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REVIEW

Immunosenescence is both functional/adaptive and dysfunctional/maladaptive

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Abstract

Alterations in the immune system with aging are considered to underlie many age-related diseases. However, many elderly individuals remain healthy until even a very advanced age. There is also an increase in numbers of centenarians and their apparent fitness. We should therefore change our unilaterally detrimental consideration of age-related immune changes. Recent data taking into consideration the immunobiography concept may allow for meaningful distinctions among various aging trajectories. This implies that the aging immune system has a homeodynamic characteristic balanced between adaptive and maladaptive aspects. The survival and health of an individual depends from the equilibrium of this balance. In this article, we highlight which parts of the aging of the immune system may be considered adaptive in contrast to those that may be maladaptive.

Keywords Immunosenescence · Inflammaging · Adaptation · Maladaptation · Trained immunity · Centenarians · Immunosuppressive mechanisms

Introduction

Due to the current COVID-19 pandemic, there is much interest in the immune system of older individuals, who are at highest risk of severe disease and death [1–5]. It seems to be common knowledge that infections and diseases are increased in the elderly and may be considered associated with the aging process itself [6–9]. In the meantime, there is an unprecedented increase both in life expectancy and in the number of centenarians and semi-supercentenarians (several "blue zones" where these oldest old individuals are "enriched" compared with the general population exist on earth) [10, 11]. Many changes have been described in the innate and adaptive immune systems with aging [12–20]. These contentions seem to represent completely contradictory trends which may be difficult to reconcile. Interestingly, two decades ago a common denominator of aging and age-related diseases called *inflammaging* was described by Franceschi et al. [9, 21–23], a concept that was largely based on the previously described age-related immune changes called as immunosenescence

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[24, 25]. As a corollary, this became for geroscience and the nine hallmarks of aging one of the basic underlying mechanisms of aging designated as "intercellular communication" [26–28]. However, a new appreciation of the data found in older adults suggests that not all changes in the immune system generally considered detrimental are actually harmful, and concomitantly the immune system of the elderly is able to perform better than it was previously suspected when adequately challenged [29, 30].

As mentioned, the common paradigm is that age-related diseases (ARDs) and the decreased vaccine response are somehow linked to immune alterations with aging, commonly called immunosenescence [16, 20]. However, several recent observations challenge this idea. First, the elderly are in fact able to sustain an adequate vaccine response compared with young subjects [30]. Second, for semi-supercentenarians the most important survival factor was proposed to be inflammation [31–33]. Third, the immune checkpoint inhibitors are as efficient in elderly as in young [34, 35]. Lastly, most infections are not fatal in the elderly, including COVID-19, and not all older adults suffer from numerous age-related diseases [36, 37].

Therefore, it could be conceptualized that the age-related immune changes may be a mix of adaptation/resilience and maladaptation/allostatic load, which are closely related to what was called the immunobiography or immunoadaptation, in line with the well-known physiological concepts hormesis and homeodynamics [25, 38–40]. In this article, we propose a framework to understand adaptation and maladaptation of the immune system and their consequences for elderly. Thus, we will describe a *holistic* conceptualization of the immune system changes during aging, called the "adaptage theory."

Aging-associated changes in the immune system

The main role of the immune response is the protection of the organism from all external and internal challenges in the form of pathogenic microorganisms as well as transformed (neoplastic) or damaged (injured) cells [7, 23]. The immune system is fully equipped to perform this complex task. However, many reports state that with aging there is not a single part of this response which would not undergo changes, and these changes were uniformly conceptualized as being only "bad," deteriorative changes, and their consequences could be only detrimental for elderly [41–43]. This notion generated the concept of removing the problem by the rejuvenation of the immune system of the aged individuals to the level of young subjects [44, 45], however in the physiological environment of an otherwise old organism.

Usually, the aging-associated changes in the immune system are described separately for its innate and adaptive compartments. Here we will try to describe the *unified* concept of these age-related changes. When we consider aging, we consider time. So, the immune system today is not the same as yesterday, neither in young nor in elderly persons. This means that at every moment challenges are arising in our external and internal environment which should be dealt with by the immune system [38] and that these challenges build on the previous state. This implies that every event occurring during life will consequently change or sculpt the immune response [25].

So, during life, we have many aggressions which can be halted by the innate immune system alone, or if they are more serious, they will need the involvement of the adaptive immune system [46, 47]. Thus, in any case, the first encounter of an external or internal pathogen is with the cells of innate immune system [48]. This system is fully equipped to deal with all aggressors in a very fast time frame starting from minutes to days. This system is composed of neutrophils, monocytes/macrophages, dendritic cells (DC) and NK cells, and numerous soluble mediators secreted by these cells, including cytokines and chemokines [49]. By itself, this system is powerful enough to clear an aggression without harm [50, 51] but also in special circumstances to turn against its own by sustaining inflammation, over time leading to chronic inflammatory diseases [52–54]. Among these are, for example, rheumatoid diseases, atherosclerosis, cancer, or asthma, the precursory stages of which may be arising very early in life [55, 56].

Acute inflammation is meant to eliminate everything which is harmful for the organism and ends with a (near) complete return to the original state. However, if the aggression is chronic, or if the innate immune system is not set back because the regulatory mechanisms are overwhelmed, the inflammatory process can become chronic and potentially harmful. When we think about a chronic process, we suppose that time plays a role; thus, aging (occurring with time) is a relevant factor [57]. This means that all these pathologies are considered ARDs. Nevertheless, we should mention that the chronic nature of such stimulation has already somehow elucidated the occurrence (explained the beginnings) of these diseases early in life [57].

The concept of trained innate immune memory sheds some light how the innate immune system may orchestrate the eventual alertness or chronicity of the innate immune response. At each aggression, innate immune cells such as monocytes are activated [58–62]. "Trained" at each occasion by intracellular immunometabolic changes/reprogramming as well as by subsequent epigenetic imprint, these cells will increase their inflammatory response [63–65]. However, this process may take two different paths. One path is the controlled, well-orchestrated innate immune memory, which helps to resolve aggressions rapidly and stop the inflammatory process, but nonetheless remains at a higher activation/readiness state

[58–62]. The other pathway is less controlled, which can lead to what has been called "immune paralysis" [66]. Not only will the response not be adequate, but these cells are already overstimulated, so a new stimulus may not trigger an efficient response and the functionality of the innate immune cells will decrease when it should increase. This has been shown also for some specific phagocytic cells' functions with aging [67]. A basal state of activation of the innate cells was demonstrated with aging, which may lead to a preparedness and readiness of the system [68–71]. This may help the innate immune system to be reactive more quickly and at a higher level. Interestingly, many tissue-resident and blood-born innate immune cells, including neutrophils and microglia, display hyperactivation phenotypes with aging [72, 73]. However, it was also shown that this may lead to a relative immune paralysis state resulting in the blunting of the innate cells functionality when specifically challenged. It should be mentioned that this does not mean that these phagocytic cells may not enhance their functions, but not in all elderly and not to the level as would be expected in case of young. This is corroborated by the findings that most elderly subjects may efficiently clear an infection, such as influenza or even SARS-CoV-2 [14, 16, 37, 74]. Certainly, this happens in fewer cases than in young subjects, but it is not impossible. Thus, this is a perfect example of the adaptation/maladaptation concept of the aged immune system.

Moreover, the innate immune response can also determine how the adaptive immune system will react [75, 76]. Cells have evolved which seem to be intermediate between the innate and the adaptive immune system and may react faster than standard adaptive immune system but keep its characteristics [76–78]. These innate lymphoid cells (ILC) are broadly classified into three main subsets: ILC1 (IFN-γ producing), ILC2 (IL-4, IL-5, and IL-13 producing), and ILC3 (IL-17 or IL-22 producing or both) [79, 80]. ILCs are either present in the tissues or in the circulation. They can rapidly react to microbial and cytokine signals. They also rapidly induce the CXCL13 chemokine, which is the ligand of CXCR5 playing a role in the tissue accumulation of these ILCs [81, 82]. By their rapid response, these cells also contribute to the eradication of the microbes constantly invading the human organism and permanently threatening its overall health.

The innate-like T cells comprise the cells displaying a γδTCR, mucosa-associated invariant T (MAIT), iNKT (Invariant Natural Killer T), GEMT (germline-encoded mycolyl lipid-reactive), and innate-like B cells [83]. These cells recognize foreign/self-lipid presented by nonclassical MHC molecules, such as CD1d, MR1, and CD1a [84]. They are activated during the early stages of bacterial infection and act as a bridge between the innate and adaptive immune systems. Unlike their conventional counterparts, innate T cells rapidly recognize foreign pathogen signals and manifest immediate effector functions after activation [85]. These innate T cells are implicated in immune responses to viral infections such as CMV, are able to recognize a broad range of cancer cells, and react to stress-induced molecules, such as MHC class I-related chains A and B (MICA and MICB) that are expressed on virus-infected cells and also participate in the general antimicrobial defense [86–88]. The nature of the antigens recognized by innate T cells is also diverse and broadly non-overlapping, involving metabolites, bacterial products, and lipids. iNKT cells have been principally shown to respond to glycolipids, γδ T cells are potently activated by (E)-4-hydroxy-3-methyl-but-2-enylpyrophosphate (HMBPP) [89], and MAIT cells can be activated by riboflavin metabolites–reduced 6-hydroxy methyl-8-δ-ribitylumazine (rRL-6-CH2OH), as well as folic acid metabolite, 6-formylpterin(6FP) [90]. So, they have some characteristics of the innate immunity such as rapid effector functions but also adaptive immunity because of the rearrangement of their TCR and thymic selection. This allows innate T cells to perform effector immune responses much earlier than conventional T cells and act as an additional "bridge" between innate and adaptive immune responses. Studies demonstrate that unconventional T cells do indeed contribute to the ability of host organisms to clear and control certain bacterial infections. These cells are able to efficiently travel to the sites of inflammation and initiate rapid responses by means of cytokine production and cytotoxic activities.

In the description of immune changes with aging, there are a few places for these essential cells. Larbi and his group devoted a lot of work to understand how these cells work during aging [91, 92]. They have shown that Vδ2+ T cells composition and functionality are not altered in older adults. They have further shown that peripheral Vδ2+ phenotype, functional capacity (cytokines, cytotoxicity, proliferation), and gene expression profile are specific to this subset when compared against all other αβ and γδ T cells in aging. Also, hallmarks of senescence including telomere length, epigenetic profile, and DNA damage response of Vδ2+ differ from all other αβ and γδ T cells. Finally, they have shown that Vδ2+ are resistant to cellular aging due to their unique epigenetic and transcriptomic signatures. These findings constitute another type of adaptation in view to compensate/complement the changes observed in adaptative T cells during aging. Future work should unravel whether this potential of being resilient to stressors in Vδ2+ could be promoted in other cell type and consequently exploited to lead to better response to infections and in the field of cancer immunotherapy or designing a vaccine utilizing Vδ2+ properties for the elderly.

Group 2 ILC (ILC2) respond to the alarmin cytokine IL-33 and are potent producers of IL-5 and IL-13 as well as a variety of other effector molecules in vitro and in vivo [93]. Tissue-resident ILC2 are implicated in tissue repair, tissue remodeling, and metabolic homeostasis [94]. Recently, it was shown in the choroid plexus of the brain that ILC2 in the aged brain

are long-lived and capable of reversibly switching between cell cycle dormancy and proliferation [95]. They are relatively resistant to cellular senescence and exhaustion under replication stress, leading to enhanced self-renewal capability. When activated in vitro and transferred intracerebroventricularly, they revitalized the aged brains and enhanced cognitive function of aged mice. These results suggest that aging may expand a unique population of brain-resident ILC2 with enhanced cellular fitness and potent neuroprotective capability, by decreasing neuroinflammation, cellular senescence, and exhaustion and moreover capable of self-renewing. It is still unclear whether similar ILC2 cells may be found elsewhere in aging organism, but this is another cell type which may resist the "detrimental" effect of aging and show adaptative traits even if is occurring locally.

The subsets of memory or memory-like T and B cells with innate-like properties have been observed to accumulate with aging [42, 96–100]. The increased numbers and activity of certain innate or innate-like immune cell subsets with aging might be considered host responses to compensate for the drastic decline in adaptive immune cell development and function [95]. These cells mirror the findings in Vδ2+ T cells as described above and show the plasticity and adaptability of the innate and innate-like cells with aging, probably maintaining some physiologically important functions when the other part of the system is fainting [91]. Thus, we can say that the effects of aging on the immune system are much more complicated than a commonly preached generalized decline in immune cell development, phenotype, and function.

Once an aggression occurs and the innate response is inefficient or insufficient to clear it, the innate system should drive the adaptive immune system to react [75, 76]. This is carried out by coordinated and efficient actions by the cells and the soluble mediators of the innate immune system. The antigens should be efficiently presented, and the mediators should prime the adaptive immunity. It has often been stated that antigen presentation is altered with aging; however, this is still controversial and probably depends on the strength of the innate stimulation [101–107]. Dendritic cells (DCs) are one type of innate immune cell known for antigen presentation, being key components linking innate and adaptive immunity through priming of naïve T cells and shaping adaptive T cell responses [108, 109]. There are two major DC subsets in human peripheral blood: conventional DCs (cDCs) and plasmacytoid DCs (pDCs). These DC subsets recognize different pathogen-associated molecular patterns by expressing distinct repertoires of Toll-like receptors (TLRs) and other receptors [110, 111]. Engagement of specific DC subset TLRs in turn triggers distinct immune response pathways. For example, pDCs produce a large amount of interferon alpha (IFN-a) in response to virus infection [112]. As mentioned, age effect studies of human DCs have been controversial [107]. While some studies demonstrated age-dependent declines, others have shown no difference in the number of circulating DCs [113, 114]. Several studies have also indicated age-related functional changes in DCs, such as impaired expression of TLRs [115]; decreased production of cytokines, chemokines, and IFN-a after TLR stimulation [112–116]; and increased responses to self-antigen [117]. An earlier study has shown that the B cell and monocyte antigen presentation in the frame of MHC did not change with age. However, what was interesting in the data reported in one study is that among the 11 elderly even if the monocyte antigen presentation was homogenously maintained, there were 4 elderly with less BCR antigen presentation [106]. Even if most of the results suggest a change in antigen presentation, the various steps leading to it are differentially affected by age from the number of DCs through the immunoproteasome processing and the final MHC dependent presentation like in B cells. Interestingly, almost a quarter century ago, one of us (JMW) had demonstrated that the level of expression of MHC class I (H-2) molecules on spleen T cells of old mice is higher than on the surface of young splenic T cells; this effect was concomitant with the significant (homeostatic?) decrease of the level of transporter of antigenic peptides (TAP)-1 in the same cells [118]. These observations were later supported by Assounga et al. [119]. Contrarily, expression of MHC Class II on macrophages derived from old mice was reported to be decreased compared with young animals [120]. These data even if contradictory may also illustrate that in the immune system, the changes are not uniform, and the system is self-adapted to compensate eventual failure of some part of the whole system. However, other non-antigen processing and presentation functions of APC, such as ability to become activated, costimulation, or cytokine/chemokine production, may play a role in the difficulties of the immune response to progress to the adaptive immune response [121]. More human studies are needed to clearly elucidate which processes are conserved and which are not in the antigen presentation process.

However, once the innate immune response is able to present the antigens, the adaptive immune response takes over with B and T lymphocytes' activation [75]. These main cell types executing the adaptive immune response have many different subpopulations [122]. This part of the immune system has been extensively studied in human aging [123–126]. There is a very broad consensus considering the adaptive immune system as the "devil" which is responsible for all the misfortunes of the immune system with age [25, 28]. The most important changes are the decrease in the naïve immune cell compartment of the $CD4^+$ and $CD8^+$ T lymphocytes, however being more important in the latter [12, 16, 96, 97]. Concomitantly, the TCR repertoire variability is also drastically decreased [127, 128]. In contrast, there is a concomitant increase in memory T and B cells which represent the

subpopulation which already encountered antigens [129–131]. This quickens the adaptive response to cognate antigens, which is evolutionarily beneficial for the survival of an (older) individual, provided he/she stays in the general area where they spent their childhood and where meeting new, previously unknown pathogens is normally infrequent. The contrary would be quite strange if we consider from an evolutionary perspective that the immune system should react to all internal and external stimulation. This state of the adaptive immune system only reflects what we called earlier as immunobiography or immune history [38, 132]. So, in this case, it should be considered neither bad nor good; it reflects only the reality of the role of the immune system. This is simply a life-long adaptation to life.

Certainly, the decrease of naïve cells in the elderly may not be advantageous for the survival of the individual when an encounter occurs with a completely new antigen such as the SARS-CoV-2 causing current (2020) pandemics of COVID-19 [15]. As we already know, these individuals may die in proportions significantly higher than young COVID-19 patients [1, 2]. The cause of this decrease of naïve T cells is the involution of the thymus which starts early in life [13]. This also should have some adaptative reasons in the life of an individual. The maintenance of such an organ (with one of the highest proportions of concurrently dividing cells) is very costly in terms of metabolic energy; so, as most of the naïve T cells have been generated early in life, there is no need for its full function later in life. Also, if it is maintained, some errors in the regulatory mechanisms may occur with time, and some diseases such as autoimmune disease may increase. On the other hand, it should be stated that once more nature has foreseen a compensatory mechanism for lack of naïve T cells of thymic origin, which is their homeostatic proliferation in the periphery [133]. There is an unsettled debate among researchers as to whether this phenomenon fully replaces the lost TCR repertoire expressed by the thymus-generated naïve T cells. However, long survival of centenarians demonstrates that it should be an efficient compensatory mechanism. It is of note that many nonagenarians and centenarians recovered form COVID-19 despite the apparent lack of naïve T cells [134].

The increase of the memory (mainly $CD8^+$) T cells is also considered quite damaging for old individuals [135, 136]. The reason is that their numerous proliferation cycles have led to what is called a senescent state or senescence [137–139]. This senescent state precludes their capacity to proliferate, mainly due to decreased CD28 expression resulting in slower and weaker activation during a known antigenic encounter, leading to decreased protection [18, 140]. In the meantime, senescent T cells, analogously to other senescent cells arising with age in the body, produce large amounts of proinflammatory cytokines (a phenomenon called senescence-associated secretory phenotype, SASP) as stated by the inflammaging characteristics of the human immune system [141, 142]. This could substantially impede the response to recall antigens in specific cases, but in the meantime, the clinical and experimental evidence both point to the fact that even in the elderly, this part of the adaptive immune system may function efficiently. In the meantime, these cells are also able to contribute to the maintenance of innate immune preparedness. The SASP phenotype elicits an autocrine role on senescent cells, but it is also involved in the recruitment of immune cells, such as macrophages, neutrophils, and natural killer (NK) cells in order to eliminate the senescent cells themselves [143]. Concomitantly, upon accumulation of senescent cells, the production of cytokines is enhanced, along with the recruitment of immune cells, jointly paving the way towards the installation of inflammaging [14, 57]. The cytomegalovirus (CMV) infection was considered one of the most important triggers of accumulation of senescent T cells [144, 145]. This consideration generated many studies to evaluate whether senescence of the immune cells could be considered detrimental or beneficial. Certainly, the accumulation of senescent cells has numerous maladaptive aspects [146, 147]; but, as many recent studies have shown, it also has adaptive aspects [148]. Finally, the exact percentage of the senescent/exhausted T cells at different ages and what role they may play physiologically is not clearly settled in this context. It may be that they (mainly exhausted T cells) are like the reserve in the army which can awaken when the well-trained T cells are not able to combat pathologies like cancer [149–151]. In view of the continuous production of immune cells, it seems likely that part of accumulated memory immune cells is not truly irreversibly senescent but rather exhausted, exhibiting reduced functional capabilities which can possibly be reversed when the circumstances may necessitate it [152].

With aging, not only phenotypic changes but also functional changes occur in the adaptive system, which may or may not be always related to the T cell subpopulations but may be due directly to the immunobiography [38]. There are documented changes in the main signaling pathways in T cells, including the TCR, costimulatory receptors, and cytokine receptors, which lead to the decrease of cytokine production, proliferation, cytotoxicity, and differentiation [153–156]. Moreover, the metabolism of these cells is also affected because of the changes in the mTOR pathway either favoring the autophagy or the anabolic effects of its stimulation [157]. The changes from OxPhos in the resting state to aerobic glycolysis characterizing activated T cells are delayed and less intense in aging T cells [158, 159]. These changes in the functioning may arise from the membrane changes with aging altering the immune synapse formation and consequently the cognate signaling pathways [160, 161]. The changes either in the feedforward or feedback pathways are very complex—as the experimental results suggest—but together, we can say that they may decrease the efficiency of the T and B cell responses

with age in certain circumstances which can really have detrimental consequences for the individual [162–164]. There are also new data that some pathways (precisely the JAK-STAT pathway [165]) in the resting T cells are activated with age.

To summarize the immune changes in the continuity from the innate to the adaptive immune response, it can be concluded that the immune response in old individuals is complex and heterogenous and probably is more dependent on the type of challenge than from the age of the subjects [166, 167]. Furthermore, many compensatory and redundant mechanisms are inbuilt to assure an adequate immune response even in the very elderly. Thus, there is an equilibrium between adaptation and maladaptation, and this balance may be disrupted depending on the type, the degree, and the acuteness of aggression (Fig. 1).

Immunosuppressive mechanisms

The performance of the immune system cannot be completely evaluated without discussing the role of the inbuilt immune suppressor mechanisms which may also be affected by age [168–170]. First, the role of Tregs is double; on the one hand, they should control the extent of the inflammation, and on the other hand, they should avoid the autoimmune processes arising continuously in the body and assure the attrition of the immune response once the danger has been eradicated [168, 171]. Given the central role of Treg cells in immune homeostasis, age-related loss of Treg function would be predicted to render the host susceptible to excessive immunity, encountered in elderly humans as a syndrome of chronic low-grade inflammation [172]. Conversely, age-dependent gain of Treg activity would expose the host to greater risk of immune failure, such as the rising risk of malignancies and infections in the aging population [171]. Emerging data suggest that some Treg populations, specifically naturally occurring Tregs (nTreg), seem to accumulate with advancing age, whereas inducible Tregs (iTreg) appear to be less available in the older host, though this is controversial [118]. Human studies assessing peripheral blood of aged versus young individuals seem to concur that the percentage of $CD4^+$ Tregs is increased in older individuals [173, 174]. All these data indicate that the $CD4^+$ Treg compartment expands with age, relative to the total $CD4^+$ T cells. Human $CD4^+FOXP3^+$ Tregs from older individuals show enhanced FOXP3 expression compared with Tregs from young individuals, while the remainder of their

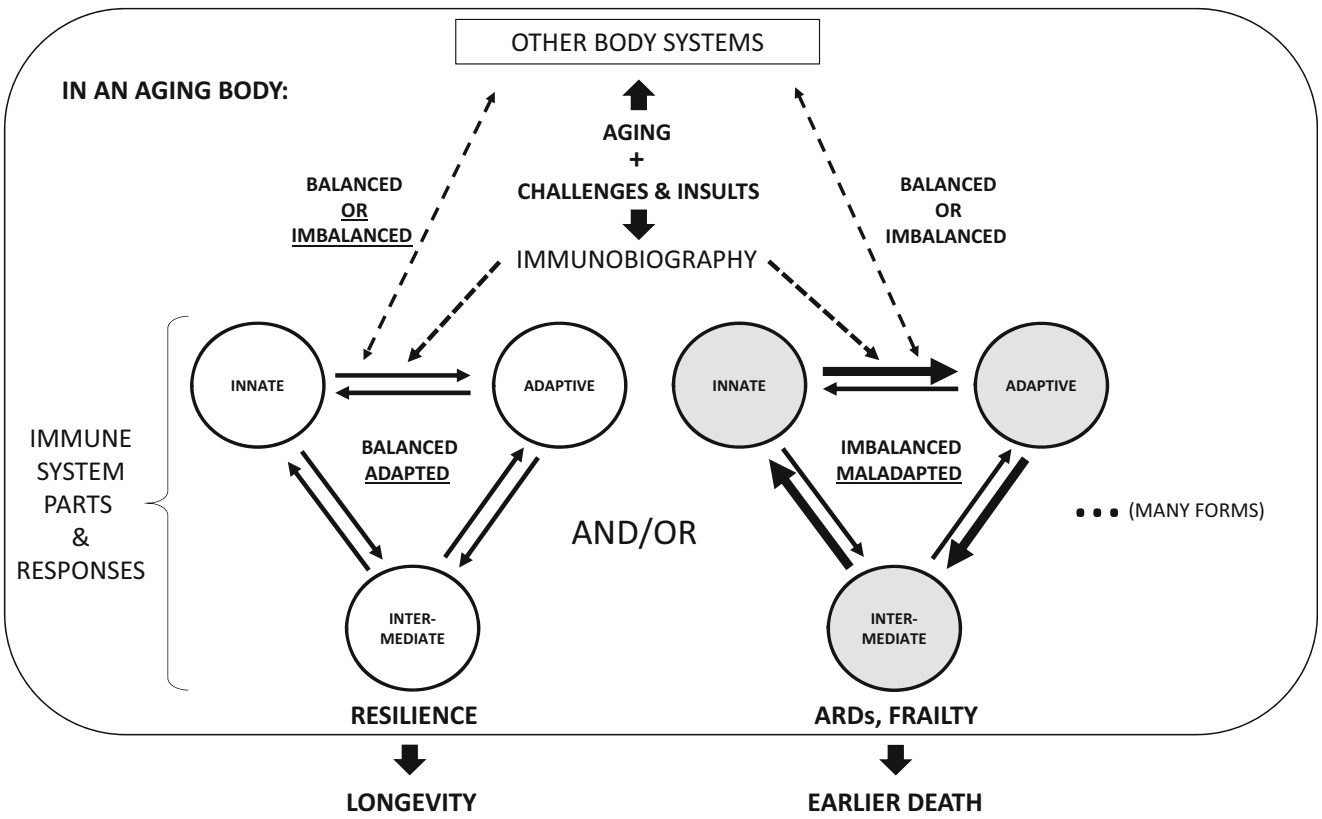

Fig. 1. The balance between the adaptive/maladaptive patterns of an individual's aging immune system. Adaptive and maladaptive immune changes can be found simultaneously in the same individual and in the same arms of the immune response (innate or adaptive). Concurrent (also balanced or imbalanced) changes in other body systems will affect the immune system. Complex integrated immunobiography over time will determine which state (balanced/adapted or imbalanced/maladapted) will predominate and towards which destiny (resilience and longevity, or aging-related diseases, frailty and earlier death) the organism will be pushed

phenotypic makeup (GITR, CTLA-4, $CD127^{low}$) is unchanged [175]. The implication of this finding is that although Tregs retain most of their functional properties, which would be responsible for suppressing immune activation against infection and tumors, while in the meantime, they may fail to control autoimmune inflammation. However, autoimmune diseases are relatively rare in elderly [176]. Such an abnormality suggests that an apparent paradox is observed during aging as an aberrant inflammation coexists with immune hyporesponsiveness to infection, vaccination, and tumors [9]. Like $CD4^+$ Tregs, the percentage of $CD8^+FOXP3^+$ Tregs has been shown to be significantly increased in the blood of older individuals [177]. Given the critical role of Tregs in immune homeostasis, any decline in Treg competence would inevitably lead to a disbalance of protective and pathogenic immunity and would favor chronic, relentless, and possibly tissue-damaging inflammation [171]. In reality, as already discussed above, aging is indeed associated with a low-grade but clinically not manifest inflammation (inflammaging) which is not out of control. This indicates that the increased Treg number sufficiently control inflammaging, in contrast to what it is commonly stated. In contrast, increased numbers of Tregs could be considered detrimental in the suppression *for the specific adaptive immune responses,* mainly in infections and eventually in cancer [168]. It is of note that in cancer Tregs were demonstrated to be immunosuppressive directly in the tumor microenvironment [178]. It is also questionable whether their role in the specific immune response is detrimental or regulatory, as the age-related inflammatory diseases start at middle age and not in old age. The well-regulated Treg activity may also prevent a hyperreactivity of the immune system, as is seen in the present COVID-19 infection in a form of cytokine storm.

There is another major immunoregulatory/suppressor cell type, namely, myeloid derived suppressor cells (MDSCs) [170, 179]. The MDSCs are specialized immunosuppressors which can control the functions of all other immune cells, thus preventing excessive inflammatory responses [180]. There is convincing evidence that the aging process increases the frequencies of circulating MDSCs in humans [181]. Verschoor et al. [182] revealed that the levels of the $CD11b^+CD15^+$ and granulocytic MDSCs were increased in the blood of community-dwelling seniors (61–76 years) and especially in frail elderly people (67–99 years). Furthermore, it was shown that the MDSCs induce the increase of Tregs [170, 183]. In this way, there is an immunosuppressive network which is created as individuals are aging as coined by Salminen et al. [184]. It seems that TGF-β, IL-10, and NO, secreted by MDSCs, are the major soluble mediators maintaining the functions of this age-related immunosuppressive network [185]. There is an abundant literature indicating that TGF-β signaling suppresses the functions of $CD4^+$ [186] and $CD8^+$ [187] T cells as well as DCs [188] and NK cells [189]. In particular, TGF-β inhibits the signaling pathways of CD28 and mTOR kinase [190]. IL-10 also inhibits the CD28-mediated signaling in T cells by activating SHP-1 tyrosine phosphatase-1 [191].

Together, the immunosuppressive network increase with aging may have several pathological consequences [184, 185], but however, in the spirit of immunobiography, this can also be considered an adaptation to decrease the lifelong activation process of the innate immune system (innate immune memory) but unfortunately in the meantime downregulate adaptive immune activation.

Centenarians

Among the elderly, the number of centenarians and semi-supercentenarians is steadily increasing, especially in the blue zones [192]. There is a debate as to whether centenarians and semi-supercentenarians are the result of selection or whether they represent the way that humans should physiologically age, with others simply having risk factors that preclude them from attaining this age even if we consider their genetic specificities. Centenarians are a category of exceptionally aged individuals that succeed in preventing or delaying the onset of age-related disorders such as CV disease, type 2 diabetes mellitus (T2DM), Alzheimer's disease, or cancer [193, 194]. It is also well-known that these centenarians do not avoid major diseases but are able to counteract their deleterious effects, which most of the other elderly are not capable of. Probably the advantage that they have is what we could call the "adaptage," which during their immunobiography resulted in the development of resilience which could overcome the many dysfunctions and lead to a maintained functionality [192]. The centenarians have adapted their immune responses which maintain an adequate functionality and, in the meantime, control inflammaging [31, 32, 195]. This means that they have an efficient anti-inflammaging machinery which may be constituted from immunosuppressive cells and soluble mediators like circulating gp130 to compensate for their increased IL-6 level [32]. In this context, Pawelec's group has shown a positive correlation between increased frequency of Tregs and survival in the elderly, which suggests the increasing importance of maintaining a balance between the adaptation and the maladaptation of immune responses and inflammation as we grew old [196].

One example of this adaptation/maladaptation is the microbiome largely influencing/shaping the functioning of all physiological systems, particularly that of the immune system in centenarians [193, 197–199]. Extreme longevity seems also to be associated with a unique shift of the gut microbiome characterized by enrichment in *Akkermansia*, *Bifidobacterium*, and *Christensenellaceae* [200]. On one hand, microbiota in centenarians show more diversity than

in young old, resembling more that found in young subjects [201]. Here, certain aspects of the changes in centenarians and semi-supercentenarians are proinflammatory, such as the decline in the abundance of the putative butyrate producers like *Faecalibacterium* (phylum Firmicutes), while on the other hand within the Bacteroidetes phylum, Rikenellaceae (*Alistipes*) and Porphyromonaceae (*Parabacteroides*, *Odoribacter*, *Porphyromonas*), also butyrate producers, were found to be increased in all centenarians [201] with the concomitant decrease of *Prevotella* (phylum Bacteroidetes) richness, sustaining the changes in microbiota holding strong anti-inflammatory activity [202, 203]. Thus, the dysbiosis, proinflammatory change in microbiota composition in the oldest old, is compensated by the increase of anti-inflammatory bacteria which are metabolically more active than the former [204]. Thus, the microbiota of centenarians support both the increase in the inflammatory load found in the sera but also a compensatory mechanism which is maintaining a fine balance, nevertheless favoring longevity.

We should also mention that not all centenarians are made equal. A recent study by Tedone et al. [192] studied telomere length and telomerase activity in T cells from low- and high-performing centenarians. They identified several parameters that are different between high- and low-performing centenarians: (a) The amount of proliferation following in vitro stimulation is dramatically greater in high-performing centenarians compared with 67- to 83-year-old controls and low-performing centenarians; (b) telomere length is greater in the high-performing centenarians; and (c) telomerase activity following stimulation is greater in the high-performing centenarians. In addition, this study has validated a number of genes whose expression was directly related to telomere length which may influence the risk and progression of multiple aging-associated conditions.

Together, centenarians have better resilience and biological reserves to effectively cope with multiple issues originated from their immunobiography. They can also better cope with inflammaging as they are able to mount a powerful anti-inflammaging response neutralizing the overall presence of inflammatory processes [32, 205]. It was clearly demonstrated in case of the semi-supercentenarians in whom the most powerful determinant of longevity was the presence of controlled inflammation [33]. They are the perfect example of hormesis and homeodynamic balance, as they have all the described supposed detrimental effect of aging on the immune system, but they have a powerful compensatory mechanism, a perfect demonstration of the "adaptage" concept of the immune changes.

COVID-19

The understanding of adaptation/maladaptation of the immune system with aging was never more relevant than during the COVID-19 pandemic. It is widely stated that the old individuals are more susceptible [6, 9, 206, 207]. This should help us to better understand the immune changes with aging which may be detrimental and which may be beneficial. As mentioned, not all elderly who are infected will progress to the severe stage and will not die either [208–211]. The SARS-CoV-2 infection is a two-step inducer of the immune response. At the beginning, a functional immune system could contain the infection even in elderly [212, 213]. An effective innate and adaptive immunity is required to try to advance the response until efficient antibody production begins. Most of the elderly can fight the infection but perhaps will not establish protective immunity with Ab. In those where the immune system is less efficient, the virus will propagate, and a massive destruction of the tissues, especially those possessing abundant ACE2 receptors, will ensue [214, 215]. Damaged cells will induce massive inflammation via the stimulation of macrophages producing the cytokine storm. As the lung is the main acute target for SARS-CoV-2, it could be that the lung epithelial cells may also participate in the inflammatory mediators' production [216]. This is not far from resembling the pathomechanism of sepsis [217, 218].

It is debatable whether good health is an advantage or not for the course of SARS-CoV-2 infection, as the huge immune response during the second phase may be a strong disadvantage [219, 220]. It is also of note that among the elderly who died in the hospitals, only 1% had comorbidities [221]. In the nursing homes, the situation is different as the old persons living in these institutions are not only comorbid but very ill; otherwise they would not be in these institutions [222–225]. In their cases, already the first step is deficient, so they die as in the case of influenza from the immunosuppressive effect of the virus and the following increased infection by bacteria or fungi [226, 227]. These differences in the elderly reflect their heterogeneity and also the differences of the immune status in each individual.

What would it take to move from the "damn-age" concept to the "adaptage" concept?

First of all, biology of aging research should dissociate itself from what can be called ageism. The idea that young individuals are by definition in a better state is a cultural belief, not a biological fact [227]. Thus, perhaps not all data should be interpreted as detrimental, but considered from an evolutionary and immunobiographic perspective, including the concepts of balanced adaptation/maladaptation as the norm. It should also move from the "good versus bad" concept that biology does not recognize, as these are moral concepts. Furthermore, researchers should not derive unequivocal conclusions from mouse data applied to humans, as they do not

always follow the same path. In fact, the majority of the immune system–related data refer to mouse data without sufficient warning about the profound difference between murine biology and human biology. These data are highly misleading and lead to many failures when applied to humans. One recent example is the failure of vaccination and use of monoclonal antibodies for treating Alzheimer's disease [228].

One of the most important criticisms of human studies is the heterogeneity of humans, which increases with age. This is absolutely true, but this is not a disadvantage but a wealth. This is the only way to unravel how the immune and other related physiological systems age. The immune system and physiology more generally are canonical examples of complex adaptive systems [229, 230], and it is well-known that linear, cause-and-effect models perform poorly for understanding such systems [231]; nonetheless, much of the research in these fields has applied methodology based on controlled experiments, which assume that results in a tightly controlled environment (e.g., lab mice) are easily extrapolatable, rather than methodologies that embrace heterogeneity and complexity. Undoubtedly, the latter are challenging, but they are also essential if we want to arrive at robust conclusions. This is more and more emphasized in research papers when they deal with aging. The one mentioned for centenarians is a bright example of this necessity if we want to understand what is occurring during aging [192]. Another example is a study published a few years ago, which has shown how to identify the drivers of the interindividual diversity of the human immune system, which is crucial to understand their consequences for immune-mediated diseases. By examining the transcriptional responses of 1000 individuals to various microbial challenges, they have shown that age and sex influence the expression of many immune-related genes, but their effects were overall moderate, whereas genetic factors affect a smaller gene set but with a stronger effect. These results enable us to understand the regulatory role of interindividual variants in the pathogenesis of immune-related diseases and improve our understanding of the respective effects of age, sex, and genetics on immune response variation [166].

Furthermore, better understanding not only of the changes in the adaptive T cell compartment but also in the innate compartment occurring with aging will help to better understand how the inflammaging concept may also have some adaptive characteristics and not only be considered the driver of age-related diseases [14]. It is of paramount importance to assess the role of the trained immune memory in aging humans [38, 67]. Furthermore, this would help also to design better vaccines. This is demonstrated by the success of Shingrix a vaccine designed for elderly to prevent herpes zoster reactivation, which uses a special adjuvant to help boost the innate immune stimulation toward an effective adaptive immune response in 80 to 90% of old individuals [29]. This would perhaps end the misleading concept that elderly do not respond to vaccination. As we have already stated, this is not the fault of the immune changes with aging but the use of inadequate vaccines, such as in the case of the influenza vaccines, and in particular vaccines that were designed for the immune systems of younger individuals. The increased success of the quadrivalent vaccine is the proof that elderly can built efficient and protective responses [232–234].

Finally, the understanding of the holistic nature as well as the step by step progression of the immune system should lead not to the "single pill" intervention model but to the multimodal/multistep intervention model.

Conclusion

Aging is a natural process which ultimately results in death. However, the aging process should not be defined only by the perspective of death, which is inevitable. Concomitantly, it is often conceptualized that aging is the major underlying cause of all alterations occurring with aging and leading to age-related diseases, forgetting that these disease processes started long before the beginning of old age. However, the aging process is very different for each individual, which means that aging is not occurring uniformly in every human being. This underlies the plasticity of the physiological functions' changes accompanying aging, including those of the immune system.

The immune system has evolved to protect us from aggressions and challenges. It is well established that its dysfunction can lead to pathologies in the elderly. However, not all elderly will suffer from these diseases: more and more are reaching a very old age, with centenarians and semi-supercentenarians having a relatively well-functioning immune system. So, the immune system during life is depending on its individual, unique immunobiography, consequently developing concomitantly adaptative and maladaptive aspects of its functioning. The balance between these functions will determine how the person will age (Fig. 1). It is possible that the effect of age may only be detrimental, as the most common paradigm is stating. However, a more positive and balanced consideration of the immune response with aging will permit us to intervene in a judicious manner. Still, many studies are needed to learn how to not intervene when it is not necessary and how to intervene in a multimodal/multistep way where it is needed. Better lifestyle, vaccines, and microbiome modulation will help to increase the adaptaging part of the immune system for a healthier life of old individuals.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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