histone modifications and constitutive transcription of CpG island-containing genes [79].

6. Effects of aging

Immunosenescence is characterized by several distinct changes in the number and functions of immune cells associated with the retention of secretion of pro-inflammatory cytokines, such as TNF, IL-6, and IL-1β [80]. Innate immune cells, including DCs, neutrophils and macrophages, become less functional and, paradoxically, more inflammatory with age. Enhanced inflammation in the absence of infection and a reduced ability to clear infections are the prevalent traits of elderly people. Therefore, less functional relevant innate responses and increased risk of infection disease might distinguish SARS-CoV-2 infected aging males more than the female counterpart. In fact, the number and proportion of pDCs declines during healthy aging [81], while the total number of B cells is lower in the blood of elderly individuals than younger ones. Of interest,

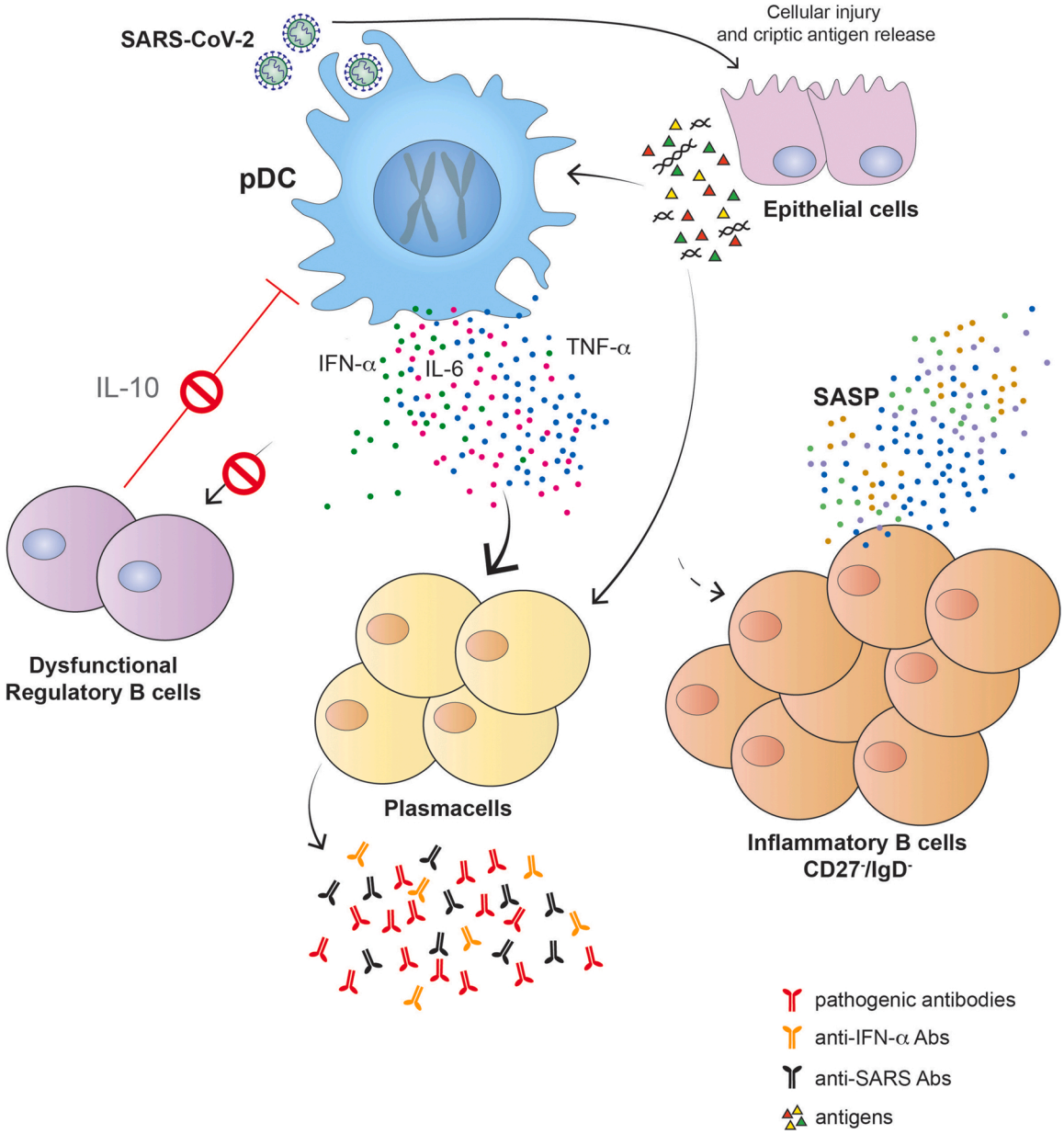

Fig. 3. Pathogenic events involving B cells contributing to life-threatening COVID-19 disease in elderly males. In the context of severe SARS-CoV-2 infection, a dysfunctional pDC-B cells crosstalk may lead to production of pathogenic auto-antibodies. In elderly male, the prevalence of inflammatory CD27-IgD- B cells, well-known to shape a SASP environment, along with the decline of the number and the function of IL-10 producing Breg cells support the production of high levels of inflammatory cytokines. In this context, pDCs, may also be activated by self nucleic acids released by infected epithelial cells further sustaining inflammatory cytokine production. In addition, epithelial-released damaged DNA and criptic antigens, via a new or previous molecular mimicry process, may induce de novo or trigger preexisting B cells to produce autoantibodies including anti-IFN-I antibodies. This signal may be further strengthened by antigen-presentation by DC to B cells.

the function of late memory B cells, defined as CD27- IgD-, increases in elderly people with respect to naïve (CD27- IgD+), IgM memory (CD27+ IgD+), switched memory (CD27+ IgD-) B cell subtypes [82]. Late memory B cells highly contributes to inflammaging as they express a senescence-associated secretory phenotype (SAPS), characterized by nondividing, metabolically active and secreting proinflammatory cytokines features [83]. Noteworthy, the increase of CD27-IgD- B cells in elderly males correlates with higher level of serum IL-6 only with respect to females [84]. Of interest, the inflammatory B-cell trait occurs together with a decline of IL-10 producing Breg cells, a condition associated with the production of autoantibodies in these subjects [85]. Therefore, in males with life-threatening COVID-19, the prevalence of inflammatory B cells simultaneously with the decline of IL-10 producing Breg cells lead to the dysregulation of IFN-I signal in pDCs and may associate with the development of autoimmunity. In this context, the onset of auto-antibodies against IFN-I could be favored by a process of cell damage releasing cryptic antigens, which may imply also antigen presentation by DCs for B cell activation [86] (Fig. 3).

7. Conclusion and perspectives

The difference in antibody response is one of the most well characterized and phylogenetically conserved sex differences in immunology, suggesting that a better antibody response could be a female adaptive advantage for reproductive purposes, including nursing to provide offspring with protective antibodies. In this review, we described the IFN-driven molecular and cellular components at the basis of the crosstalk between pDCs and B cells, accounting for the higher aptitude of females with respect to males to mount antibody responses as a major trait for the sex different outcome in SARS-CoV-2 infection. Considering the recent promising results relating to the use of immune sera as an effective therapy for the treatment of COVID-19, here we focused on humoral immunity as an essential component limiting SARS-CoV-2 spread and allowing resolution of the infection. Neverthless, the dysregulation of these events may be at the basis of pathogenic response in severe COVID-19 patients. This concept is tightly linked to the fact that sex differences in COVID-19 are age-dependent. Immune sex differences become more evident after sexual maturation, with the contribution of both hormonal and genetic factors, and immune functions progressively decline with age with a different process in females and males [87]. As a consequence, severe outcome from infectious diseases is greater for elderly male individuals than females. Therefore, young subjects and females, although susceptible to SARS-CoV-2 infection, exhibit mild symptoms, as a results of a prompt activation of the immune mechanisms to respond to infections, while limiting potential harmful effects. In this complex scenario, some elements of the immune response are crucial for a positive outcome of viral infection. The plasticity of the innate immune responses, recalled by the trained immunity, is a key component shaped by pivotal mediators such as IFN-I. These cytokines put in place several molecular and cellular signaling, including the epigenetic reprogramming, to strengthen the host defense. Likewise, in an inflammatory context their dysregulated activation may lead to enhanced pathogenic traits of life-threatening COVID-19 patients.

Given the current lack of effective therapies for the treatment of SARS-CoV-2 infection [88], IFN-I, with a long history of clinical success in the treatment of viral infections, have been considered as potential repositioning drugs to treat patients with COVID-19. However, the principles that have moved up to this moment these attempts fall within the framework of using of IFN-I according to the modality of a typically antiviral drug [89–91], not taking into account its equally important effects in linking innate to adaptive immunity. Obviously, this last aspect requires a re-evaluation of the therapeutic regimen and the methods of administration of the cytokine, taking into consideration both its strong immune activation capacity and its potential harmful effects from its prolonged use over time. Based on the considerations illustrated in this review, IFN-α administration limited to the early stages immediately following infection may be effective in subverting SARS-CoV-2-induced immune evasion and stimulating a prompt antibody response necessary for limit viral spread and resolve the infection. Indications in this direction come from a recent study of IFN-α administration by the mucosal route [69], even if the study has limitations due to its retrospective design. Conversely, the complex inflammatory scenario of severe COVID-19 patients requests more extensive investigations to evaluate the multiple factors, including the pre-exiting genetic background, affecting the outcome of suitable therapeutic interventions.

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Declaration of Competing Interest

The authors reported no declarations of interest.

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