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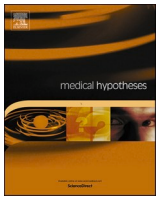
Medical Hypotheses 167 (2022) 110943

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy



COVID-19 diverse outcomes: Aggravated reinfection, type I interferons and antibodies

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ARTICLE INFO

Keywords:
SARS-CoV-2
Reinfection
Type I interferons
Antibodies

ABSTRACT

SARS-CoV-2 infection intrigued medicine with diverse outcomes ranging from asymptomatic to severe acute respiratory syndrome (SARS) and death. After more than two years of pandemic, reports of reinfection concern researchers and physicists. Here, we will discuss potential mechanisms that can explain reinfections, including the aggravated ones. The major topics of this hypothesis paper are the disbalance between interferon and antibodies responses, HLA heterogeneity among the affected population, and increased proportion of cytotoxic CD4+ T cells polarization in relation to T follicular cells (Tfh) subtypes. These features affect antibody levels and hamper the humoral immunity necessary to prevent or minimize the viral burden in the case of reinfections.

Hypotheses

Introduction

SARS-CoV-2 infection is associated with exceptionally multiple outcomes, varying from asymptomatic to severe acute respiratory syndrome (SARS) development and death [1]. The factors that lead to these differences can be very diverse, but certainly is influenced by the viral load in the moment of infection [2], the replicative and infectivity of the virus within host cells [3,4], the anti-viral immune response [4], host genetic variability and age [5,6] and comorbidities of the infected population [6]. As an airborne pathogen the SARS-CoV-2 viral load will be influenced by different factors, like masks, wind speed, and other environmental factors that will impact the amount of infective virus reaching the upper airways of susceptible individuals.

Reinfection cannot be considered a rare phenomenon affecting vertebrates. Several pathogens possess escape mechanisms from the host immune response that allow multiple reinfections, like *Plasmodium sp*. the etiologic agent of malaria and influenza virus [7,8]. Usually, reinfections are associated with antigenic changes [9]. Memory responses are faster and more robust than the primary immune response and are usually associated with a milder infection [10]. In the case of viral diseases, infected cells death mediated by memory CD8+ cytotoxic T cells and NK cells plays a crucial role in eradicating virus reservoirs and producing machines [11]. Neutralizing antibodies, produced by memory B cells, and their effects, such as antibody dependent cytotoxicity mediated by phagocytes and IFNγ-primed NK cells, are also a crucial part of the memory response against viruses [12]. At the center stage of the memory response, CD4+ T cells mediate early secretion of cytokines, such as TNFα and IFNγ, and provide the appropriate support and coordination of adaptive immunity, being important, for example, to antibody class-switch [13]. Thus, reinfections are not usually observed in infectious viral diseases, unless an antigenic change occurs. Aggravated reinfections can also be considered an unusual event. Dengue virus and other flaviviruses can cause aggravated reinfections associated with antibody dependent enhancement (ADE) due to antigenic differences between different serotypes of the viruses. Interestingly, both dengue virus and SARS-CoV-2 pathogenesis include a phenom known as cytokine storm, which refers to an exacerbated and life-threatening systemic inflammatory reaction to infectious agents [14]. Cytokine storm is associated with increased levels of cytokines, such as TNFα and IL-6 (possibly exacerbated in memory responses), tissue damage and shock [14]. In relation to respiratory viral diseases, memory immune responses, after vaccination, were associated with enhanced disease in

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https://doi.org/10.1016/j.mehy.2022.110943
Received 17 February 2022; Received in revised form 29 June 2022; Accepted 30 June 2022
Available online 9 September 2022

infants infected with respiratory syncytial virus [15]. The mechanisms behind the disease enhancement were a Th2/Th17 mediated immunopathology, with eosinophilic, neutrophilic and monocytic lung infiltration [16]. Importantly, eosinophilic immunopathology was also observed in early vaccine studies in mice against SARS-CoV, a coronavirus that possesses several similarities with SARS-CoV-2, although the immunized mice were protected from lethal virus challenge [17,18]. Fortunately, later formulations and studies did not support an important role of vaccine enhanced respiratory disease (VAERD) in relation to SARS-CoV-2 [19]. Nevertheless, reported cases of aggravated reinfection are being described and are interesting and emerging topics of discussion between researchers in the field of immunology and virology [20].

The hypothesis

We believe that the aggravated reinfections occur, in part, due to unsustainable neutralizing antibody levels triggered by combined mechanistic elements. In particular, an atypical disbalance of antibody-interferons interplay may display key roles in establishing aggravated reinfections. Furthermore, an increased proportion of memory CD4+ T cells polarized into cytotoxic CD4+ T cells can antagonize T follicular helper cells (Tfh) sub-type, and also contribute to aggravated reinfections. The cytotoxic CD4+ T cells polarization can be influenced by the viral species and the initial induction of adaptive immune responses, especially governed by HLA polymorphisms. Therefore, aggravated reinjection is present but uncommon among SARS-CoV-2 affected individuals, since it requires a conjunction of intrinsic and unique factors.

Lack of antibody development after the first infection: Importance to reinfection

Antibody development is crucial to control viral infections [21]. As such, specific antibodies, observed after vaccination, are considered good predictors of vaccine effectivity [22]. Antibodies are produced by plasma cells (activated B cells), including long lasting plasma cells (LLPCs), and memory B cells, generated after activation [23]. Memory B cells and LLPCs are related to long-lasting protective immunity against reinfections, similar to the antibody levels produced by them. There are 5 classes of antibodies, also called immunoglobulins (Ig). Antibody class switch occurs in a T cell dependent manner, driving the constitutive IgM and IgD to switch to IgG, IgE and IgA, based on the cytokines expressed by T follicular helper cells (Tfh) during interaction with B cells, in B cell follicles on the draining lymph nodes [24]. IgG possesses the longest half-life among the different antibody's isotypes (about 25 days) [25], with important functions in order to restrain viral infections, such as neutralization, opsonization, activation of NK cells leading antibody dependent cytotoxicity (ADCC) and complement activation [26]. Neutralization can be associated with both destabilization of viral structure (also performed by complement activation) or blockage of viral entry, through inhibition of cell receptor interaction, or exit [26]. Furthermore, IgG can cross the placental barrier, being an important mechanism for fetus protection against pathogens [26]. While IgE does not seem to exert anti-viral effects, with little or no neutralization ability [27], IgA is the most prevalent class of antibodies in mucosal surfaces and is also responsible for neutralization of pathogens and toxins [28]. Thus, IgA is an important barrier to be overcome by viruses in which mucosal surfaces are the entry site, such as SARS-CoV-2 and HIV. Hence, it would be interesting to quantify IgA antibodies against epitopes from SARS-CoV-2 in studies evaluating reinfection or vaccine efficacy [29–31]. IgM and IgD are expressed on B cell surface, as receptors of antigens. Secreted IgM can reach mucosal surfaces and may restrain SARS-CoV-2 infection, especially cross-reactive neutralizing IgM from natural repertoire in uninfected individuals, at least in theory [32]. IgD functions have now been unraveled and its role in viral infections needs further evaluation (reviewed by [33]). Secreted IgD seems to enhance protection to vesicular stomatitis virus (VSV) in IgM deficient mice, establishing a possible compensatory and redundant role of IgD in relation to IgM [33]. In addition, IgD, as a receptor of B cells, is important to attenuate self-reactive B cells response, tuning antibody production [33]. Thus, IgD allows B cells accumulation, without pathogenic self-reactivity. Secreted IgD also seems to be important to "arm" mast cells and basophils, promoting their activation after antigen binding [34].

Interestingly, some people do not develop antibodies after the first infection with SARS-CoV-2, which usually correlates with mild-symptomatic disease [35]. Several reasons can be pointed out to explain the lack of antibodies in some individuals (Fig. 1):

(i)*Effective innate immune response*: the innate immune response was sufficient to eradicate the infection without activation of adaptive immunity and memory, due to low viral load or high expression of type I interferons (IFN-I). This is observed in the case of some viral models in mice, in which type I interferons are sufficient to control infection even in the absence of T and B lymphocytes [36].

(ii) *Excessive activation of PRRs from innate immune cells and increased levels of type I interferons:* High doses of IFN-I and pattern recognition receptors (PRRs) activation prior to antigen presentation by dendritic cells (DCs) [37,38] can reduce antibody production by plasma cells. IFN-I and PRRs are important players of the inflammatory immune response and must be properly regulated in order to prevent excessive inflammation. Excessive inflammation can not only lead to tissue destruction, but also restrain antibody responses, as already mentioned. Accordingly, phospholipase A_2G2D (PLA_2G2D), which possess anti-inflammatory activity, is important to antibody development and memory responses, as assessed in genetic deficient mice compared to wild type (WT) [39]. After sub-lethal infection with Middle East respiratory syndrome coronavirus (MERS-CoV), followed by lethal challenge, WT mice were fully protected to the challenge [39]. Curiously, PLA_2G2D genetic deficient mice were more resistant to primary sub-lethal infection, but were not protected to the lethal challenge. This study demonstrated two interesting facts: the importance of inflammatory mediators to control MERS-CoV primary infection; and the impact of these inflammatory mediators in adaptive immunity development, restraining antibodies release. Excessive pro-inflammatory cytokines expression by DCs, like IL-1β, were associated with increased cell death in lymph nodes and impaired polarization of follicular CD4+ T cells (Tfh) in this infection model [39]. Thus, the innate immune response can influence antibody development if not properly regulated to optimal levels.

(iii) *Activation and polarization of CD4+ T helper cells into cytotoxic CD4+ cells*: The adaptive immunity of the individuals with low antibodies levels after the first infection was based primarily on cytotoxic CD4+ T cells, instead of Tfh that support B cell activation and antibody class-switch [40]. The antagonism of CD4+ cytotoxic T cells and Tfh is governed by the bcl-6 transcription factor, crucial to Tfh polarization. After single cell transcriptomic analysis, Donnaruma et al. [40] identified that granzyme B+ CD4+ Cytotoxic T cells (CTL) had an opposing gene signature compared to follicular T cells. The transcription factors bcl-6 and Tcf-1, and the inhibitory receptors PD-1 and LAG3 jointly favored the balance into Tfh polarization, instead of CTL CD4+ T cells. This balance was greatly dependent on the type of infecting virus used in the study, with adenovirus driving CD4+ T cells with CTL potentials and retrovirus driving Tfh. Cytotoxic T cells (especially $CD8^+$ T cells, but also CD4+ T cells with CTL potential) are crucial to control several viral infections, but they are not sufficient to drive full resistance, and antibodies are important mediators of viral replication containment, especially through viral neutralization [41]. This cytotoxic T cell based adaptive immunity would still be important to restrain infection, but can also contribute to direct tissue damage, especially if the secondary exposure occurs with high viral loads, at least in the case of experimental infection with respiratory syncytial virus [42]. In addition, as memory CD4+ T cells exert superior responses over naïve T cells [43], memory cytotoxic T $CD4^+$ may restrain follicular T cell polarization, similar to

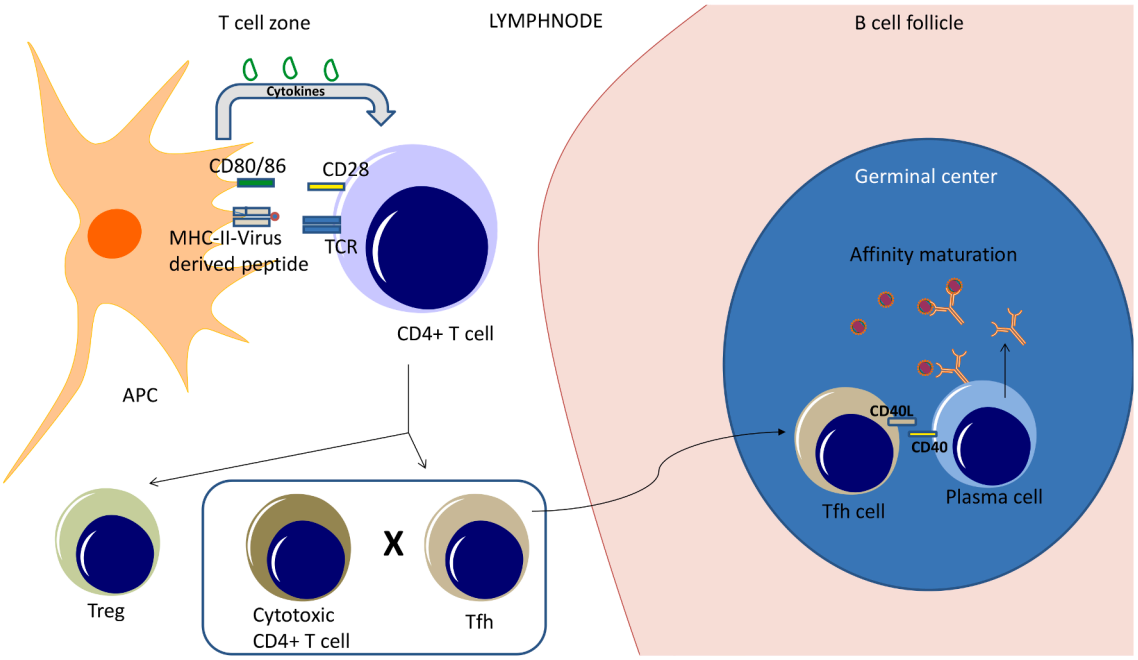

Fig. 1. Mechanisms involved in low antibody levels after the first infection: In the draining lymph nodes, professional antigen presenting cells (APCs) interact, in T cell zones, with naive T cells. This interaction is a crucial step in the activation and polarization of CD4+ T cells into distinct sub-types, depending on 3 signals derived from molecular interactions between (i) MHC-II-peptide complex and TCR; (ii) co-stimulatory molecules (CD80, CD86) from APCs and CD28 receptors in T cells; (iii) cytokines secreted by APCs and cytokine receptors in T cells [51]. Tfh and cytotoxic CD4+ T cells antagonize each other polarization [40]. Thus, cytotoxic CD4+ T cells polarization can possibly be associated with a reduction in antibody responses, because Tfh cells support antibody class-switch in B cell follicles and affinity maturation in germinal centers [52]. Treg cells polarization can also restrain Tfh activity and humoral responses [47], contributing to low antibody levels after primary infections. Finally, during antigen presentation by APCs, increased IL-1β levels correlates with cell death in lymph nodes and hampered polarization of CD4+ T cells to Tfh [39].

what is observed in relation to Th2 antagonism against Th1 cells polarization in a delayed hypersensitivity model [44]. This would cause an important delay in the generation of T $CD4^+$ follicular cells, a feature that might also contribute to aggravated reinfection. Intriguingly, cytotoxic CD4+ T cells are increased in severe SARS-CoV-2 infections, along with a decrease in the number of CD4+ T regulatory follicular cells (Tfr) [45]. Tfr cells support antibody diversity, restraining Tfh cell survival stimuli to B cells, fine-tuning antibody affinity, after somatic hypermutation of these cells [46].

(iv) *Presence of regulatory T cells (Treg) specific to SARS-CoV-2 antigens:* Generation of Treg cells specific to SARS-CoV-2 antigens after primary infection can possibly lead to ablated antibody production [47]. Induced Treg (iTreg) can develop in intestinal lymph nodes against foreign antigens, especially in the presence of TGF-β at the time of antigen presentation [48]. Thus, the entry site or the organs affected by SARS-CoV-2 in primary infection can be determinant to the type of adaptive immunity unleashed by it [49]. Since SARS-CoV-2 is known to infect intestinal epithelial cells, it wouldn't be surprising to observe iTregs against SARS-CoV-2 antigens in severe cases. Thus, secondary infections can also be aggravated in people who acquired iTregs, restraining disease resistance governed by immune responses [50].

Aggravated reinfection: What else drives these exceptional cases?

The majority of case reports describing reinfection were associated with a less dramatic coronavirus disease, probably due to combined T and B cell memory responses [53]. However, reports of a higher pathogenesis and even death in the secondary infections are presents [20,54]. The mechanisms associated with the aggravated reinfection are not completely understood, but some considerations can be made (Fig. 2). First, immune dysfunction, a feature similar to anergy, governed by epigenetic changes after highly inflammatory infections, from viral or bacterial etiologies [55,56] can let individuals susceptible to secondary infections. It is not determined if immune dysfunction is present in the case of SARS-CoV-2 aggravated reinfections, but it is a possibility, especially in the presence of an inefficient adaptive immunity memory. Second, antibody-dependent enhancement (ADE) is a process under discussion for other coronaviruses, especially after vaccination [57]. ADE happens in the presence of non-neutralizing antibodies that will enhance viral entry and replication inside host cells, mediated by Fc receptors and complement proteins, especially inside macrophages and neutrophils [58]. In this sense, it is expected that non-neutralizing antibodies, including cross-reactive antibodies from seasonal coronaviruses, might contribute to both infectivity and increased inflammation [59]. Thus, if the affected person develops memory B cells that produce non-neutralizing antibodies, the boosted response after reinfection is potentially harmful and might lead to systemic inflammation and possibly cytokine storm, both pathogenic features present in SARS-CoV-2 infection. In addition, it had been shown that antibodies against SARS-CoV Spike (S) proteins (crucial for virus-host cell receptor interaction and viral internalization), conserved among all coronavirus, can increase the infectivity of SARS-CoV in host cells, when S proteins are mutated [60–62]. However, in relation to a possible role of ADE in SARS-CoV-2 infections, we must highlight that ADE is not an important issue for other viruses that affect the respiratory tract, like influenza virus [63]. Furthermore, antibody levels seem to be inversely correlated with the possibility of reinfection for seasonal coronaviruses [64], and the benefits related to the presence of antibodies after vaccination [65] do not support ADE as a hypothesis for aggravated reinfections or the genesis of SARS-CoV-2-mediated cytokine storm. Compellingly, even in the presence of antibodies against S proteins associated with increased viral infectivity in B cells, a stronger protection was observed in hamsters infected with SARS-CoV [60].

It is important to highlight that reinfection with distinct variants of SARS-CoV-2 might recapitulate the original antigenic sin phenom,

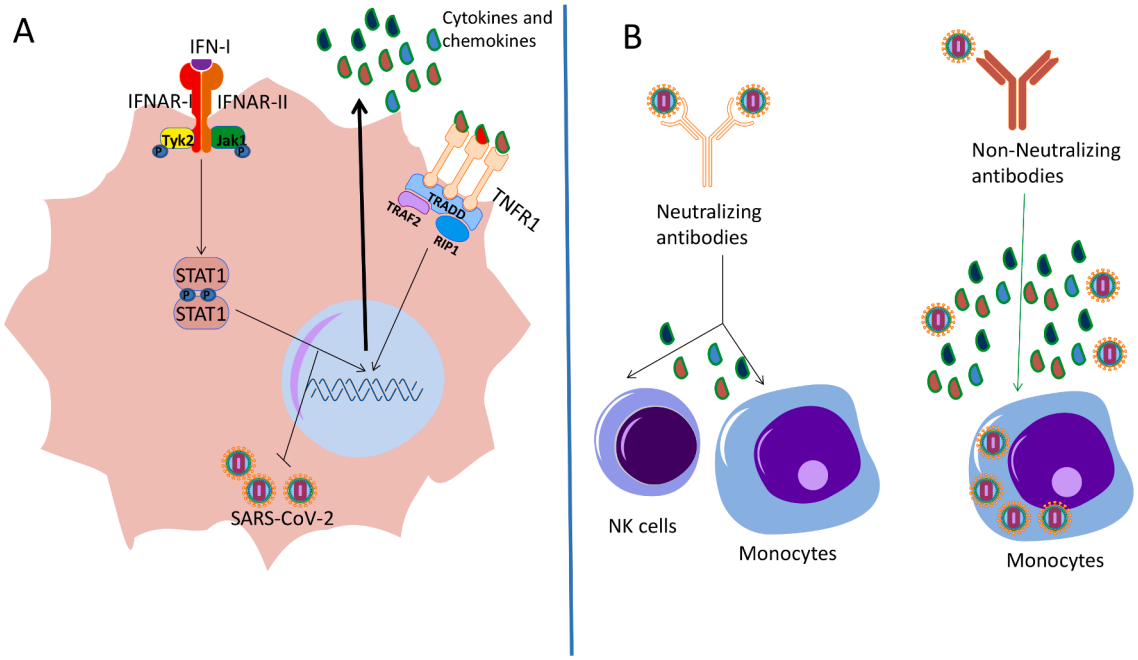

Fig. 2. IFN-I and antibody-mediated protective or detrimental mechanisms associated with SARS-CoV-2 infections: A) IFN-I mediate autocrine and paracrine signaling through its receptor (IFNAR), present in almost all nucleated cells in physiologic conditions. IFNAR drives signaling cascades dependent on protein kinases (tyrosine kinase 2-Tyk2- and Janus kinase 1-Jak1) leading to the formation of different signal transducer and activator of transcription (STAT) complexes (including STAT1 homodimers and STAT1/2 heterodimers) and nuclear translocation [78]. In the nucleus STATs act as transcription factors, promoting the expression of several genes, such as protein kinase R (PKR) and Mxl that restrain viral proteins translation and assembly to form infective particles, respectively [79,80]. On the other side, IFN-I can significantly contribute to inflammatory damage, enhancing TNF-mediated inflammation [73], which depends on TNF receptors (TNFR) and signaling molecules, such as the E3 ubiquitin ligase TNFR associated factor 2 (TRAF2) and the serine/threonine kinase receptor interacting protein 1 (RIP1). IFN-I can also restrain antibody responses [36]. B) Neutralizing antibodies are crucial to anti-viral immunity, leading to ADCC by NK cells and monocytes, and hampering viral dissemination to susceptible and permissive cells. However, non-neutralizing antibodies can increase viral dissemination to permissive cells, through Fc receptors [81], possibly contributing to tissue damage due to excessive inflammation and viral titers. Furthermore, antibodies-mediated FcγRIIb activation can hamper IFN-I-mediated viral control [68] and a fine regulation of both IFN-I and antibodies levels are crucial for appropriate control of viral infections. The development of auto-antibodies that reacts and neutralize IFN-I can also be associated with a poorer control of SARS-CoV-2 infection and disease severity, as reviewed elsewhere [82].

already observed for influenza virus. This phenom refers to the prevalence of antibodies response against antigens derived from the virus variant from the first infection [66]. Once more, if these antibodies do not neutralize new virus variants, they will not drive host resistance, potentially contributing to viral pathogenesis. Though somatic hypermutation can increase the affinity of cross-reactive antibodies [67], if a huge modification is needed in order to convert non-neutralizing antibodies into neutralizing ones, it is much probable that the random events of somatic hypermutation will not properly lead to neutralization. Furthermore, in theory, polymorphisms in the genes responsible for the process of somatic hypermutation, especially the one that codes for activation induced deaminase (AID) enzyme, can potentially be associated with distinct efficacy of the affinity maturation process. However, to our knowledge, no studies have correlated AID polymorphisms, somatic hypermutation and antibody affinity maturation, though AID polymorphisms have been associated with antibody class-switch to IgE [68].

Antibodies might also be responsible for attenuated IFN-I responses, through stimulation of FCγRIIb in severe cases [69]. Type I IFNs are crucial to control SARS-CoV-2 infection as showed by different studies examining genetic differences associated with severe SARS-CoV-2 disease. Furthermore, it might explain the increased susceptibility of older adults that possess reduced ability to secrete type I IFNs [70–72]. On the other hand, IFN-I can contribute to cytokine storm [73], TNF-mediated inflammation [74] and delayed antibody development [75], which are associated with disease severity. Thus, the kinetics of neutralizing antibody production and IFN-I responses might hold the key to the outcome. In this sense, early exacerbated IFN-I secretion can impair antibodies production, leading to an inappropriate viral control and subsequent increased late antibodies levels. At this stage, excessive antibodies levels can impair IFN-I cellular immunity, after stimulation of FCγRIIB. Altogether, these would lead to inappropriate immune response kinetics, driving increased viral load initially, and late impaired type I interferons signaling. Anyway, it is important to note that conclusions based on correlation between antibody levels and disease severity might be misleading. High viral load and persistence will greatly impact on antibodies levels and might be the actual player in the pathogenesis.

It is crucial to mention the well-recognized Human Leukocyte Antigens (HLAs) as a central molecule associated with genetic susceptibility/resistance to infections, including SARS-CoV-2 [76]. HLAs, the human ortholog of MHCs, are polymorphic and polygenic glycoproteins, expressed on cell surface, that will bind peptide epitopes from self and non-self-proteins (microorganism's derived ones) within the cells. HLAs-peptides complex will be involved in antigen presentation to T cells, after interaction with T cell receptors (TCRs). Different epitopes will bind to specific HLAs, which means that each individual will generate a unique and specific repertoire of cellular and humoral adaptive immunity at the molecular level to the same microorganisms. As already discussed, T cells will orchestrate adaptive immunity, depending on its sub-types, including antibody class-switch by plasma cells (activated B cells). Thus, HLA types are linked to broadly neutralizing antibodies production and can greatly impact both primary and secondary immune responses to SARS-CoV-2. This issue is well explored by others [77].

Discussion

All the features here discussed may explain such diverse outcomes

after SARS-CoV-2 reinfection. The development of other infectious disease is known to be influenced by the entry site of the etiological agent, impacting in both disease resistance and tolerance of the host, and virulence of the microorganism [83,84]. In addition, the viral load in airborne infections, the genetic variation of the population and the comorbidities presented by the individuals will combine themselves and be crucial to the diverse outcomes [85,86]. As already cited, epigenetic changes in myeloid cells, after exacerbated inflammation, seem to modulate susceptibility to infections, through inflammation-induced anergy of myeloid cells, a feature that can lead to aggravated reinfections [87,88]. In this sense, exacerbated inflammation can lead to increased immunopathology and dysregulated effective immune responses in older adults and obese individuals, as both groups possess chronic low-grade inflammation, which will be amplified after infection [89,90]. Older adults and obese individuals also possess important disparities in cellular and humoral immunity compared to younger and non-obese individuals, for example, both groups possess qualitative differences in antibodies repertoires and neutralization ability, and increased circulating myeloid derived suppressor cells [91–94]. In the case of older adults, it seems that many factors contribute to these features, associated or not with chronic low-grade inflammation, including lymph nodes stromal cells changes during ageing [95].

Polymorphisms and mutations in genes associated with antibody development and type I interferons' pathways can predict COVID-19 severity [69,96]. Here, we highlight studies that show the complex interplay between these two predictors of severity and how dysregulated antibody production and type I interferons' responses can impact each other. In a simplistic way, both antibodies and IFN-I are complementary key mediators of anti-viral immunity, driving extracellular virus neutralization and hampering intracellular virus replication, respectively. However, as already discussed, both can also lead to excessive inflammation and tissue damage, and a negative counter-regulation between these two key mediators is not surprising. In this sense, exacerbated expression of IFN-I, due to (i) high viral load infection, (ii) individual polymorphisms, (iii) trisomy of chromose 21[97], (iv) abnormal regulation of innate immunity or previously established inflammatory processes, can be associated with delayed development of antibodies [36,37,89,98]. Inappropriate control of virus infectivity due to delayed antibody development will generate increased (late) titers of antibodies that can contribute to inflammatory damage governed by Fc receptors and restrain IFN-I mediated viral control, through FcγRIIb signaling [68]. These features combined can lead to an inappropriate cascade of events that are associated with irreversible tissue damage and death. On the other side, sub-optimal expression of IFN-I responses, due to polymorphisms, old age or obesity [99,69,87], can lead to uncontrolled viral replication followed by increased levels of antibodies and viral and inflammatory tissue damage, mediated by viral PAMPs and Fc receptors activation. However, in the majority of SARS-CoV-2 infections, IFN-I will be expressed in optimal levels, leading to early control of infection, with no impairment on antibody development.

Genomic studies are very important to identify possible polymorphic players and pathways associated with pathogenesis [5], but well-controlled research in suited animal models is fundamental for specific therapies development [100]. One interesting possibility is to revisit literature against more virulent coronaviruses, such as MERS-CoV and SARS-CoV, or use animal models suited for these, in order to better understand and identify therapeutic compounds in a well-controlled fashion [101,102], while animal models to SARS-CoV-2 are not available to the majority of researchers [103].

Finally, we believe that a better understanding of what drives cytotoxic CD4+ T cells can point out promising molecular targets to prevent aggravated reinfections and drive vaccination to viral diseases, as cytotoxic CD4+ T cells can potentially hamper Tfh polarization and antibodies production. All the features discussed in this text highlight that SARS-CoV-2 cause a multifactorial disease. Thus, the combination of targeted therapies, as already made for other viral diseases, like acquired immunodeficiency syndrome (AIDS) and hepatitis, might be crucial to better outcomes.

Funding statements

This manuscript development was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil, and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

Consent statement/Ethical approval

Not required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We acknowledge the Brazilian Coordenação de aperfeiçoamento de pessoal superior (CAPES) and Fundação de amparo à pesquisa do estado do Rio de Janeiro (FAPERJ) for the support.

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