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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 inflammasomes 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

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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 "alienness" 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 machineries 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 naïve 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 dysfunctionality) 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 inflammaging [21, 22, 29].

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

1.3.1. Increased ratio of memory to naïve 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 naïve T lymphocytes. The reasons for this phenomenon are dual. First, naïve 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 naïve 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 naïve 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 naïve 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

mediastinal thymus (as is typical for other mammals including humans), but also a few cervical thymi 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 (T_{SCM}) 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+ T_{SCM} numbers in periphery do not change significantly between 18 and 90 years of age, while the numbers of CD8+ T_{SCM} 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 (tTregs) which have a role in intrathymic elimination of self-reactive clones of naïve T cells. With aging, also the production of these tTregs decreases, which may be the reason behind increased chance for autoimmune processes (including more autoreactive T cells and elevated production of autoantibodies by the B cells) in the elderly [44, 45].

While tTregs 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 II 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 IFNβ, IL-6 and IL-27 contributing to inflammaging [62]. Interestingly, the expansion of cytotoxic CD4+ T cells has been documented in supercentenarians 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 TNFα, 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), co-receptors, 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 ubiquitous, cytoplasmic, 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, NFκB, 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 is 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. Immunosenescence 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 lysosomal 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 naïve 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

cells [21, 51, 106-109]. In extended explanation the inflammaging is the consequence of multiple forms of life-long, permanent or periodic, stresses. The stressors include antigenic challenges, metabolic modifications, oxidative stress, physical and chemical insults, accumulation of internal (cell- and matrix-derived) garbage, called the garb-aging, and modification of gut and other microbiota towards the state of dysbiosis [110]. Each and all of these, above certain thresholds – especially being crossed in a short time - would (and do) elicit a full-fledged, acute inflammatory reaction. However here we talk not about acute, high level challenges but about much smaller ones, extended back in time even to the early years of age. On top of these we have the whole, already mentioned, immunobiography of each and every one of us, individualizing the features presented by the immune systems of different individuals. Thus, inflammaging, as immunosenescence, does not appear only in the aging or old organism. Rather, both processes slowly – with age – rise from being altogether undetectable to detectable by the assessment of qualitative and quantitative properties of various cellular and humoral components of the immune system and finally to manifest their consequences in the form of aging-related diseases (ARDs) [108]. In fact, all of the major ARDs, including the atherosclerosis and its clinical complications: ischemic (coronary) heart disease and ischemic stroke, malignancies, neurodegenerative diseases leading to dementia (especially the Alzheimer disease and vascular dementia), metabolic syndrome (type 2 diabetes, obesity, arterial hypertension), chronic respiratory disease (COPD) and finally COVID-19 have a common denominator: pathomechanisms of all of them include chronic inflammatory processes [111]. Thus, they are a form of imbalance between proinflammatory and anti-inflammatory reactions of the immune systems 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 pandemics of COVID-19, which is due to so far poorly controllable infection by a viral pathogen (SARS-CoV-2) leading to acute inflammatory 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 NLRP3 inflammasome and activation of the transcription factor NF-kB), which contribute to secretion of proinflammatory 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 organisms, 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 immune 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 naïve T cells from involuted thymus [113, 114]. Next, the immunosenescence - 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 antibodies, 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 telomeres [118, 119]. This may indicate the role of immunobiography for COVID-19 severity; those with higher proportions of exhausted and senescent 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 proinflammatory cytokines known a cytokine storm. It consists of massive release of interferons, interleukins (mainly IL-1 and IL-6), tumor-necrosis factors, chemokines and other mediators in relatively short time. Appearance of all these mediators leads to hyperinflammation, aggravates 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 NLRP3 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 inflammaging (as mentioned above, participating in the development of ARDs), may in fact lead to the buildup of strong innate immune responses in elderly, possibly facilitating and amplifying the hyperinflammation.

Considering the above, one needs to ask the question about successful 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, modification 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 immunosenescence and inflammaging would be to influence immunobiography 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 inflammatory 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 synbiotics.

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 inflammaging 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 inflammaging, which – with dwindling adaptive response to pathogens – augments (to the extent) the innate responses, thus extending the lifespan [39, 92, 131]. The same inflammaging (increased proinflammatory cytokine levels) can homeostatically trigger an anti-inflammatory response which would then counteract the age-related accumulation of pro-inflammatory events [21, 39, 92, 99, 132, 133]. However, as mentioned above, too much inflammation/inflammaging 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 inflammaging 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 (involution of the thymus, genetic and epigenetic changes, mitochondrial dysfunction and loss of proteostasis), four secondary hallmarks (naive-memory imbalance, reduction of the TCR repertoire, T cell senescence, and lack of effector plasticity) and finally two integrative hallmarks – immunodeficiency (immunosenescence) and inflammaging [61]. All of these were reviewed in this paper.

The ten hallmarks of T cell aging described above directly stem from the concept of already classical 9 hallmarks of aging which seem to be pertinent to all mammals and actually include five of these. Thus, the nine hallmarks of aging in turn include genomic instability and epigenetic alterations, loss of proteostasis, telomere attrition, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence, stem cell exhaustion and altered intercellular communication [134]. Of course, the immune cells follow not only the five abovementioned aging hallmarks, but also the remaining four. Thus, intense bouts of clonal proliferation of lymphocytes responding to antigens are leading to measurable, significant shortening (attrition) of their telomeres, despite the temporarily upregulated activity of telomerase (which is also lower with aging) [135, 136]. Interestingly, T cell telomeres of rheumatoid arthritis (RA) patients are shorter than these of healthy individuals of the same age, lending credibility to the theory envisaging RA as a disease accompanied by accelerated immune system cells' aging, likely associated with specific genetic makeup [32, 137].

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 this changes. Main features of the aging immune systems, i.e., immunosenescence and inflammaging, 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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References

[1] E.J. Douzery, E.A. Snell, E. Bapteste, F. Delsuc, H. Philippe, The timing of eukaryotic evolution: does a relaxed molecular clock reconcile proteins and fossils? Proc. Natl. Acad. Sci. U. S. A. 101 (43) (2004) 15386–15391.
[2] R.W. Piast, Shannon's information, Bernal's biopoiesis and Bernoulli distribution as pillars for building a definition of life, J. Theor. Biol. 470 (2019) 101–107.
[3] E.A. Groisman, J. Casadesus, The origin and evolution of human pathogens, Mol. Microbiol. 56 (1) (2005) 1–7.
[4] J.M. Pearce-Duvet, The origin of human pathogens: evaluating the role of agriculture and domestic animals in the evolution of human disease, Biol. Rev. Camb. Philos. Soc. 81 (3) (2006) 369–382.
[5] N. Yutin, M.Y. Wolf, Y.I. Wolf, E.V. Koonin, The origins of phagocytosis and eukaryogenesis, Biol. Direct 4 (2009) 9.
[6] A.I. Tauber, Metchnikoff and the phagocytosis theory, Nat. Rev. Mol. Cell Biol. 4 (11) (2003) 897–901.
[7] T.N. Schumacher, R.D. Schreiber, Neoantigens in cancer immunotherapy, Science 348 (6230) (2015) 69–74.
[8] L.B. Alexandrov, S. Nik-Zainal, D.C. Wedge, S.A. Aparicio, S. Behjati, A. V. Biankin, G.R. Bignell, N. Bolli, A. Borg, A.L. Borresen-Dale, S. Boyault, B. Burkhardt, A.P. Butler, C. Caldas, H.R. Davies, C. Desmedt, R. Eils, J.E. Eyfjord, J.A. Foekens, M. Greaves, F. Hosoda, B. Hutter, T. Ilicic, S. Imbeaud, M. Imielinski, N. Jager, D.T. Jones, D. Jones, S. Knappskog, M. Kool, S. R. Lakhani, C. Lopez-Otin, S. Martin, N.C. Munshi, H. Nakamura, P.A. Northcott, M. Pajic, E. Papaemmanuil, A. Paradiso, J.V. Pearson, X.S. Puente, K. Raine, M. Ramakrishna, A.L. Richardson, J. Richter, P. Rosenstiel, M. Schlesner, T. N. Schumacher, P.N. Span, J.W. Teague, Y. Totoki, A.N. Tutt, R. Valdes-Mas, M. M. van Buuren, L. van 't Veer, A. Vincent-Salomon, N. Waddell, L.R. Yates, I. Australian Pancreatic Cancer Genome, I.B.C. Consortium, I.M.-S. Consortium, I. PedBrain, J. Zucman-Rossi, P.A. Futreal, U. McDermott, P. Lichter, M. Meyerson, S.M. Grimmond, R. Siebert, E. Campo, T. Shibata, S.M. Pfister, P. J. Campbell, M.R. Stratton, Signatures of mutational processes in human cancer, Nature 500 (7463) (2013) 415–421.
[9] B.A. Heesters, C.E. van der Poel, A. Das, M.C. Carroll, Antigen Presentation to B Cells, Trends Immunol. 37 (12) (2016) 844–854.
[10] P. Guermonprez, J. Valladeau, L. Zitvogel, C. Thery, S. Amigorena, Antigen presentation and T cell stimulation by dendritic cells, Annu. Rev. Immunol. 20 (2002) 621–667.
[11] Q. Ouyang, W.M. Wagner, D. Voehringer, A. Wikby, T. Klatt, S. Walter, C. A. Muller, H. Pircher, G. Pawelec, Age-associated accumulation of CMV-specific CD8+ T cells expressing the inhibitory killer cell lectin-like receptor G1 (KLRG1), Exp. Gerontol 38 (8) (2003) 911–920.
[12] S. Koch, R. Solana, R.O. Dela, G. Pawelec, Human cytomegalovirus infection and T cell immunosenescence: a mini review, Mech. Ageing Dev 127 (6) (2006) 538–543.
[13] S. Vasto, G. Colonna-Romano, A. Larbi, A. Wikby, C. Caruso, G. Pawelec, Role of persistent CMV infection in configuring T cell immunity in the elderly, Immun. Ageing 4 (2007) 2, 2.
[14] S. Koch, A. Larbi, D. Ozcelik, R. Solana, C. Gouttefangeas, S. Attig, A. Wikby, J. Strindhall, C. Franceschi, G. Pawelec, Cytomegalovirus infection: a driving force in human T cell immunosenescence, Ann. N. Y. Acad. Sci 1114 (2007) 23–35, 23-35.
[15] A.N. Thorburn, P.M. Hansbro, Harnessing regulatory T cells to suppress asthma: from potential to therapy, Am. J. Respir. Cell Mol. Biol. 43 (5) (2010) 511–519.
[16] W. van de Veen, B. Stanic, O.F. Wirz, K. Jansen, A. Globinska, M. Akdis, Role of regulatory B cells in immune tolerance to allergens and beyond, J. Allergy Clin. Immunol. 138 (3) (2016) 654–665.
[17] G. Pawelec, E. Picard, V. Bueno, C.P. Verschoor, S. Ostrand-Rosenberg, MDSCs, ageing and inflammageing, Cell. Immunol. 362 (2021), 104297.
[18] S.L. Orozco, S.P. Canny, J.A. Hamerman, Signals governing monocyte differentiation during inflammation, Curr. Opin. Immunol. 73 (2021) 16–24.
[19] P.J. Murray, Immune regulation by monocytes, Semin. Immunol. 35 (2018) 12–18.
[20] N. Dilek, N. Poirier, C. Usal, B. Martinet, G. Blancho, B. Vanhove, Control of transplant tolerance and intragraft regulatory T cell localization by myeloid-derived suppressor cells and CCL5, J. Immunol. 188 (9) (2012) 4209–4216.
[21] T. Fulop, A. Larbi, G. Pawelec, A. Khalil, A.A. Cohen, K. Hirokawa, J. M. Witkowski, C. Franceschi, Immunology of Aging: the Birth of Inflammaging, Clin. Rev. Allergy Immunol. (2021).

[22] A. Ciabattini, C. Nardini, F. Santoro, P. Garagnani, C. Franceschi, D. Medaglini, Vaccination in the elderly: the challenge of immune changes with aging, Semin. Immunol. 40 (2018) 83–94.
[23] G. Pawelec, A. Bronikowski, S.C. Cunnane, L. Ferrucci, C. Franceschi, T. Fulop, P. Gaudreau, V.N. Gladyshev, E.S. Gonos, V. Gorbunova, B.K. Kennedy, A. Larbi, J.F. Lemaitre, G.H. Liu, A.B. Maier, J.A. Morais, O.T. Nobrega, A. Moskalev, M. O. Rikkert, A. Seluanov, A.M. Senior, S. Ukraintseva, Q. Vanhaelen, J. Witkowski, A.A. Cohen, The conundrum of human immune system "senescence", Mech. Ageing Dev. 192 (2020), 111357.
[24] N.P. Weng, G. Pawelec, Research on immunity and ageing comes of age, Immun Ageing 16 (2019) 8.
[25] M.K. Andrew, S.K. Bowles, G. Pawelec, L. Haynes, G.A. Kuchel, S.A. McNeil, J. E. McElhaney, Influenza Vaccination in Older Adults: recent Innovations and Practical Applications, Drugs Aging 36 (1) (2019) 29–37.
[26] C.R. Balistreri, G. Candore, G. Accardi, M. Bova, S. Buffa, M. Bulati, G.I. Forte, F. Listi, A. Martorana, M. Palmeri, M. Pellicano, L. Vaccarino, L. Scola, D. Lio, G. Colonna-Romano, Genetics of longevity. data from the studies on Sicilian centenarians, Immun Ageing 9 (1) (2012) 8.
[27] I. Martinez de Toda, I. Mate, C. Vida, J. Cruces, M. De la Fuente, Immune function parameters as markers of biological age and predictors of longevity, Aging (Albany NY) 8 (11) (2016) 3110–3119.
[28] P. Sansoni, R. Vescovini, F. Fagnoni, C. Biasini, F. Zanni, L. Zanlari, A. Telera, G. Lucchini, G. Passeri, D. Monti, C. Franceschi, M. Passeri, The immune system in extreme longevity, Exp. Gerontol. 43 (2) (2008) 61–65.
[29] C. Franceschi, S. Salvioli, P. Garagnani, M. de Eguileor, D. Monti, M. Capri, Immunobiography and the Heterogeneity of Immune Responses in the Elderly: a Focus on Inflammaging and Trained Immunity, Front. Immunol. 8 (2017) 982.
[30] L. Al-Harthi, G. Marchetti, C.M. Steffens, J. Poulin, R. Sekaly, A. Landay, Detection of T cell receptor circles (TRECs) as biomarkers for de novo T cell synthesis using a quantitative polymerase chain reaction-enzyme linked immunosorbent assay (PCR-ELISA), J. Immunol. Methods 237 (1–2) (2000) 187–197.
[31] K. Naylor, G. Li, A.N. Vallejo, W.W. Lee, K. Koetz, E. Bryl, J. Witkowski, J. Fulbright, C.M. Weyand, J.J. Goronzy, The influence of age on T cell generation and TCR diversity, J. Immunol 174 (11) (2005) 7446–7452.
[32] K. Koetz, E. Bryl, K. Spickschen, W.M. O'Fallon, J.J. Goronzy, C.M. Weyand, T cell homeostasis in patients with rheumatoid arthritis, Proc. Natl. Acad. Sci. U. S. A 97 (16) (2000) 9203–9208.
[33] S. Emmrich, F. Tolibzoda Zakusilo, A. Trapp, X. Zhou, Q. Zhang, E.M. Irving, M. G. Drage, Z. Zhang, V.N. Gladyshev, A. Seluanov, V. Gorbunova, Ectopic cervical thymi and no thymic involution until midlife in naked mole rats, Aging Cell 20 (10) (2021) e13477.
[34] N. Minato, M. Hattori, Y. Hamazaki, Physiology and pathology of T-cell aging, Int. Immunol. 32 (4) (2020) 223–231.
[35] S. Ferrando-Martinez, E. Ruiz-Mateos, A. Hernandez, E. Gutierrez, M. Rodriguez-Mendez Mdel, A. Ordonez, M. Leal, Age-related deregulation of naive T cell homeostasis in elderly humans, Age (Dordr) 33 (2) (2011) 197–207.
[36] S. Tahir, Y. Fukushima, K. Sakamoto, K. Sato, H. Fujita, J. Inoue, T. Uede, Y. Hamazaki, M. Hattori, N. Minato, A CD153+CD4+ T follicular cell population with cell-senescence features plays a crucial role in lupus pathogenesis via osteopontin production, J. Immunol. 194 (12) (2015) 5725–5735.
[37] K. Contrepois, C. Coudereau, B.A. Benayoun, N. Schuler, P.F. Roux, O. Bischof, R. Courbeyrette, C. Carvalho, J.Y. Thuret, Z. Ma, C. Derbois, M.C. Nevers, H. Volland, C.E. Redon, W.M. Bonner, J.F. Deleuze, C. Wiel, D. Bernard, M. P. Snyder, C.E. Rube, R. Olaso, F. Fenaille, C. Mann, Histone variant H2A.J accumulates in senescent cells and promotes inflammatory gene expression, Nat. Commun. 8 (2017) 14995.
[38] R.I. Martinez-Zamudio, H.K. Dewald, T. Vasilopoulos, L. Gittens-Williams, P. Fitzgerald-Bocarsly, U. Herbig, Senescence-associated beta-galactosidase reveals the abundance of senescent CD8+ T cells in aging humans, Aging Cell 20 (5) (2021) e13344.
[39] T. Fulop, A. Larbi, K. Hirokawa, A.A. Cohen, J.M. Witkowski, Immunosenescence is both functional/adaptive and dysfunctional/maladaptive, Semin. Immunopathol. (2020).
[40] M. Banic, S. Plesko, M. Urek, Z. Babic, D. Kardum, Immunosenescence, Inflammaging and Resilience: an Evolutionary Perspective of Adaptation in the Light of COVID-19 Pandemic, Psychiatr Danub 33 (Suppl 4) (2021) 427–431.
[41] L.L. Cunha, S.F. Perazzio, J. Azzi, P. Cravedi, L.V. Riella, Remodeling of the Immune Response With Aging: immunosenescence and Its Potential Impact on COVID-19 Immune Response, Front. Immunol. 11 (2020) 1748.
[42] M. Li, D. Yao, X. Zeng, D. Kasakovski, Y. Zhang, S. Chen, X. Zha, Y. Li, L. Xu, Age related human T cell subset evolution and senescence, Immun Ageing 16 (2019) 24.
[43] C. Stemberger, M. Neuenhahn, F.E. Gebhardt, M. Schiemann, V.R. Buchholz, D. H. Busch, Stem cell-like plasticity of naive and distinct memory CD8+ T cell subsets, Semin. Immunol. 21 (2) (2009) 62–68.
[44] C. Dejaco, C. Duftner, M. Schirmer, Are regulatory T-cells linked with aging? Exp. Gerontol. 41 (4) (2006) 339–345.
[45] A.V. Churov, K.Y. Mamashov, A.V. Novitskaia, Homeostasis and the functional roles of CD4(+) Treg cells in aging, Immunol. Lett. 226 (2020) 83–89.
[46] E. Bryl, M. Gazda, J. Foerster, J.M. Witkowski, Age-related increase of frequency of a new, phenotypically distinct subpopulation of human peripheral blood T cells expressing lowered levels of CD4, Blood 98 (4) (2001) 1100–1107.
[47] E. Bryl, J.M. Witkowski, Decreased proliferative capability of CD4(+) cells of elderly people is associated with faster loss of activation-related antigens and accumulation of regulatory T cells, Exp. Gerontol 39 (4) (2004) 587–595.
[48] R. Simone, A. Zicca, D. Saverino, The frequency of regulatory CD3+CD8+CD28-CD25+ T lymphocytes in human peripheral blood increases with age, J Leukoc Biol 84 (6) (2008) 1454–1461.
[49] L. Wang, Y. Xie, L.J. Zhu, T.T. Chang, Y.Q. Mao, J. Li, An association between immunosenescence and CD4(+)CD25(+) regulatory T cells: a systematic review, Biomed. Environ. Sci. 23 (4) (2010) 327–332.
[50] E. Derhovanessian, S. Chen, A.B. Maier, K. Hahnel, A.J. de Craen, H. Roelofs, R. Westendorp, G. Pawelec, CCR4+ Regulatory T Cells Accumulate in the Very Elderly and Correlate With Superior 8-Year Survival, J. Gerontol. A Biol. Sci. Med. Sci. 70 (8) (2015) 917–923.
[51] A. Bektas, S.H. Schurman, R. Sen, L. Ferrucci, Human T cell immunosenescence and inflammation in aging, J Leukoc Biol 102 (4) (2017) 977–988.
[52] A. Batista-Duharte, A. Pera, S.F. Alino, R. Solana, Regulatory T cells and vaccine effectiveness in older adults. Challenges and prospects, Int. Immunopharmacol. 96 (2021), 107761.
[53] Z. Guo, G. Wang, B. Wu, W.C. Chou, L. Cheng, C. Zhou, J. Lou, D. Wu, L. Su, J. Zheng, J.P. Ting, Y.Y. Wan, DCAF1 regulates Treg senescence via the ROS axis during immunological aging, J. Clin. Invest. 130 (11) (2020) 5893–5908.
[54] A. Salminen, K. Kaarniranta, A. Kauppinen, Immunosenescence: the potential role of myeloid-derived suppressor cells (MDSC) in age-related immune deficiency, Cell. Mol. Life Sci. 76 (10) (2019) 1901–1918.
[55] A. Salminen, Activation of immunosuppressive network in the aging process, Ageing Res. Rev. 57 (2020), 100998.
[56] D.N. Posnett, R. Sinha, S. Kabak, C. Russo, Clonal populations of T cells in normal elderly humans: the T cell equivalent to "benign monoclonal gammapathy", J. Exp. Med. 179 (2) (1994) 609–618.
[57] R. Schwab, P. Szabo, J.S. Manavalan, M.E. Weksler, D.N. Posnett, C. Pannetier, P. Kourilsky, J. Even, Expanded CD4+ and CD8+ T cell clones in elderly humans, J. Immunol. 158 (9) (1997) 4493–4499.
[58] C.L. Mackall, R.E. Gress, Thymic aging and T-cell regeneration, Immunol. Rev. 160 (1997) 91–102.
[59] A. Wack, A. Cossarizza, S. Heltai, D. Barbieri, S. D'Addato, C. Fransceschi, P. Dellabona, G. Casorati, Age-related modifications of the human alphabeta T cell repertoire due to different clonal expansions in the CD4+ and CD8+ subsets, Int. Immunol. 10 (9) (1998) 1281–1288.
[60] J.J.P. van Beek, M. Rescigno, E. Lugli, A fresh look at the T helper subset dogma, Nat. Immunol. 22 (2) (2021) 104–105.
[61] M. Mittelbrunn, G. Kroemer, Hallmarks of T cell aging, Nat. Immunol. 22 (6) (2021) 687–698.
[62] Y. Elyahu, I. Hekselman, I. Eizenberg-Magar, O. Berner, I. Strominger, M. Schiller, K. Mittal, A. Nemirovsky, E. Eremenko, A. Vital, E. Simonovsky, V. Chalifa-Caspi, N. Friedman, E. Yeger-Lotem, A. Monsonego, Aging promotes reorganization of the CD4 T cell landscape toward extreme regulatory and effector phenotypes, Sci. Adv. 5 (8) (2019) eaaw8330.
[63] K. Hashimoto, T. Kouno, T. Ikawa, N. Hayatsu, Y. Miyajima, H. Yabukami, T. Terooatea, T. Sasaki, T. Suzuki, M. Valentine, G. Pascarella, Y. Okazaki, H. Suzuki, J.W. Shin, A. Minoda, I. Taniuchi, H. Okano, Y. Arai, N. Hirose, P. Carninci, Single-cell transcriptomics reveals expansion of cytotoxic CD4 T cells in supercentenarians, Proc. Natl. Acad. Sci. U. S. A. 116 (48) (2019) 24242–24251.
[64] E. Bryl, A.N. Vallejo, C.M. Weyand, J.J. Goronzy, Down-regulation of CD28 expression by TNF-alpha, J. Immunol 167 (6) (2001) 3231–3238.
[65] A.N. Vallejo, E. Bryl, K. Klarskov, S. Naylor, C.M. Weyand, J.J. Goronzy, Molecular basis for the loss of CD28 expression in senescent T cells, J. Biol. Chem 277 (49) (2002) 46940–46949.
[66] A. Bano, A. Pera, A. Almoukayed, T.H.S. Clarke, S. Kirmani, K.A. Davies, F. Kern, CD28 (null) CD4 T-cell expansions in autoimmune disease suggest a link with cytomegalovirus infection, F1000Res 8 (2019).
[67] J.M. Witkowski, E. Bryl, Paradoxical age-related cell cycle quickening of human CD4(+) lymphocytes: a role for cyclin D1 and calpain, Exp. Gerontol. 39 (4) (2004) 577–585.
[68] E. Bryl, J.M. Witkowski, Decreased proliferative capability of CD4(+) cells of elderly people is associated with faster loss of activation-related antigens and accumulation of regulatory T cells, Exp. Gerontol. 39 (4) (2004) 587–595.
[69] J.S. Lefebvre, A.R. Masters, J.W. Hopkins, L. Haynes, Age-related impairment of humoral response to influenza is associated with changes in antigen specific T follicular helper cell responses, Sci. Rep. 6 (2016) 25051.
[70] J.J. Goronzy, G. Li, M. Yu, C.M. Weyand, Signaling pathways in aged T cells - a reflection of T cell differentiation, cell senescence and host environment, Semin. Immunol. 24 (5) (2012) 365–372.
[71] A.Le Page, G. Dupuis, A. Larbi, J.M. Witkowski, T. Fulop, Signal transduction changes in CD4(+) and CD8(+) T cell subpopulations with aging, Exp. Gerontol. 105 (2018) 128–139.
[72] T. Fulop, A.Le Page, C. Fortin, J.M. Witkowski, G. Dupuis, A. Larbi, Cellular signaling in the aging immune system, Curr. Opin. Immunol. 29 (2014) 105–111.
[73] T. Fulop, J.M. Witkowski, A.Le Page, C. Fortin, G. Pawelec, A. Larbi, Intracellular signalling pathways: targets to reverse immunosenescence, Clin. Exp. Immunol. 187 (1) (2017) 35–43.
[74] L. Robert, T. Fulop, Aging of cell communication: loss of receptor function, Interdiscip Top Gerontol 39 (2014) 142–162.
[75] A. Larbi, G. Pawelec, S.C. Wong, D. Goldeck, J.J. Tai, T. Fulop, Impact of age on T cell signaling: a general defect or specific alterations? Ageing Res. Rev. 10 (3) (2011) 370–378.
[76] T. Fulop, G. Barabas, Z. Varga, J. Csongor, M. Hauck, S. Szucs, I. Seres, A. Mohacsi, D. Kekessy, J.P. Despont, Transmembrane signaling changes with aging, Ann. N. Y. Acad. Sci 673 (1992) 165–171, 165-171.

[77] T. Fulop, G. Barabas, Z. Varga, C. Jozsef, S. Csabina, S. Szucs, I. Seres, E. Szikszay, Z. Jeney, A. Penyige, Age-dependent changes in transmembrane signalling: identification of G proteins in human lymphocytes and polymorphonuclear leukocytes, Cell Signal 5 (5) (1993) 593–603.
[78] T. Fulop, Signal transduction changes in granulocytes and lymphocytes with ageing, Immunol. Lett 40 (3) (1994) 259–268.
[79] T. Fulop, N. Douziech, A. Larbi, G. Dupuis, The role of lipid rafts in T lymphocyte signal transduction with aging, Ann. N. Y. Acad. Sci 973 (2002) 302–304, 302-304.
[80] G. Herbein, A. Varin, T. Fulop, B. NF-kappa, AP-1, Zinc-deficiency and aging, Biogerontology 7 (5–6) (2006) 409–419.
[81] A. Varin, A. Larbi, G.V. Dedoussis, S. Kanoni, J. Jajte, L. Rink, D. Monti, M. Malavolta, F. Marcellini, E. Mocchegiani, G. Herbein, T. Fulop, In vitro and in vivo effects of zinc on cytokine signalling in human T cells, Exp. Gerontol. 43 (5) (2008) 472–482.
[82] A. Larbi, N. Douziech, G. Dupuis, A. Khalil, H. Pelletier, K.P. Guerard, T. Fulop, Age-associated alterations in the recruitment of signal-transduction proteins to lipid rafts in human T lymphocytes, J. Leukoc. Biol 75 (2) (2004) 373–381.
[83] T. Fulop, A.Le Page, H. Garneau, N. Azimi, S. Baehl, G. Dupuis, G. Pawelec, A. Larbi, Aging, immunosenescence and membrane rafts: the lipid connection, Longev Healthspan 1 (2012) 6.
[84] N. Douziech, I. Seres, A. Larbi, E. Szikszay, P.M. Roy, M. Arcand, G. Dupuis, T. Fulop, Modulation of human lymphocyte proliferative response with aging, Exp. Gerontol. 37 (2–3) (2002) 369–387.
[85] G. Pawelec, K. Hirokawa, T. Fulop, Altered T cell signalling in ageing, Mech. Ageing Dev. 122 (14) (2001) 1613–1637.
[86] T. Fulop, D. Gagne, A.C. Goulet, S. Desgeorges, G. Lacombe, M. Arcand, G. Dupuis, Age-related impairment of p56lck and ZAP-70 activities in human T lymphocytes activated through the TcR/CD3 complex, Exp. Gerontol. 34 (2) (1999) 197–216.
[87] A. Mikosik, J. Foerster, A. Jasiulewicz, J. Frackowiak, G. Colonna-Romano, M. Bulati, S. Buffa, A. Martorana, C. Caruso, E. Bryl, J.M. Witkowski, Expression of calpain-calpastatin system (CCS) member proteins in human lymphocytes of young and elderly individuals; pilot baseline data for the CALPACENT project, Immun Ageing 10 (1) (2013) 27.
[88] A. Mikosik, A. Jasiulewicz, A. Daca, I. Henc, J.E. Frackowiak, K. Ruckemann-Dziurdzinska, J. Foerster, A.Le Page, E. Bryl, T. Fulop, J.M. Witkowski, Roles of calpain-calpastatin system (CCS) in human T cell activation, Oncotarget 7 (47) (2016) 76479–76495.
[89] P. Lopatniuk, Z. Puchalska, A. Mital, A. Mikosik, J. Frackowiak, A. Hellmann, A. Daca, E. Bryl, T. Fulop, J.M. Witkowski, Excessive amount and activity of mu-calpain affects apoptotic machinery in chronic B-cell leukemia cells and influences the course of the disease, Acta Biochim. Pol. 67 (2) (2020) 247–257.
[90] J.M. Witkowski, A. Mikosik, E. Bryl, T. Fulop, Proteodynamics in aging human T cells - The need for its comprehensive study to understand the fine regulation of T lymphocyte functions, Exp. Gerontol. 107 (2018) 161–168.
[91] J.M. Witkowski, E. Bryl, T. Fulop, Proteodynamics and aging of eukaryotic cells, Mech. Ageing Dev. 194 (2021), 111430.
[92] T. Fulop, A. Larbi, G. Dupuis, A.Le Page, E.H. Frost, A.A. Cohen, J.M. Witkowski, C. Franceschi, Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: friends or Foes? Front. Immunol. 8 (2017) 1960.
[93] M.A. Verity, C.F. Tam, M.K. Cheung, D.C. Mock, R.L. Walford, Delayed phytohemagglutinin-stimulated production of adenosine triphosphate by aged human lymphocytes: possible relation to mitochondrial dysfunction, Mech. Ageing Dev. 23 (1) (1983) 53–65.
[94] E. Beregi, O. Regius, Relationship of mitochondrial damage in human lymphocytes and age, Aktuelle Gerontol. 13 (6) (1983) 226–228.
[95] M. Pollack, C. Leeuwenburgh, Apoptosis and aging: role of the mitochondria, J. Gerontol. A Biol. Sci. Med. Sci. 56 (11) (2001) B475–B482.
[96] W. Xu, A. Larbi, Markers of T Cell Senescence in Humans, Int. J. Mol. Sci. 18 (8) (2017).
[97] R. Sharma, Perspectives on the dynamic implications of cellular senescence and immunosenescence on macrophage aging biology, Biogerontology 22 (6) (2021) 571–587.
[98] R. Solana, R. Tarazona, I. Gayoso, O. Lesur, G. Dupuis, T. Fulop, Innate immunosenescence: effect of aging on cells and receptors of the innate immune system in humans, Semin. Immunol. 24 (5) (2012) 331–341.
[99] T. Fulop, G. Dupuis, S. Baehl, A.Le Page, K. Bourgade, E. Frost, J.M. Witkowski, G. Pawelec, A. Larbi, S. Cunnane, From inflamm-aging to immune-paralysis: a slippery slope during aging for immune-adaptation, Biogerontology 17 (1) (2016) 147–157.
[100] T. Fulop, G. Dupuis, J.M. Witkowski, A. Larbi, The Role of Immunosenescence in the Development of Age-Related Diseases, Rev. Invest. Clin. 68 (2) (2016) 84–91.
[101] J.J. Goronzy, F. Fang, M.M. Cavanagh, Q. Qi, C.M. Weyand, Naive T cell maintenance and function in human aging, J. Immunol. 194 (9) (2015) 4073–4080.
[102] L. Zhang, R. Mack, P. Breslin, J. Zhang, Molecular and cellular mechanisms of aging in hematopoietic stem cells and their niches, J. Hematol. Oncol. 13 (1) (2020) 157.
[103] J.M. SanMiguel, K. Young, J.J. Trowbridge, Hand in hand: intrinsic and extrinsic drivers of aging and clonal hematopoiesis, Exp. Hematol. 91 (2020) 1–9.
[104] M.Y. Balkhi, Q. Ma, S. Ahmad, R.P. Junghans, T cell exhaustion and Interleukin 2 downregulation, Cytokine 71 (2) (2015) 339–347.
[105] E.J. Wherry, M. Kurachi, Molecular and cellular insights into T cell exhaustion, Nat. Rev. Immunol. 15 (8) (2015) 486–499.
[106] C. Franceschi, M. Bonafe, S. Valensin, F. Olivieri, L.M. De, E. Ottaviani, B.G. de, Inflamm-aging. An evolutionary perspective on immunosenescence, Ann. N. Y. Acad. Sci 908 (2000) 244–254, 244-254.
[107] A. Larbi, G. Dupuis, N. Douziech, A. Khalil, T. Fulop, Low-grade inflammation with aging has consequences for T-lymphocyte signaling, Ann. N. Y. Acad. Sci 1030 (2004) 125–133, 125-133.
[108] T. Fulop, A. Larbi, J.M. Witkowski, Human Inflammaging, Gerontology 65 (5) (2019) 495–504.
[109] T. Fulop, J.M. Witkowski, F. Olivieri, A. Larbi, The integration of inflammaging in age-related diseases, Semin. Immunol. 40 (2018) 17–35.
[110] C. Franceschi, P. Garagnani, G. Vitale, M. Capri, S. Salvioli, Inflammaging and 'Garb-aging, Trends Endocrinol. Metab. 28 (3) (2017) 199–212.
[111] M.V. Blagosklonny, From causes of aging to death from COVID-19, Aging (Albany NY) 12 (11) (2020) 10004–10021.
[112] J. Marcinkiewicz, J.M. Witkowski, R. Olszanecki, The dual role of the immune system in the course of COVID-19. The fatal impact of the aging immune system, Cent Eur J Immunol 46 (1) (2021) 1–9.
[113] W. Wang, R. Thomas, J. Oh, D.M. Su, Thymic Aging May Be Associated with COVID-19 Pathophysiology in the Elderly, Cells 10 (3) (2021).
[114] S. Palmer, N. Cunniffe, R. Donnelly, COVID-19 hospitalization rates rise exponentially with age, inversely proportional to thymic T-cell production, J. R. Soc. Interface 18 (176) (2021), 20200982.
[115] C. Vellas, P. Delobel, P. de Souto Barreto, J. Izopet, COVID-19, Virology and Geroscience: a Perspective, J. Nutr. Health Aging 24 (7) (2020) 685–691.
[116] S. Shenoy, Coronavirus (Covid-19) sepsis: revisiting mitochondrial dysfunction in pathogenesis, aging, inflammation, and mortality, Inflamm. Res. 69 (11) (2020) 1077–1085.
[117] P.H. Yang, Y.B. Ding, Z. Xu, R. Pu, P. Li, J. Yan, J.L. Liu, F.P. Meng, L. Huang, L. Shi, T.J. Jiang, E.Q. Qin, M. Zhao, D.W. Zhang, P. Zhao, L.X. Yu, Z.H. Wang, Z. X. Hong, Z.H. Xiao, Q. Xi, D.X. Zhao, P. Yu, C.Z. Zhu, Z. Chen, S.G. Zhang, J.S. Ji, F.S. Wang, G.W. Cao, Increased circulating level of interleukin-6 and CD8(+) T cell exhaustion are associated with progression of COVID-19, Infect Dis Poverty 9 (1) (2020) 161.
[118] R. Sanchez-Vazquez, A. Guio-Carrion, A. Zapatero-Gaviria, P. Martinez, M. A. Blasco, Shorter telomere lengths in patients with severe COVID-19 disease, Aging (Albany NY) 13 (1) (2021) 1–15.
[119] A. Aviv, Telomeres and COVID-19, FASEB J. 34 (6) (2020) 7247–7252.
[120] D. Ragab, H. Salah Eldin, M. Taeimah, R. Khattab, R. Salem, The COVID-19 Cytokine Storm; What We Know So Far, Front. Immunol. 11 (2020) 1446.
[121] K. Kawahara, H. Hohjoh, T. Inazumi, S. Tsuchiya, Y. Sugimoto, Prostaglandin E2-induced inflammation: relevance of prostaglandin E receptors, Biochim. Biophys. Acta 1851 (4) (2015) 414–421.
[122] Y. Tang, J. Liu, D. Zhang, Z. Xu, J. Ji, C. Wen, Cytokine Storm in COVID-19: the Current Evidence and Treatment Strategies, Front. Immunol. 11 (2020) 1708.
[123] C. Pantos, I. Tseti, I. Mourouzis, Use of triiodothyronine to treat critically ill COVID-19 patients: a new clinical trial, Crit. Care 24 (1) (2020) 209.
[124] E.O. Gubernatorova, E.A. Gorshkova, A.I. Polinova, M.S. Drutskaya, IL-6: relevance for immunopathology of SARS-CoV-2, Cytokine Growth Factor Rev. 53 (2020) 13–24.
[125] A. Copaescu, O. Smibert, A. Gibson, E.J. Phillips, J.A. Trubiano, The role of IL-6 and other mediators in the cytokine storm associated with SARS-CoV-2 infection, J. Allergy Clin. Immunol. 146 (3) (2020) 518–534, e1.
[126] M. Doss, Are We Approaching the End of the Linear No-Threshold Era? J. Nucl. Med. 59 (12) (2018) 1786–1793.
[127] A. Rossnerova, A. Izzotti, A. Pulliero, A. Bast, S.I.S. Rattan, P. Rossner, The Molecular Mechanisms of Adaptive Response Related to Environmental Stress, Int. J. Mol. Sci. 21 (19) (2020).
[128] E.J. Calabrese, E. Agathokleous, R. Kapoor, W.J. Kozumbo, S.I.S. Rattan, *Re*-analysis of herbal extracts data reveals that inflammatory processes are mediated by hormetic mechanisms, Chem. Biol. Interact. 314 (2019), 108844.
[129] S.I. Rattan, Molecular gerontology: from homeodynamics to hormesis, Curr. Pharm. Des. 20 (18) (2014) 3036–3039.
[130] T. Fulop, U. Munawara, A. Larbi, M. Desroches, S. Rodrigues, M. Catanzaro, A. Guidolin, A. Khalil, F. Bernier, A.E. Barron, K. Hirokawa, P.B. Beauregard, D. Dumoulin, J.P. Bellenger, J.M. Witkowski, E. Frost, Targeting Infectious Agents as a Therapeutic Strategy in Alzheimer's Disease, CNS Drugs 34 (7) (2020) 673–695.
[131] J.M. Witkowski, E. Bryl, T. Fulop, Should we Try to Alleviate Immunosenescence and Inflammaging - Why, How and to What Extent? Curr. Pharm. Des. 25 (39) (2019) 4154–4162.
[132] A. Santoro, E. Bientinesi, D. Monti, Immunosenescence and inflammaging in the aging process: age-related diseases or longevity? Ageing Res. Rev. 71 (2021), 101422.
[133] A.A. Cohen, B.K. Kennedy, U. Anglas, A.M. Bronikowski, J. Deelen, F. Dufour, G. Ferbeyre, L. Ferrucci, C. Franceschi, D. Frasca, B. Friguet, P. Gaudreau, V. N. Gladyshev, E.S. Gonos, V. Gorbunova, P. Gut, M. Ivanchenko, V. Legault, J. F. Lemaitre, T. Liontis, G.H. Liu, M. Liu, A.B. Maier, O.T. Nobrega, M.G.M. Olde Rikkert, G. Pawelec, S. Rheault, A.M. Senior, A. Simm, S. Soo, A. Traa, S. Ukraintseva, Q. Vanhaelen, J.M. Van Raamsdonk, J.M. Witkowski, A.I. Yashin, R. Ziman, T. Fulop, Lack of consensus on an aging biology paradigm? A global survey reveals an agreement to disagree, and the need for an interdisciplinary framework, Mech. Ageing Dev. 191 (2020), 111316.
[134] C. Lopez-Otin, M.A. Blasco, L. Partridge, M. Serrano, G. Kroemer, The hallmarks of aging, Cell 153 (6) (2013) 1194–1217.
[135] I.J. Rodriguez, N. Lalinde Ruiz, M. Llano Leon, L. Martinez Enriquez, M.D. P. Montilla Velasquez, J.P. Ortiz Aguirre, O.M. Rodriguez Bohorquez, E.

A. Velandia Vargas, E.D. Hernandez, C.A. Parra Lopez, Immunosenescence Study of T Cells: A Systematic Review, Front Immunol 11 (2020), 604591.

[136] M. Patrick, N.P. Weng, Expression and regulation of telomerase in human T cell differentiation, activation, aging and diseases, Cell. Immunol. 345 (2019), 103989.

[137] S.O. Schonland, C. Lopez, T. Widmann, J. Zimmer, E. Bryl, J.J. Goronzy, C. M. Weyand, Premature telomeric loss in rheumatoid arthritis is genetically determined and involves both myeloid and lymphoid cell lineages, Proc. Natl. Acad. Sci. U. S. A 100 (23) (2003) 13471–13476.