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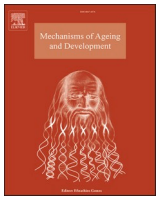

Immunosenescence and COVID-19

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ABSTRACT

Ageing is associated with modified function of both innate and adaptive immunity. It is believed that changes occurring in ageing immune system are responsible for increased severity and deadliness of COVID-19 in the elderly. Although supported by statistics and epidemiology, these finding do not compute at the mechanistic level as depending solely on chronological and biological ageing. The phenomena describing changes in the aging immune system are immunosenescence and inflammageing, which develop in time depending on challenges to the individual immune system (immunobiography). Thus, "richer" immunobiography (in addition to other factors, including genetic, epigenetics or metabolic) may adversely affect the reactivity to the SARS-CoV-2 not only at later decades of life, but also earlier, in young and middle-aged individuals. On the other hand, infection with SARS-CoV-2 is affecting the function of both innate and adaptive branches of the immune system, adding to the individual immunobiography. Summarizing, immunosenescence and inflammaging may aggravate, but also may be aggravated by SARS-CoV-2 infection.

1. Introduction

A new zoonotic disease due to infection by a coronavirus dubbed SARS-CoV-2 and named COVID-19 is affecting worldwide human population since late 2019, and at the time of writing this article (early December 2021) took lives of more than 5.3 million people out of more than 242.5 million identified as infected with the virus (COVID-19 Coronavirus Pandemic, 2021). These figures increased to more than 6 million and 462,8 million respectively at the time of revision of this text (March 2022). The same source of information states, that considering all clinical cases diagnosed as COVID-19, 99.6% is in mild, while 0.4% in severe or critical condition. Recent (November 2021) information provided online by the United States Centers for Disease Control and Prevention compares rates of COVID-19-associated hospitalizations and deaths in various age groups, taking 18–29 years old as a reference group. Rates of hospitalization were already twice as big among 30–39 years old, and, rising steadily, among 85 years old were 10 times bigger than in the reference group. These differences became even more striking regarding the rates of COVID-19-related deaths. Here the rates for 30–39 years old were already four times bigger than the reference, for those 40–49 years old 10x, for 65–74 years old 65 times and for those older than 85 years an astonishing 370 times (CDC Covid-19, 2021). These data clearly demonstrate strong correlation between age and COVID-19 severity and related mortality. However, they do not stress (as was initially believed) that COVID-19 is the disease of elderly and old individuals, but rather show life-long, age-associated linearity in progression of infected individuals to disease requiring hospitalization or being deadly, as shown in recent meta-analyses (Romero Starke et al., 2020). Interestingly, some centenarians seem to go through the SARS-CoV-2 infection asymptomatically or with mild symptoms, although still the mortality due to COVID-19 increases with advanced age and in the oldest old is very high (Marcon et al., 2020). It is now well recognized, that comorbidities which are typical for older individuals, but can befall middle-aged and even younger individuals (including the cardiovascular disease, type 2 diabetes mellitus, chronic respiratory disease, arterial hypertension and various malignancies, but, according to a recent metaanalysis, stressing the role of dementia and dyspnea) significantly increase the death rate of COVID-19 patients compared to those with no pre-existing conditions (Damayanthi et al., 2021). For the latter the death rate is below 1%, while for those with one of the above-mentioned diseases it may reach from 7 to even 13% and, obviously, it is even more for those with multimorbidity. However, with the

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advent of new variants of the SARS-CoV-2, (currently world-wide variant *delta* and incoming *omicron*) it becomes more and more clear that the disease is becoming more and more dangerous also for people in their thirties and younger. Even if not killed, many of these previously healthy individuals are going through severe clinical manifestations requiring intensive care, and eventually are left partly incapacitated by the "long covid" for at least months afterwards.

2. What do we know about the IS reactivity to SARS-CoV-2 and how does it change with ageing?

SARS-CoV-2 enters the organism mostly with an aerosol via the upper respiratory tract and infects various cell types provided they are equipped on their surface in the ACE2 (the anchoring receptor for the viral "spike" or S protein and TMPRSS2 protease modifying the S protein itself. Interestingly, ACE2 expression is reduced in old rat lungs and in the elderly, at least theoretically decreasing the chance for cellular infection, although other reports question these observations (AlGhatrif et al., 2020; Barker and Parkkila, 2020; Xie et al., 2006). However, it is necessary to mention here that the ACE2/TMPRSS2 anchor for SARS-CoV-2 is by no means the only. Among the other is, notably, the LFA-1 molecule, which was very recently (March 2022) demonstrated to mediate the entry of SARS-CoV-2 into human T lymphocytes, making them another target (or victim) of the virus. Admittedly, neither human T and B cells nor monocyte/macrophages express ACE2 or TMPRSS2 (Shen et al., 2022). Direct SARS-CoV-2 infection of T cells is proposed to be the mechanism of lymphopenia seen in severe COVID-19 patients (Gao et al., 2021). In our opinion this finding is extremely important for understanding the relations between changes occurring during aging of the immune system and the consequences of SARS-CoV-2 infection.

The SARS-CoV-2 belongs to RNA viruses and upon being endocytosed it releases its single stranded RNA genome which directly serves as mRNA for all structural and nonstructural proteins (Brant et al., 2021). Being the viral disease, COVID-19, or rather any (even asymptomatic) infection with the SARS-CoV-2 virus engages the same immunological mechanisms and reactions as any other viral infection. These mechanisms include the recognition of the virus as a foreign entity by both the innate and adaptive immune cells.

The former (mainly monocyte/macrophages and dendritic cells) detect viral RNA via (mainly) the intracellular TLR7/8 and TLR3 receptors built in in the membranes of endosomes. It is necessary to mention here, that monocyte/macrophage cells can also be infected by functional, replicating viruses (which might affect their functions or even lead to their death), although the details of ways of entry of the virus into these cells are not yet established; surface TLR species and LFA-1 are proposed as the entryways, but conclusive research is still missing (Codo et al., 2020; Shen et al., 2022; Zheng et al., 2021). Ligation of TLR7/8 provides strong activating signal in the monocyte/macrophages which stimulates the inflammasome and leads to the production and secretion of IL-1β which stimulates the secretion of IL-6, MCP-1, MIP-1 A, TNF-α, and virus-protective type 1 interferons (Khanmohammadi and Rezaei, 2021). These cytokines directly activate the innate, and indirectly help the adaptive responses to the virus not only in its primary entry port – the cells of the respiratory system – but also in multiple other organs, including lungs, brain, intestines, endothelia, cardiac muscle and kidneys, and – as mentioned above – also the cells of the immune system. All of these organs have been shown to be affected in COVID-19 patients, and activation of the innate immunity in such case seems to have a direct protective role against the infection. However, overactivation of the inflammasomes as seen in the severe cases of COVID-19 regardless of the age of infected individual fuels the secretion of excessive amounts of these proinflammatory cytokines (the "cytokine storm") leading to the damage of affected organs and increased coagulation (DIC) which precipitates the ARDS, multiorgan failure, and ultimately death of the patient.

It is of notice that coronaviruses (including the SARS-CoV-2) can activate the inflammasome in the innate immune cells not only by triggering the TLRs, but also by modifying the ion balance inside and outside the infected cells using the viroporins (viral proteins that built into the cell membrane and form nonselective ion channels, effectively releasing K^+ to the extracellular fluid; loss of cytoplasmic K+ is one of strong signals for inflammasome induction and activation (Chen et al., 2019; de Rivero Vaccari et al., 2020). Considering that ageing is associated with reduced kidney function and changed concentration of K^+ in the extracellular fluid (ECF; hypo- or hyperkaliemia), an elderly organism provides that way the overall environment facilitating the stronger inflammasome activation in COVID-19 patients (Beck, 2000; Noori et al., 2021). Indeed, old patients tend to develop the cytokine storm and its dire consequences more frequently than younger people. The reasons behind this observation are many. In brief, they include features that became the nine pillars (hallmarks) of aging, including but not limited to mitochondrial dysfunction and increased production of ROS (oxidative stress) (Farshbafnadi et al., 2021; Lopez-Otin et al., 2013; Pinti et al., 2014; Rydyznski Moderbacher et al., 2020; Wissler Gerdes et al., 2021), but also mentioned above comorbidities mostly being chronic inflammatory diseases, decreased output of steroid (at any age, especially sex) hormones, poor nutrition, restricted activity (culminating in the frailty syndrome) and, last but not least, the immune dysregulation (Farshbafnadi et al., 2021; Lopez-Otin et al., 2013; Pinti et al., 2014; Rydyznski Moderbacher et al., 2020; Wissler Gerdes et al., 2021). The latter consists of two concurrent processes of immunosenescence and inflammaging, greatly affected by the *individual* history of challenges to the immune system, both external (pathogens and vaccines) and internal (neoplastic and dying cells) called the immunobiography (Franceschi et al., 2017b).

3. Cellular senescence, immunosenescence and inflammaging - how do they fit in (if anyhow) as part of human immune system ageing and how do they impact the host/pathogen interaction in case of SARS-CoV-2?

The immunosenescence, understood as dysregulation and modified (reduced) function of the immune system in elderly, although even this definition may be questioned (Pawelec et al., 2020), should not be confused with cellular senescence in general, although it does involve the senescence of the immune cells and in many facets the two processes are identical (Salminen, 2021b). Thus, cellular senescence consists of multiple phenotypic changes of long living (old) cells, including short telomeres, cessation of proliferation, enlarged size, acquisition of increased activity of the lysosomal acidic beta-galactosidase called the Senescence-Associated (SA)-βGal serving as biomarker of senescent cells regardless their tissue or organ of origin (Blagosklonny, 2020; Campbell et al., 2021; Meftahi et al., 2020; Wissler Gerdes et al., 2021; Yao et al., 2020). However, the most important feature of the senescent cells is acquisition of the senescence-associated secretory phenotype (SASP) which enables these cells to secrete significant amounts of proinflammatory cytokines (including IL-6, TNF-α, IL-1β, IL-8 and other) (Bandaranayake and Shaw, 2016; Ito et al., 2017; Nacarelli et al., 2019; Pawelec et al., 2020; Witkowski et al., 2021b). Accumulation of senescent or senescent-associated cells occurs with advanced age also among the innate immune cells, including monocyte/macrophages and dendritic cells (Campbell et al., 2021; De Maeyer and Chambers, 2021; Jing et al., 2009; Lee and Linterman, 2021; Linton and Thoman, 2014; Ong et al., 2018; Panda et al., 2010). Accumulation of these senescent macrophages, which concurrently decrease their output of anti-inflammatory IL-10, may be due to the influence of the ageing tissue environment and signals, as well as to intrinsic changes in the macrophage population itself, which were recently described as "macrophageing" (Franceschi et al., 2000; Prattichizzo et al., 2016; Zhang et al., 2015). Ageing macrophages display increased expression of cyclin inhibitor $p16^{INK4a}$ as well as of the SA-β-Gal; however, they apparently do not lose their proliferative capabilities altogether (Hall et al., 2017; Liu

et al., 2019). In fact, some researchers posit that in the case of macrophages the expression of $p16^{Ink4a}$ is rather an indicator of their polarization; thus, ageing would lead to modification of the proportions (and so ratio) of proinflammatory M1 (decreasing), anti-inflammatory and pro-proliferative M2 (increasing) and other non-classical macrophages (Hall et al., 2017; Salminen, 2021a). The M2 macrophages were also described to be regulatory (Mregs)/ immunosuppressive (Salminen, 2021b). This effect of aging on macrophages and the shifts of their populations was described for example in murine lungs which, if similar in humans, would likely participate in reduced clearance of respiratory tract-infecting viruses (including the SARS-CoV-2) and increased severity of COVID-19 in the old individuals (Jackaman et al., 2013; Wang et al., 2015). In fact recently the accumulation of M2 (M2-like) macrophages was demonstrated (in addition to M1cells) in the lung (bronchoalveolar lavage, BALF) of severe COVID-19 patients; these cells are both anti-inflammatory and profibrotic and their accumulation was associated with expression of immunoregulatory genes A2M, GPR183 and CCL13 and profibrotic genes TREM2, TGFB1 and SPP1, as well as of M2-promoting TFEB, NR1H3, PPARA and CREB1(Liao et al., 2020).

Consequences of "macrophageing" may be the reduced ability of the macrophages to remove other senescent cells and to interact with adaptive immune cells (including antigen presentation). It is worth mentioning that SASP is not only proinflammatory, but, especially at early stages of development of this phenotype, also immunosuppressive (due to secretion of TGF-β1 and TGF-β3), dampening the efficiency immune responses, as well as profibrotic, leading to more severe lung fibrosis (Ito et al., 2017; Nacarelli et al., 2019; Parimon et al., 2021). These features very likely participate in increased severity of COVID-19 in the elderly.

The accumulation of senescent cells in the ageing tissues is currently suggested to be one of the important causes of inflammaging (Fulop et al., 2016, 2017a, 2017b, 2020a, 2021; Pawelec et al., 2020; Salminen, 2021a). However, this by no means is the sole reason for inflammaging. The process may result also from accumulation of cellular by-products, remnants and debris (cumulatively dubbed the garb-aging, due to progressive loss of autophagy, mitophagy and proteostasis in older cells (Franceschi et al., 2017a). Another reason for its appearance is the development of trained innate immunity – conferring increased protection against further infections (Netea et al., 2020; Quintin et al., 2014). Increased with age leak of mitochondrial DNA, triggering the TLR, may be another reason (Pinti et al., 2014). The latter mechanism may be amplified in male severe COVID-19 patients and lead to hyper-inflammation (Storci et al., 2021). Inflammaging may also result in part from dysbiosis of the gut microbiome, which shifts its effect on the immune system from regulatory and immunosuppressive to proinflammatory; dysbiosis is more frequently observed among the elderly, mainly due to changing dietetic habits and infections requiring therapy with antibiotics (Vaiserman et al., 2017). Also, individuals (at any age) with paucisymptomatic chronic inflammatory diseases, sometimes not even diagnosed, would secrete more proinflammatory cytokines defining their (sometimes early) inflammaging. This process, defined as increasing the amounts of proinflammatory cytokines (as well as multiple chemokines) in the plasma of elderly without overt manifestation of inflammatory disease has broad implications for the proinflammatory and immunosuppressive state of an organism in which it develops (Franceschi et al., 2000, 2007; Franceschi and Campisi, 2014; Fulop et al., 2021). Clear manifestations of the latter might be the increase of numbers of the myeloid-derived suppressor cells (MDSCs) in the blood of elderly people and mice (Flores et al., 2017; Grizzle et al., 2007; Verschoor et al., 2013). There is likely a direct relation between inflammaging and the increase of MDSC; however, due to scarcity of different types of MDSC in human peripheral blood the data concerning this topic are scarce and so far limited and based on (successful) experiments where MDSC were induced from human monocytes in vitro by cocktail of proinflammatory cytokines (Pawelec et al., 2021; Salminen, 2021b; Veglia et al., 2018). This is clearly relevant for the interaction of aging organism with the SARS-CoV-2, as it was demonstrated that expansion of MDSC may inhibit the virus-specific T cells (especially cytotoxic cells) and predict fatal outcome of COVID-19 (Agrati et al., 2020; Bordoni et al., 2020; Sacchi et al., 2020).

Another likely consequence of inflammaging may be the increased numbers of peripheral blood regulatory T cells (Tregs) seen both in aging humans and mice (Bryl et al., 2009; Bryl and Witkowski, 2004; Churov et al., 2020; Gregg et al., 2005; Lisowska et al., 2014). Still, there is a relative paucity of data linking the accumulation of Tregs with increased levels of proinflammatory cytokines. Thus, a relation between the proinflammatory Th17 lymphocytes and Tregs was demonstrated to change with advancing age and may depend on increased secretion of IL-6 (Churov et al., 2020; Deng et al., 2022; Kimura and Kishimoto, 2010; Mysliwska et al., 1998, 1997; Salminen, 2021c; Schmitt et al., 2013). The data on the functionality of Tregs in aging individuals are conflicting; some papers indicate their increased immunosuppressive activities, other point at its reduction; it is noteworthy, that studies performed on mice may not correspond to the observations of Tregs in humans (Churov et al., 2020; Deng et al., 2022; Guo et al., 2020; Salminen, 2021b, 2021c).

Generally, low grade inflammation, whether due to the causes described above, or to the chronic inflammatory diseases at paucisymptomatic state is conductive for immune dysregulation and increased severity of COVID-19 (Bonafe et al., 2020; Suarez-Reyes and Villegas-Valverde, 2021).

The above-mentioned state of trained immunity, reflecting improved reactivity of (mainly) macrophages (and NK cells) to pathogens upon non-specific stimulation e.g. by vaccines may in this context be a double-edged sword. On one hand, it has been shown that prior vaccinations against influenza, tuberculosis and other infections may convey increased protection from COVID-19 and postulated that ongoing vaccinations against these diseases may lessen the burden of COVID-19 (Aspatwar et al., 2022; Debisarun et al., 2021; O'Neill and Netea, 2020; Sharma, 2021). According to the cited authors, trained immunity may act via epigenetic reprogramming of monocytes. On the other hand, a recent paper has demonstrated that an extensive sequential homology exists between the SARS-CoV-2 spike (S) protein, and BCG HSP-65 protein, which puts in doubt the trained innate immunity role, pointing – at least in this specific case - at the direct antigenic stimulation and cross-reactivity (Finotti, 2022). On yet another hand, SARS-CoV-2 nucleocapsid (N) proteins were found to dually regulate the innate response, with inhibitory effects (including lower production of proinflammatory cytokines) at lower doses and highly stimulatory at higher. The mechanism of such dual action of the N protein includes dual effect on phosphorylation of IRF3, STAT1, and STAT2 and on their nuclear translocation (Zhao et al., 2021). It was also demonstrated, that training of innate immunity using the BCG, beta-glucan or LPS, acting respectively via AKT/mTOR and MAPK/p38 pathways increases the production of IL-1, IL-6, IL-32 and TNF, thus possibly adding to the state of inflammaging (Brueggeman et al., 2022; Franceschi et al., 2017b).

As mentioned above, the innate response to the viral infection includes also the natural killer (NK) cells, which recognize and lyse the infected cells. Apart from reducing the viral load and curbing its increase, this function allows the NK also to destroy infected macrophages and other cells releasing the proinflammatory cytokines, preventing cytokine storm (Ghasemzadeh et al., 2021).

During ageing the $CD56^{+}$ NK cell population tends to grow both in percentage as well as in absolute numbers (Hazeldine et al., 2012; Le Garff-Tavernier et al., 2010), even if the production and proliferation of the NK cells is reduced (Zhang et al., 2007). This might signify the accumulation of long-lived NK cells and in fact increased numbers and proportion of $CD57^{+}$ NK cells considered more mature are observed in the elderly (Witkowski et al., 2020). Other studies have shown that older adults possess significantly fewer $CD56^{bright}$ NK cells which are likely replaced by the $CD56^{dim}$ NK cells (Hazeldine et al., 2012; Le Garff-Tavernier et al., 2010). Important surface molecules of the NK

cells, helping them bind with the virally-infected cells, including the KLRG1, NKG2A and its binding partner CD94 have been reported to be reduced in expression on the surface of NK cells of elderly individuals (Hazeldine and Lord, 2013). At functional level, aging is associated with reduced per cell cytotoxicity of the NK cells due in part to reduced expression of perforin and compensated to the extent by increased frequency of $CD56^{dim}$ NK cells.

The SARS-CoV-2 infection greatly reduces the functions of the NK cells. Thus, the virus evades their antiviral reactivity, including by prevention of upregulation of the HLA Class I signaling by targeting the STAT1-IRF1-NLRC5 axis (Yoo et al., 2021). On top of that, the NK cells of COVID-19 patients show reduced numbers and an exhausted phenotype (changed expression of NKG2A antigen), which may aggravate the severity of the disease by compromising viral clearance (Cunningham et al., 2021; Zheng et al., 2020). The reduced function of NK cells in the patients leads also to dysregulation of the immune response manifesting as the increased ratio of neutrophil to lymphocyte and monocytosis. In consequence, we assist to excessive secretion of IL-6 which promotes blood coagulation and further decreases function of cytotoxic lymphocytes by reducing expression of perforin and granzyme B (Cunningham et al., 2021; Li et al., 2020). The effect is sometimes described as "pathogenic auto-inflammatory feedback loop" (Cunningham et al., 2021). The numbers and functions of the NK cells (both cytokine-producing $CD56^{bright}$ and cytotoxic $CD56^{dim}$ cells) were found to be reduced more in patients with severe COVID-19 than in those with milder disease (d'Alessandro et al., 2021; Maucourant et al., 2020). Also, among the remaining NK cells (both $CD56^{bright}$ and $CD56^{dim}$) there are fewer cells expressing significant amounts of perforin in COVID-19 patients. Severe COVID-19 patients show shift in NK cell phenotypes towards lower expression of NKG2C and HLA-E, both molecules being important for effective antiviral activity (Vietzen et al., 2021).

Concluding, SARS-CoV-2 infection impairs functioning of the antiviral and antineoplastic cytotoxic NK cells; this may impair the resistance to both types of pathogens at any age of the infected person; however, will be more likely to affect it in the elderly. Generally, increased inflammaging may increase the susceptibility to COVID-19 (Santoro et al., 2021).

4. Ageing of the adaptive branch of the immune system and its role for the state of COVID-19 patients

Function of the adaptive branch of the immune system, composed of various populations of lymphocytes, both circulating and residing in the lymphatic organs and infiltrating tissues, changes (generally decreases) with individual ageing (Bandaranayake and Shaw, 2016; Zhou et al., 2021). Concerning the specific antiviral response, the main players here would be cytotoxic $CD8^+$ T cells (along with the NK cells destroying the SARS-CoV-2- and other virus-infected cells using similar mechanisms of cytotoxicity) and antibody-producing B lymphocytes and their progeny – tissue plasma cells providing specific antibodies recognizing and neutralizing viral antigens, preventing virus entry into susceptible host cells and facilitating clearing of the extracellular virus forming immune complexes. However, the helper $CD4^+$ T cells, by token of their response being by production of scores of different immunoregulatory cytokines and chemokines recognized and responded to by other adaptive and innate immune cells have a very important role in overall antiviral protection. Functional effectiveness of the adaptive immune cells depends on their antigen receptor diversity (making possible the recognition of pathogen-derived antigens), capability to mount a robust proliferative response (producing large responsive clones of relevant lymphocytes and eventually leaving behind large numbers of memory T and B cells equipped for future confrontations with the pathogen) and ability to manufacture appropriate amounts of effector and immunoregulatory humoral factors. All these functions are adversely affected by ageing which may result in more severe course of viral infections (including COVID-19) in the elderly.

The T cell receptor (TCR) diversity is known to decrease with ageing, both due to the decreased (by orders of magnitude) output of new naïve T cells from the involuting thymus and exhaustion/senescence of certain clones (Naylor et al., 2005; Wang et al., 2021). This phenomenon likely leads to decreased reactivity of old immune systems to new antigens brought in by the SARS-CoV-2. Recently it was demonstrated that TCR diversity in COVID-19 patients is significantly lower than that observed in the healthy controls; it was also demonstrated that this diversity was further reduced with advanced age of the patients (Hou et al., 2021). Cited authors speculate that ageing-associated reduction of TCR repertoire may be a factor in increased severity of COVID-19 in older age groups; it remains unclear if the interaction of SARS-CoV-2 with the immune system may decrease the TCR diversity by "using up" the clones which recognized and reacted to the virus. Interestingly, COVID-19 patients studied by this group presented some apparently disease-associated TCRβ clones, which could serve to help distinguish COVID-19 patients from healthy controls and victims of other respiratory viruses (Hou et al., 2021). This could suggest the expansion of the T cells displaying the virus antigen-sensitive TCR. Still, these clones, especially tissue resident ones, were reported to be less effective in protection against viral infection and by this feature responsible for chronic sequelae (Goplen et al., 2020).

The reason of lower effectiveness of ageing lymphocytes in fight against viral infections is clearly associated with their lower capability to proliferate upon contact with antigens and nonspecific mitogens (Bryl and Witkowski, 2004; Witkowski and Bryl, 2004). In most elderly, fewer T and B cells respond to stimulation by proliferation; instead, higher proportion of these cells becomes apoptotic (Bryl and Witkowski, 2004; Witkowski and Bryl, 2004). Reasons for this are many. First of all, with age the chance to encounter a naïve lymphocyte specific for a new antigen (e.g. those of SARS-CoV-2) is reduced due to mentioned decreased output of such from the thymus and lower probability that peripheral naïve T cells produced by the mechanism of homeostatic proliferation will be recognizing specific antigens (in this case those of SARS-CoV-2). Secondly, the "ecological niche" for the proliferating lymphocytes (secondary lymphatic organs, Peyer's patches and solitary lymphatic follicles in the tissues is taken over by the memory lymphocytes. The remaining (or newly created) SARS-CoV-2-specific naïve T cells are in an old organism adversely influenced by proinflammatory and immunosuppressive environment as described above. A reason for lower overall proliferation in response to mitogens and pathogens might also be higher proportion of senescent (i.e. nonproliferating) lymphocytes in the aged. Still, we need to acknowledge the state of the T lymphocyte exhaustion, which is not terminal and likely precedes the immunosenescence (Cunha et al., 2020). Furthermore, the effector T and B lymphocytes do age themselves. They follow all of the pillars of ageing, as well as the specific pillars of immune system ageing (Mittelbrunn and Kroemer, 2021). There are multiple changes in the proportion of different T and B cell populations (including, but not limited to mentioned increase of memory cells at the expense of naïve ones, as well as increased proportion of Treg cells which further dampens the immune responses cells. This ageing of lymphocytes includes lower secretion of cytokines (especially stimulatory, like IL-2 and IL-4) by helper T cells, decreased production of perforins and granzymes by cytotoxic $CD8^+$ T cells, and reduced output of immunoglobulins by the B cells and plasma cells, associated with lower specificity of these antibodies (Frasca, 2018). The mechanism of lymphocyte ageing includes multiple changes in the signal transduction from the relevant antigen receptors to the promoters of genes involved in different aspects of the immune response (Fulop, 1994; Fulop et al., 1992, 1993, 1999, 2006, 2014, 1991, 2017c; Fulop and Seres, 1994; Larbi et al., 2004, 2008, 2011; Le Page et al., 2018; Mikosik et al., 2016; Pawelec et al., 2002, 2001; Robert and Fulop, 2014; Solana et al., 2012). Among this changes one can list decreased numbers of costimulatory receptors like CD28 on both $CD4^+$ and $CD8^+$ T cells, resulting in prolongation of transition of antigen- or mitogen-stimulated lymphocytes from the resting G0 state to the onset

of first mitotic cycle (Bryl and Witkowski, 2004; Witkowski and Bryl, 2004). Interestingly, reduced expression of CD28 is due to action of TNFα regulating the promoter of its gene (Bryl et al., 2001; Vallejo et al., 2002). Thus we can speculate that one way through which inflammaging would be immunosuppressive is via the TNFα-CD28 axis. Another reason behind lower effectiveness of immune response by old lymphocytes (immunosenescence) is their inability to mount sufficient increase of Ca^{2+} concentration in cytoplasm within few minutes from contact with the antigenic/mitogenic stimulus, suppressing calcium-dependent responses, including the necessary electrical changes (action potentials) in the membranes of elderly lymphocytes (Miller et al., 1997b; Witkowski and Micklem, 1992; Witkowski and Miller, 1999; Witkowski and Mysliwski, 1991). A very important cause of improper signal transduction in ageing lymphocytes are changed amounts and activities of multiple protein kinases and phosphatases regulating the activities of other key proteins (Fulop et al., 2006, 2017c; Miller et al., 1997a; Pawelec et al., 2001; Robert and Fulop, 2014). All these lead to dysregulated adaptive immunity, which may impact on the course of COVID-19 (Rydyznski Moderbacher et al., 2020).

Finally, clearing of dysfunctional, used-up or aggregated intracellular proteins (proteostasis) is greatly impaired in old immune cells due to changes in autophagy, mitophagy, activities of the enzymes in lysosomes and proteasomes, reduced activities of modulatory proteases (calpains) coupled with rising amounts of these proteins due to faults in transcription and translation (Witkowski et al., 2021a, 2018). These phenomena also impair the functions of immune cells in elderly, again affecting adversely their antiviral capabilities.

5. Conclusion

Both immunosenescence and inflammaging are suggested to be not only deleterious, but also an adaptation of the immune system to the changing conditions in the ageing body, leading to the remodeling of the IS aiming at preserving at least some anti-pathogen and anti-cancer measures and prolong lives of ageing individuals. The two processes occur in concert and likely start far before an individual reaches old age. Thus, they are extremely individualized, with some (relatively fewer) people showing the immune dysregulation precipitating symptomatic/severe/deadly COVID-19 relatively early in life, due to genetic, epigenetic, environmental and other influences, and other who in response to SARS-CoV-2 infection mount protective immune responses rather than deadly cytokine storm. We observe different trajectories of the immune system ageing with different conclusions (Fulop et al., 2018). Interestingly, centenarians are reported to robustly go through the contact with SARS-CoV-2 which indicates that it is not the chronological age and accumulated aging-associated immune dysfunctions, but rather the ability to contain and compensate the disease, pertinent to any age. One reason for some centenarians to not develop the deadly cytokine storm on contact with SARS-CoV-2 may that the levels of cytokines involved in inflammaging are much lower than predicted by their chronological age (Marcon et al., 2020). This brings us again to the concept of "immunobiography" (also coined by Claudio Franceschi) (Franceschi et al., 2017b; Fulop et al., 2020, 2021). However, we should include the effect of SARS-CoV-2 infection in the equation, likely affecting the immunobiography of the infected person. Immunobiography is the cumulation of history of challenges to the immune system of an individual, including infection by pathogens, environmental challenges, generation of transformed neoplastic cells, cell death from any cause leading to the release of damage-associated molecular patterns (DAMPs, alarmins), and finally vaccinations. Obviously immunobiography of an individual starts with their biography, i.e. in childhood, and affects the individual's ability to neutralize infections (including notably by SARS-CoV-2). Depending on the genetic and epigenetic characteristic of the individual in question, as well as on the load of the aforementioned challenges throughout the lifespan, immunobiography may result in slower or faster development of both immunosenescence (understood as terminal exhaustion of the effectiveness of the immune responses) and inflammaging, eventually leading to healthy (successful) or unhealthy (unsuccessful) aging burdened with the ARDs (Franceschi et al., 2018). This seems extremely important now, with the advent of COVID-19 and its epidemiology changing from mainly the disease of ageing people to that affecting more and more middle-aged individuals, children and even infants. This phenomenon is clearly due to mutations in the genome of SARS-CoV-2, especially those changing the properties of its "spike" (S) surface protein, increasing the infectivity of the virus. The most recent *omicron* variant of SARS-CoV-2 is reported to have 50 mutations in the relevant gene compared to the original virus. At this state of knowledge it is hard to predict if COVID-19 in children will become just another infective childhood disease with relatively minor consequences on the immunobiography of the affected children, or will become a more important factor, possibly accelerating the immune system (and general) ageing of the SARS-CoV-2 infected young individuals. Although highly speculative at this time, the notion of early SARS-CoV-2 infection bearing on immunobiography and increasing inflammaging may have some merit. It was found that severe COVID-19 is associated with higher levels of proinflammatory cytokines leading from inflammaging to immunoparalysis (Muller and Di Benedetto, 2021; Pirabe et al., 2021).

Described features of "long covid" include the protracted or newly appearing (sometimes many weeks or months from initial infection with SARS-CoV-2) include symptoms from multiple organs and systems, including the central nervous ("brain fog"), respiratory, cardiovascular, gastro-intestinal, urinary, endocrine etc. Notably, although it is still too early for deeper research on the topic, there are reports indicating higher proportion of autoimmune diseases appearing in those who contracted COVID-19 than in general population, suggesting that SARS-CoV-2 infection exerts prolonged, deleterious (dysregulating) effect on the immune system of patients. The reported symptoms of "long covid" could be at least in part explained by ongoing, chronic or chronicizing, inflammatory condition. Its occurrence in the post-COVID-19 patients at ever younger age might, in our opinion, lead to earlier development of manifest immunosenescence and inflammaging, leading to earlier occurrence and likely stronger manifestation of ageing-related diseases (ARDs) (Fig. 1). Also the age at which an individual would be infected with SARS-CoV-2 would play a role in the consequences of this infection (Fig. 2). However it must be said here that the above suggestions do not (yet?) have strong observational or experimental support.

Thus, it may be tempting to conceive some measures (pharmacological or other) preventing the development of either immunosenescence, or inflammaging, or both, which in theory would maintain the youth of the immune system in an old organism (and possibly allow it to better fight infections, including COVID-19). However, such a manipulation might lead to further disbalance in the (already dysbalanced) immune system if applied to elderly individuals. From what we wrote above, the effects of immunobiography are likely to accumulate through life; thus any prophylactic/preventive measures (including multivaccinations, ascertaining optimal diet and lifestyle, and senolytics should be started early in life when, however, their remote effects would be largely unpredictable, at least without deeper studies (Witkowski et al., 2019).

In the light of what was discussed above, is this possible to successfully, prophylactically protect the aging part of population from COVID-19 – related death, severe or even symptomatic disease? Common belief is that – due to decreased function of the immune system in general – old individuals do not mount sufficient, protective responses to vaccines. However, it is more and more clear that this lower response is not due to the immune system of the elderly, but to the composition of vaccines. It was shown that modification of antigen concentration and especially of the adjuvant concentration and composition in flu, zoster and anti-pneumococci vaccines increases the response of the elderly immune system (titers of protective antibodies) to that similar to obtained in vaccinated young people (Fielding and Lambert, 2015; George and Lawrence, 2015; Goudsmit et al., 2021; Lal et al., 2015). In case of

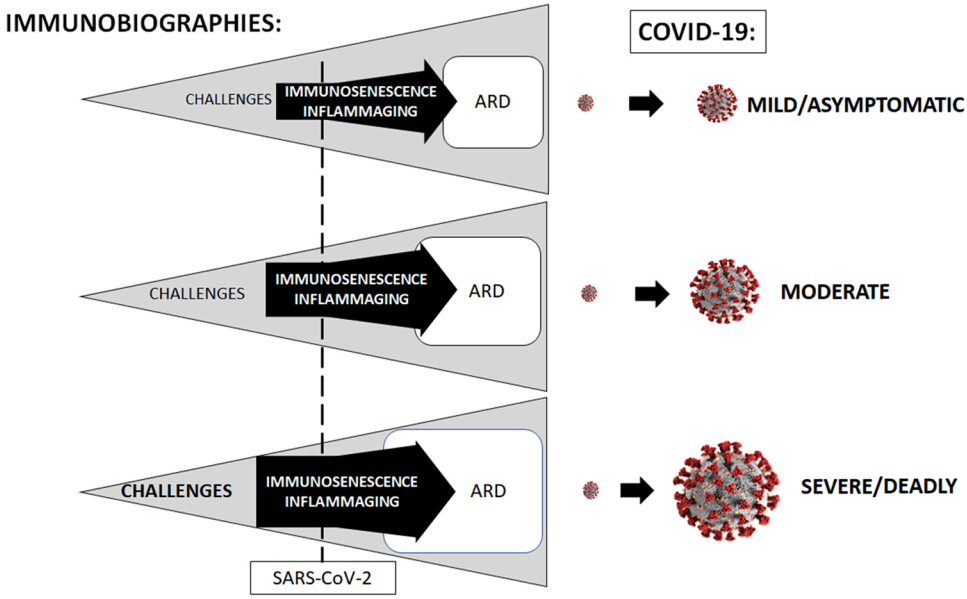

Fig. 1. Individual dynamics of the immune system ageing, inflammaging and immunosenescence modifies the severity of infectious diseases. Faster progression and increased intensity of immunosenescence and inflammaging (black arrows) due to "richer" immunobiography (higher load of lifelong adverse challenges) may lead to earlier occurrence and higher severity of aging-related diseases (ARD) and aggravate COVID-19. Also SARS-CoV-2 infection may add its effect to the immunobiography of an individual.

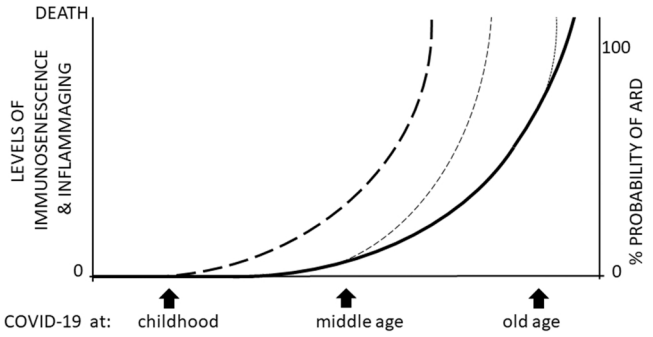

Fig. 2. Potential trajectories of development of immunosenescence, inflammaging and ageing-related diseases (ARD) depending on the age at contact with SARS-CoV-2 (black arrows) and development of COVID-19. The solid line indicates SARS-CoV-2 infection-free trajectory, dotted and dashed lines show the earlier acquisition of high levels of immunosenescence and inflammaging and of high probability of aging-related diseases (ARDs) when contact with SARS-CoV-2 was late in life, at middle age, or in childhood respectively.

modern mRNA anti-SARS-CoV-2 vaccines, the mRNA in them is not only the information to be translated to antigenic peptide of the virus, but itself serves as an adjuvant recognized by the TLR7/8 in the cells. Also, lipids used for encapsulating the mRNA are acting as strong adjuvants. Together, the components of anti-SARS-CoV-2 mRNA vaccines are stimulating the immune systems of most elderly individuals to the levels similar to obtained for young recipients of the vaccines.

Data availability

No data was used for the research described in the article.

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