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Review

Immune system aging and the aging-related diseases in the COVID-19 era

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ABSTRACT

The interest in the process of aging, and specifically in how aging affects the working of our immune system, has recently enormously grown among both specialists (immunologists and gerontologists) and representatives of other disciplines of health sciences. An obvious reason for this interest is the current pandemics of COVID-19, known to affect the elderly more than younger people. In this paper current knowledge about mechanisms and complex facets of human immune system aging is presented, stemming from the knowledge about the working of various parts of the immune system, and leading to understanding of immunological mechanisms of chronic, inflammatory, aging-related diseases and of COVID-19.

1. Immune system aging – basics

Understanding of aging of human immune system (IS) has recently become a topic of interest even for non-specialist. The obvious reason for this is the current pandemics of multiorgan inflammatory disease COVID-19, being the consequence of infection with the SARS-CoV-2 coronavirus. However, considering the importance of the IS for well-being of an individual on one side, and observed immune phenomena associated with advanced metrical age on the other, it has become obvious already decades ago that understanding of the mechanisms of the IS aging may lead to detection (and, in future, manipulation) of potential targets for intervention. Their identification, at least theoretically, may bring significant prolongation of healthy lifespan (healthspan) and reduce the aging-related diseases (ARDs). However, in order to produce the appropriate background and then discuss these phenomena and (patho)mechanisms of the IS aging, we need first to briefly summarize the basics of construction and functions of healthy immune system.

1.1. The healthy IS in a nutshell

The immune systems evolved early in the history of life on Earth (likely already around one billion years ago), likely as one of the first semi-specialized cell types of early multicellular organisms, trying to protect themselves from infection by already omnipresent unicellular organisms (bacteria, later unicellular Eukaryotes) and viruses [1, 2]. Human pathogens are definitely much “younger”, but still at least some of them co-evolved with early hominids already during Paleolithic, around two million years ago [3, 4].

First line of defense of early multicellular organisms was phagocytosis. In fact it is speculated that this ability of early Eukaryotes to engulf and later intracellularly kill a protobacteria had evolved at the time when some of these protobacteria had become mitochondria [5]. Here, one cannot miss the seed discoveries by I.I. Metchnikoff, who had first demonstrated the ability of some cells of starfish larva to “eat” bacteria and foreign bodies introduced in the larva, and coined the term phagocytosis more than a hundred years ago [6].

To make the long story short, our so-called innate immune system comprises of three main types of cells capable of phagocytosis and internal killing of cellular pathogens: monocyte/macrophages, polymorphonuclear leucocytes (PMN) or neutrophils and dendritic cells (DCs). In addition, a population of lymphoid cells called the natural killer cells (NK cells) is included in the group. They evolved multiple sets of so-called pattern recognition receptors (PRRs), which recognize pathogen-associated molecular patterns (PAMPs) on the surface or coming from inside of the pathogens. These PAMPs include e.g. membrane or cell wall proteins, lipopolysaccharides, flagellar proteins, viral capsid proteins, as well as bacterial and viral DNA and RNA. The PRRs include the surface and cytoplasmic Toll-like receptors (TLRs), NOD-like receptors (NLRs) and other. Their ligation by respective PAMPs leads to activation of multiple forms of inflammamasomes which starts the inflammatory reaction (secretion of proinflammatory cytokines, increased phagocytosis and pathogen killing etc.). Other than that, the mentioned cells of the innate IS kill the pathogens inside themselves, using reactive oxygen species (ROS) and bactericidal proteins and other molecules, and outside (be releasing the bactericidal chemicals to their immediate...
environment or even by ejecting their DNA and associated proteins in the process of NETosis (performed by the neutrophils), where bacteria are trapped, immobilized and then killed. Monocyte/macrophages and especially the DCs are also capable of elaborating the pathogen-derived peptides in a way that makes them possible to be presented to the lymphocytes of adaptive immune system, i.e., to act as antigen-presenting cells (APCs). On the other hand the neutralization or elimination of infecting viruses is the domain of cytotoxic NK cells, which can recognize “alien” viral peptides presented in the context of MHC (HLA) class I on the surface of infected cells end kill such cells releasing membrane-spanning perforins and via them injecting the cells with granzymes (causing the cell death mainly by apoptosis). Another obvious “aleness” comes from our own neoplastically transformed cells. The NK cells and cytotoxic CD8+ T cells can recognize neoplastic (cancerous) cells based on the formation of neoantigens and kill them the same way they kill virus-infected cells [7, 8]. All these defensive activities of the innate IS require effective recognition and killing machinery in respective cell types.

The innate APCs (said DCs and other) present the fragments of proteins elaborated from the engulfed pathogens to the members of adaptive immune system, i.e., T and B lymphocytes, in order to elicit their respective, antigen-specific, reactivities [9, 10].

The T and B lymphocytes have specific receptors for antigenic epitopes presented in the context of MHC/HLA molecules and respond by either producing multiple lymphocyte growth- and differentiation-inducing cytokines (helper CD4+ T cells), activating the cell-killing processes (cytotoxic CD8+ T cells), or making antibodies (immunoglobulins, by B cells and plasma cells). This effector phases are preceded by outburst of massive clonal proliferation of lymphocytes recognizing specific antigens. Another common denominator of adaptive immune response is the manufacturing of memory T and B lymphocytes with characteristic surface phenotypes. These memory cells are clonally expanded and so more numerous than the original naive T or B cells specific for a given antigen; also they are capable of mounting much more vigorous response to an antigen upon the second and consecutive encounters; they are also necessary for effective vaccination.

Finally, one needs to say here that any immune reaction, especially its adaptive branch, is a huge energy- and resources/substrates-consuming process. Therefore it is paramount that it last only until the threat (of spreading infection or cancer) is neutralized. One could say that elimination of the pathogen from the body should be enough; however, such elimination is not always complete and in fact a form of balance appears between the “antigen-oriented” adaptive immunity and the pathogen itself. An example of such balance, very relevant for the topic of this paper, is the infection with cytomegalovirus (CMV) pervading most of human populations and in some exceeding 50% of individuals. This cytopathogenic virus, if rampant as in immunocompromised or immunosuppressed individuals, may damage multiple infected organs leading to their failure and death. However, in a healthy person it is kept at bay by the effort of clones of always active CMV-specific T cells [11-14].

Extensive activity of adaptive immune cells beyond the need associated with pathogen control and/or removal may not only dissipate the body resources but also, by the token of necessary bouts of proliferation of these cells accompanied by reactivation of the telomerase, may lead to neoplastic transformation. Also, it may be conductive to autoimmune reactivity. Thus, the system has built-in safety valves, including: 1. activation induced cell death (AICD), where the lymphocytes respond to stimulation by apoptosis rather than by proliferation, and 2. various populations of regulatory immune cells. These consist first of the regulatory (immunosuppressive) T cells (Tregs), Bregs derived from among the B cells, monocyte-derived Mregs and finally bone-marrow-derived (myeloid-derived) suppressor cells (MDSCs). The Tregs act via humoral factors including cytokines like IL-10 and TGFβ, as well as via direct cytotoxicity and induction of apoptosis (using perforins and granzymes, galectin, or the CD95/CD95L (Fas/Fasl) and PD1/PD1-L systems); they can also reduce costimulation of the effector T cells, and decrease maturation and antigen presentation by the DCs [15]. The Bregs act inter alia by secretion of IL-10 (suppressing the macrophages, DCs and T cells, as well as by at least some of the receptor/ligand pairs mentioned for the Tregs) [16]. Finally the Mregs and MDSCs act along multiple pathways, depending of their origin and target effectors [17-20].

All the above is apparently textbook immunology in a nutshell. However, we need to recapitulate it here in order, on one hand, to highlight the complexity of the intricate IS network which must work in concert and balance to ascertain protection and survival, and on the other hand to facilitate the readers’ understanding of what happens during the IS aging to its different components and what are the consequences of these changes.

1.2. What then are the clinical symptoms of aging of the IS?

With aging, we assist to increased frequency and severity of infectious diseases, both bacterial and viral, aggravated by generally lower response to most vaccines (lower titers of neutralizing antibodies), increased incidence of malignancies (and generally neoplasms), and autoimmune diseases [21-25].

These changes do not accumulate altogether linearly with advancing age; rather, some of the oldest old (centenarians, semi-supercentenarians and supercentenarians) seem to retain relatively robust immune responses, especially the innate one [26-28]. Also, they are not occurring at the same rate in all aging and old individuals. The reasons behind this variability are many, starting from genetics and epigenetics which affect the functionalities of the immune systems. The next important factor is immunobiography of an individual – a term coined by Claudio Franceschi and relating actual functionality (or dys-functionality) of the immune system of an individual with the life-long history of challenges to this person’s immune system (infections, emerging neoplasms, injuries etc.), overlaid upon the mentioned genetic and epigenetic features, aggravated by environmental exposures (toxins, dietary factors etc.) and leading to progressive exhaustion and remodeling of the IS functionalities, culminating in immunosenescence and inflamming [21, 22, 29].

1.3. Mechanisms behind the observed clinical symptoms of the IS aging

1.3.1. Increased ratio of memory to naive T cells

One of the earliest observations concerning the aging of mammalian immune systems is stepwise increase in the numbers and proportions of memory T cells at the expense of dwindling population of naive T lymphocytes. The reasons for this phenomenon are dual. First, naive T cells originate from the thymus, a primary lymphatic organ localized in the mediastinum. There, the bone-marrow-derived T cell precursors go through constitutive steps of maturation and differentiation, eventually yielding the naive T cells with a plethora of TCR specificities (which ascertains the ability of – especially early life – adaptive IS to build an effective response to almost any foreign antigen). At the same time the thymus is the site of severe selection of emerging naïve T cells, aiming at preventing the appearance of self- (or auto-) reactive T cells which could lead to autoimmunization. However, in most mammals studied, including humans, thymus undergoes a process of physiological involution – starting at puberty reduction of size of the organ, replacement of the immunopoietic tissue and stroma with fat tissue, and which manifests as reduced output of new naive thymic emigrant cells, possible to measure and demonstrate by detection of reduced numbers of peripheral T cells containing the so-called TRECs (T cell receptor excision circles) [30-32]. Fewer naive T cells mean lower chance to recognize and effectively react to new, previously unencountered, antigens; this is the case for example with yearly infections with new variants of influenza virus or with current SARS-CoV-2 pandemics.

Interestingly, the extremely long-lived subterranean rodent – the naked mole rat – has recently been shown to have not just one
memory T cells (as is typical for other mammals including humans), but also a few cervical thymus which apparently ascertain constant provision of new naïve T cells, prevent thymic involution until midlife of the mole rats, and in consequence, produce an extreme resistance of these animals to infections and cancers and increase their longevity [33]. Not surprisingly, this discovery yielded support to the search for ways of rejuvenation of our own thymuses as a way of prolonging healthy life.

Decreasing thymic output of naïve T cells after the onset of puberty and involution of the organ is not associated with a decrease in the T cell numbers, even in old individuals. One reason for this is so-called homeostatic naïve T cell proliferation in the periphery [34]. However, it is known for more than a decade, that also the peripherally generated naïve T cells lose proliferative capacities which, apart from other changes, precludes their effective reaction to antigenic challenges [34, 35]. Still, the notion of T cells senescence remains controversial, even if they show features typical for other senescent cells, including reduced or no proliferation, increased expression of SA-β-Gal enzyme, the SASP phenotype, short telomeres and accumulation of H2A.X and H2A.J proteins characterizing the other senescent cells; thus, some authors choose to call these lymphocytes the senescence-associated T (SA-T) cells, rather than senescent T cells [34, 36-38]. Both processes – decreased output of (presumably) functional naïve T cells from the involuting thymus and senescence of peripheral naïve T cells – lead to decreased ability of the IS of the aged individuals to react to new antigenic challenges, be it new variants of cognate pathogens (like the flu virus or SARS-CoV-2) or neoantigens associated with neoplastic transformation of own cells.

Yet, thymic involution is not the only reason behind the shift in the proportions of naïve and memory T cells occurring with advancing age. The second one is the accumulation of rising numbers of memory T cells, being the result of consecutive antigenic challenges, which start at birth and last for the lifetime. These challenges are resulting in the – already mentioned - individual immunobiography of each individual, which in turn results in greatly heterogenous immune responses in the elderly, including varying severity of the diseases, effectiveness of vaccinations etc. [21, 22, 29, 39, 40]. These memory lymphocytes are paramount for effective adaptive immune response to cognate antigens for most of lifespan. However, with aging, also they undergo the effects of time and use, and may become exhausted or (immune)senescent, with both processes leading to decreased response to cognate antigens [41]. Interestingly, recently a new form of memory T cells, called the stem cell memory T cells (TSCM) have been described in humans. As their name calls for, they are fast responders to antigen stimulation, tend to preferentially survive after the neutralization of antigens, can reconstitute the memory cell compartment from their small numbers and may provide protection from specific pathogens for decades [42, 43]. According to the study by Li et al., the CD4+ TSCM numbers in periphery do not change significantly between 18 and 90 years of age, while the numbers of CD8+ TSCM cells are significantly reduced, which likely results in decreased homeostasis (and functionality) of CD8+ T cells, and relatively maintained homeostasis of the CD4+ T cells in old age [42].

1.3.2. Changes in the regulatory immune cells – Tregs and beyond

Thymus is also the source of thymic regulatory T cells (Tregs) which have a role in intrathymic elimination of self-reactive clones of naïve T cells. With aging, also the production of these Tregs decreases, which may be the reason behind increased chance for autoimmune processes (including type 1 autoimmune diseases and elevated production of autoantibodies by the B cells) in the elderly [44, 45].

While Tregs numbers are (for intuitively obvious reasons) reduced with advancing age, these of peripheral Tregs induced during the adaptive response to an antigenic challenge (iTregs) not only do not dwindle, but in fact increase in the elderly. We were among the first to show this phenomenon at the beginning of the 21st century, and were followed by many similar observations [46-52]. This finding may in part explain the decreased effectiveness of the immune responses in the aged (relatively more “braking”). On the other hand, it was demonstrated on a relatively small population of 85+ year-olds that those of them who had increased median frequencies of CCR4+ Tregs had a better 8-year survival rates than their counterparts with lower proportions of these Tregs. This was the first demonstration of a positive correlation between survival and frequency of Tregs in the aged [50]. On the other hand, some observations suggest that, although more numerous, the iTregs of the elderly are less functional, which may be associated with exposure to excessive amounts of ROS [53].

Other regulatory immune cells, including notably the MDSC, but also regulatory phenotypes of macrophages (Mreg), dendritic (DCreg), natural killer (NKreg), and type I natural killer T (NKT) cells are affected by aging and may, therefore, affect the immune responses in the aged [54, 55].

1.3.3. TCR repertoire contraction

One of the main characteristic features of the adaptive immune system is the apparently infinite variability of the antigen receptors (TCR and BCR) generated respectively by somatic recombination and somatic hypermutability of genes coding the component peptides of the receptors, and allowing for detection of (and in consequence response to) myriads of different antigens, coming from pathogenic microorganisms and own transformed cells. This ability seems of paramount importance with the advent of novel, mainly viral, diseases including inter alia the zika, nipah, earlier coronavirus-caused SARS and MERS, and the current COVID-19. Common characteristics of these “new” diseases includes the zoonotic origin and likely we are for many more such diseases challenging our IS. Unfortunately, studies of the T cell receptor repertoire in aging individuals which started in last decade of the 20th century convincingly show that this repertoire is profoundly affected by aging, with apparent clonal expansion of certain variants and reduction (or elimination) of the other [31, 56-59]. The consequence of such changes may only be decreased ability of aging immune systems to respond to certain (classes of) antigens. The mechanisms of this contraction of TCR repertoire in elderly certainly include the decreased output of naïve T cells (equipped with new TCR configuration) by involuting thymus, not balanced by peripheral homeostatic proliferation of these naïve T cell; on the other hand, T cells bearing some TCR variants may become exhausted and then senescent with time and recurrent infection by the same pathogens.

1.3.4. Lack of effector plasticity

Classically, the subtypes of differentiated helper T cells include the Th1, Th2, Th9, Th17, Th22, TFH and Tregs. Recently it was postulated that the antigenic challenges and the needs of the IS for specific subtype to counter the challenge are deciding about the increased proportion of specific subtype and that all of these subtypes form a continuum rather than real, independent T cell classes [60, 61]. With aging, this continuum seems to be broken, as more and more T cells acquire the terminally differentiated phenotype, which compromises the ability of the aging IS to effectively respond to new antigenic challenges [61]. Thus, the aging IS accumulates exhausted T cells, as well as the CD4+CD28low/nul cells with cytotoxic properties, and, as mentioned above, also the activated Tregs. There is a bias towards the Th1 and Th17 types, which at least in part explains increased proinflammatory properties of the system, which secretes more IFNγ, IL-6 and IL-27 contributing to inflammaging [62]. Interestingly, the expansion of cytotoxic CD4+ T cells has been documented in some centenarians which may suggest that these cells are a form of pro-survival adaptation of the aging IS [63]. As mentioned above, these cytotoxic CD4+ lymphocytes are characterized by decreased (or even lack of) expression of the costimulatory molecule CD28, which may be partly a result of their prolonged exposure to proinflammatory environment, mainly higher amounts of TNFa, or be associated with persistent CMV infection [64-66]. One could speculate that partial or even complete loss of costimulatory signal would impede the response of aging T cells to stimulation, especially their ability for...
clonal expansion. We have shown such relation for aging human CD4+ cells, especially prolongation of the period from the initial contact with stimulant to the onset of first mitotic cycle strongly correlating with reduced numbers of CD28 molecules on their surfaces [67, 68].

Aging not only causes (semi)permanent shifts in the proportions of different T cell types, but it also affects the function of these various T cells, modifying their influence on other cells of the aging IS. Thus for example the follicular helper T cells TFH (among other helper T cells) increase their numbers with aging, but lose functionality towards helping the B cells, likely due to defects in intracellular signal transduction [61, 69, 70].

1.3.5. Aging-related modifications of intracellular signal transduction in the immune cells

Reduced numbers of CD28 molecules on aging CD4+ lymphocytes and their relation with modified dynamics of proliferation of these cells directly suggest that the signal transduction processes occurring between the ligated surface antigen receptors (TCR and BCR), costimulators, and inhibitory molecules (including the CTLA-4 and PD-1) and the activation of relevant genes by the transcription factors migrating to the nuclei of activated T cells might be severely affected by aging. Studies of changes of signal transduction over last decades had indeed shown many issues with phosphorylation, dephosphorylation and otherwise processing of consecutive molecules forming links of the chains of signal transduction, as well as with formation and function of the immune synapses [71–83]. The results would be decreased proliferation, cytokine output and general functional imbalance observed for aging T cells [84–86].

We have recently shown one more possibility for signal transduction in aging lymphocytes to be defective. Thus, we have demonstrated that limited, modulating proteolysis effected by ubiquitins, cytoplasmin, calcium-dependent cysteine proteases called calpains is significantly reduced in all aging T and B lymphocytes [87]. Our further, as yet unpublished data indicate that this reduction in calpain amounts and activities is common also for other peripheral immune cells, including monocytes and NK cells. On the other hand we have shown that inhibition of calpains in the resting T cells leads to their decreased proliferation, cytokine secretion, and activation in relation to changed levels of activation of some molecules important for T cell signal transduction, including phospholipase C gamma, p56Lck, NFKB, and ZAP-70, all of which were earlier demonstrated to be affected by aging [88, 89].

Changed activity of calpains in the immune cells of the elderly is an illustration of a broader issue of improper protein manufacturing, maturation, posttranslational modifications, misfolding, aggregation, inefficient removal (by autophagy) etc., which goes under the common heading of modified proteodynamics in aged cells, immune and otherwise [90, 91].

1.3.6. Mitochondrial defects associated with aging

Maintenance of functional proteomes and their more or less immediate functions for a long time (for some memory T cells approaching the length of the lifespan) requires vast amounts of metabolic energy (ATP), in the resting lymphocytes provided mainly by oxidative phosphorylation (OXPHOS), while the activated cells tend to rely on glycolysis (Warburg effect) [91, 92]. It is recognized for more than 4 decades already that aging has a profound effect on mammalian mitochondria, including reduced output of ATP, increased production of ROS (and, consequently, increased oxidative stress) and numerous mutations in mitochondrial (mt)DNA, likely contributing to mentioned dysfunction. Almost the same time had passed from the first reports on reduced ATP output in aging human lymphocytes, attributed to mitochondrial defects [93, 94]. Mitochondria may serve also as a source of proapoptotic signals and this was demonstrated to increase with aging [67, 95].

2. Immunosenesence and inflammaging

Two most characteristic, unique features associated with aging of the IS are immunosenescence and inflammaging.

2.1. Immunosenescence – description, mechanisms and consequences

Immunosenescence is the main factor reducing the effectiveness of both the adaptive and innate immune responses to pathogens, and thus limiting the survival [96]. One has to stress here that immunosenescence should not be confused with cellular senescence seen in many (if not all) other cell types living long enough, even if the factors inducing both states may be similar or even identical [97]. In fact, lymphocytes (or, in that matter, also monocyte/macrophages, dendritic and NK cells) are undergoing the cellular senescence with all due characteristics of such [51, 98]. Thus, senescent lymphocytes would cease proliferation to antigenic (or in vitro mitogenic) stimulation; they would acquire the senescence-associated secretory phenotype (SASP, characterized by increased output of some proinflammatory cytokines), would exhibit increased activity of lyosomal senescence-associated beta-galactosidase (SA-b-Gal) and greatly shortened telomeres [92, 99-101]. Such senescent immune cells stop performing their roles in the immune response to pathogenic challenges, but they remain alive and metabolically active, with time using more space in the “niches” including bone marrow and peripheral lymphatic organs [102, 103]. It was shown that also the hematopoietic stem cells undergo senescence, which likely does reduce the output of immune cell precursors [102, 103].

However one needs to understand that immunosenescence is not only related to the individual fates of lymphocytes (pertinent more to their senescence per se), but also to the population shifts (quantitative and qualitative aging-related changes in the proportion of immune cells with different phenotypes, the most characteristic being the mentioned accumulation of memory at the expense of naive T cells. Deleterious changes would occur in the cells belonging to these shifting populations, in effect leading to decreased effectiveness of such population as a whole. The latter would lead to improper interaction and reactivities of various populations of the immune cells, culminating in the development of aging-related diseases [100]. The most prominent changes would stem from immunosenescence of the CD4+ (helper T cell) compartment, as this is the pivotal lymphocyte population affecting all facets of the immune response.

The abovementioned states of immune (mainly T) cell exhaustion and immunosenescence seem, to the extent, to be a continuum, where the former state is (at least partially) reversible, while the latter is not [104, 105]. At the molecular level, T cell exhaustion reduces the response to antigens, including clonal expansion and secretion of stimulatory cytokines (e.g. IL-2 and IFN-gamma), and is hallmarked by the upregulated expression of co-inhibitory receptors, including PD-1, CTLA-4, LAG-3, ICOS, TIM-3 and KLRG-1. Ligation of these leads to downregulation of signal transduction from the TCR/CD3 complex [41]. Immunosenescence however, at cellular level manifesting itself by cessation of T cell proliferation and secretion of stimulatory cytokines in response to antigenic challenge, short telomeres increased SA-b-Gal and acquisition of the SASP, is phenotypically characterized by increased expression of CTLA-4 and LAG-3, but not PD-1 and TIM-3, and by upregulation of the (also co-inhibitory) T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT) [41]. The acquisition of SASP by senescent lymphocytes and other cells is one of the prerequisites for the parallel process of inflammaging.

2.2. Inflammaging - description, mechanisms and consequences

The term inflammaging, coined in the year 2000 by Claudio Franceschi, means sterile, chronic, low-grade inflammation manifesting mainly by elevated levels of proinflammatory cytokines not associated with any apparent/detectable challenge to the cytokine-manufacturing
infection by a viral pathogen (SARS-CoV-2) leading to acute inflam-
proinflammatory and anti-inflammatory reactions of the immune sys-
ems which likely are fueled by both immunosenescence and
inflammatory processes [111]. Thus, they are a form of imbalance between
proinflammatory and anti-inflammatory reactions of the immune sys-
tems which likely are fueled by both immunosenescence and
inflammaging.

3. COVID-19 – why it is more severe and deadly in elderly?

A special paragraph in this paper should be devoted to the current
demics of COVID-19, which is due to so far poorly controllable
fection by a viral pathogen (SARS-CoV-2) leading to acute inflam-
atory reactions in the (mainly) lungs and other organs of the patients.
One of the symptoms of COVID-19 is the “cytokine storm” – sudden
output of massive quantities of different proinflammatory cytokines: 
interleukin (IL)–6, tumor necrosis factor α (TNF-α), IL-1, monocyte 
 chemoattractant protein-1 (MCP-1) and IL-10. Cytokine storm is a
hyperinflammatory immune response due to the release of large amount
of reactive oxygen species (ROS) from infected epithelial cells. ROS 
stimulate the synthesis of NLPR3 inflammasome and activation of the 
transcription factor NF-kB), which contribute to secretion of proin-
flammatory cytokines [112].

It was noticed early into the pandemics, that the death toll and the 
score of most severe cases were the highest among the elderly. This 
epidemiological observation still holds, despite the fact that the newer
variants of SARS-CoV-2 eagerly infect, cause symptomatic and severe 
COVID-19 also in the rising numbers of middle-aged and even young people.

Severe COVID-19 is a consequence of raging inflammation, 
destructive to the tissue of lungs and other affected organs. Eventually it 
may result in (multi)organ failure and death. Obviously, if the infection 
befalls to aging individuals, its course will depend on the current state of 
their organs, which greatly vary from apparently good health similar 
to that of much younger people to worse health due to one or more 
chronic diseases described above as the ARDs. Thus, aging of the im-
une system itself would both directly and indirectly affect the course of 
COVID-19. The first reason would be the decreased ability of the aging IS 
to recognize the new virus, SARS-CoV-2, due to greatly reduced output 
of new naive T cells from involuted thymus [113, 114]. Next, the
immunosenesence - remodeled IS of the elderly individuals would 
reduce its ability to build effective response to the virus, which exists in 
significantly higher load in the elderly, especially burdened with 
advanced immunosenescence [41, 115]. Aging of all the IS components, 
both the innate and adaptive, is responsible for poor neutralizing 
response to SARS-CoV-2, observed as low titers of neutralizing anti-
bodies, lower numbers of NK and cytotoxic CD8+ T cells recognizing 
and killing infected cells [116, 117]. This advanced IS aging in severe 
COVID-19 patients manifests itself inter alia by short lymphocyte telo-
meres [118, 119]. This may indicate the role of immunobiography for 
COVID-19 severity; those with higher proportions of exhausted and se-
nescent immune cells due to more immunological challenges during 
whole life preceding the infection would be more susceptible.

Decreased neutralizing capacity of the aging IS towards the SARS-
CoV-2 is only one side of the coin being symptomatic, severe COVID-
19. The other side is the uncontrolled secretion of high levels of proin-
flammatory cytokines known a cytokine storm. It consists of massive 
release of interferons, interleukins (mainly IL-1 and IL-6), tumor-ne-
crosis factors, chemokines and other mediators in relatively short time. 
Appearance of all these mediators leads to hyperinflammation, aggra-
mates the multi-organ damage, first of all leading to the acute respiratory 
distress syndrome (ARDS) and respiratory failure, also by induction of 
the coagulation cascade [120]. The likely culprit behind cytokine storm 
is the release of oxygen free radicals (ROS) and prostaglandin E2 (PGE2)
by the infected cells [121–123]. The ROS stimulate the synthesis of 
NLPR3 inflammasome and nuclear factor (NF-kB) in macrophages and 
neutrophils; both factors participate in development of the cytokine 
storm [124, 125]. These events, overlaid on the background of inflam-
maging (as mentioned above, participating in the development of 
ARDS), may in fact lead to the buildup of strong innate immune re-
ponses in elderly, possibly facilitating and amplifying the 
hyperinflammation.

Considering the above, one needs to ask the question about suc-
cessful vaccination of elderly against the SARS-CoV-2 (and, in fact, any 
other infectious disease). On one hand we already have very successful 
vaccines generated using different platforms (including the newest 
mRNA platform). On the other hand however, aging immune system 
loses ability to efficiently respond to antigenic challenges, also those by 
the antigens included in the vaccines. This leads to lower, and more 
rapidly disappearing, titers of neutralizing antibodies. A remedy could 
be in different formulation of vaccines offered to the older groups of 
people, including increased doses of pathogen antigens and/or different 
adjuvants; this technique has proven itself effective in the vaccines 
against shingles or influenza directed at older population [22, 25].

4. Can we boost the balanced immune response in the elderly?

The answer is “yes” and in many ways, including – where possible
-change in the lifestyle to more physically and mentally active, modifi-
cation of diet to more nutritional, normalizing the composition of gut 
microbiome to prevent proinflammatory dysbiosis as well as careful 
pharmacological interventions (utilizing the beneficial part of the 
hormesis curve) [126–129]. An important way to prevent early immu-
ynosence and inflammaging would be to influence immunobiog-
raphy by early detection and successful elimination of viral, bacterial 
and other pathogens, widespread prevention of infectious diseases by 
polyvaccination, early anti-inflammatory treatment of emerging in-
flammatory events [130]. However this preventive approach can only be 
explored in full for young(er) generations, as it would be less effective 
in those with already manifest inflammaging and immunosenescence. Still, 
all its aspects may ameliorate and slow down the effects of the IS aging 
even in older individuals, where they could be amplified by successful 
removal of senescent cells using senolytics, and regulation of the 
microbiome by pre-, pro- and symbiotics.

5. Immunosenescence and inflammaging as an adaptation

Yet, despite all the detrimental effects of immunosenescence and
inflammaging (culminating in ARDs including COVID-19), these
processes, intrinsic to the aging of the immune system, have yet another side. Accumulating data suggest that both immunosenescence and inflamming are forms of adaptation of an aging organism to other effects of aging on its ability to cope with pathogens and neoplasms, including those depending on aging of the endocrine and neurological functions which, together with immunity, form the neuro-endocrine-immunological axis. In this concept, immunosenescence (similarly to cellular senescence in general) would decrease probabilities of neoplastic transformation of the immune cells and their precursors, despite life-long accumulation of cancerogenic exposures. On the other hand, the same immunosenescence decreases the immune systems’ control over infections, which by itself is anti-survival. Here comes inflamming, which—with dwindling adaptive response to pathogens—augments (to the extent) the innate responses, thus extending the lifespan [59, 92, 131]. The same inflamming (increased proinflammatory cytokine levels) can homeostatically trigger an anti-inflammatory response which would then counteract the age-related accumulation of pro-inflammatory events [21, 92, 99, 132, 139]. However, as mentioned above, too much inflammation/inflamming features accumulating over time means (chronic) inflammatory disease(s) (ARDs) characteristic for unsuccessful aging.

Thus, considering the modifying, preventive and therapeutic approaches towards issues related with aging of the immune system we need to remember that neither immunosenescence nor inflamming is purely detrimental.

6. Hallmarks of T cell aging

Recently (May 2021) Mittelbrunn and Kroemer had integrated all the above described features of the aging immune system (especially T cells) and proposed the 10 hallmarks of T cell aging, consisting of 4 primary hallmarks (involvement of the thymus, genetic and epigenetic changes, mitochondrial dysfunction and loss of proteostasis), four secondary hallmarks (involution of the thymus, genetic and epigenetic changes, accumulation of pro-inflammatory events [21, 39, 92, 99, 132, 133]). However, as mentioned above, too much inflammation/inflamming features accumulating over time means (chronic) inflammatory disease(s) (ARDs) characteristic for unsuccessful aging.

Thus, considering the modifying, preventive and therapeutic approaches towards issues related with aging of the immune system we need to remember that neither immunosenescence nor inflamming is purely detrimental.

7. Conclusions

Aging is a complex, multi-faceted process of accumulating changes and continuous adaptation of the body systems to these changes. This statement is especially true for aging of the immune system, where deleterious changes leading to decreased reactivity to, and in consequence neutralization/elimination of pathogens of external and internal origins are accompanied by adaptation to these changes. Main features of the aging immune systems, i.e., immunosenescence and inflamming, are also adaptive and serve to prolong the individual life, provided they are balance in the aging organism. However, their imbalance leads to predominance of inflammatory reactions, culminating in chronic, inflammatory, eventually debilitating, aging-related diseases. One of such diseases is COVID-19. Deeper understanding of the processes underlying the aging of immune system and its effects on survival may yield targets for mitigation of the process of IS aging and in consequence prolongation of healthspan, e.g. by pharmacological, dietary, immunological and other interventions.

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