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The conundrum of human immune system "senescence"

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ABSTRACT

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There is a great deal of debate on the question of whether or not we know what ageing is (Ref. Cohen et al., 2020). Here, we consider what we believe to be the especially confused and confusing case of the ageing of the human immune system, commonly referred to as "immunosenescence". But what exactly is meant by this term? It has been used loosely in the literature, resulting in a certain degree of confusion as to its definition and implications. Here, we argue that only those differences in immune parameters between younger and older adults that are associated in some definitive manner with detrimental health outcomes and/or impaired survival prospects should be classed as indicators of immunosenescence in the strictest sense of the word, and that in humans we know remarkably little about their identity. Such biomarkers of immunosenescence may nonetheless indicate beneficial effects in other contexts, consistent with the notion of antagonistic pleiotropy. Identifying what could be true immunosenescence in this respect requires examining: (1) what appears to correlate with age, though generality across human populations is not yet confirmed; (2) what clearly is part of a suite of canonical changes in the immune system that happen with age; (3) which subset of those changes accelerates rather than slows aging; and (4) all changes, potentially population-specific, that accelerate agig. This remains an immense challenge. These questions acquire an added urgency in the current SARS-CoV-2 pandemic, given the clearly greater susceptibility of older adults to COVID-19.

1. Introduction

Contributions to this Special Issue of Mech Ageing Dev address the outcomes of a recent symposium on the biology of aging asking whether or not we know what ageing is (Cohen et al., 2020) and see https://www.fourwav.es/view/1393/info/). Regarding this question of what is ageing in the specific context of immunity, one thing is clear: it is incontrovertible that the human immune system, like any other normal somatic tissue, appears to be different in younger and older adults both in its architecture, composition and function. Clearly, organisms must display changes to many phenotypic traits across developmental and later life-history stages that are age-associated but not necessarily senescence. Some of these changes, perhaps especially those seen in the immune system, are the result of the execution of a life-history strategy that has been shaped by both natural and sexual selection (Schmid--Hempel, 2003). Under the umbrella term "immunosenescence", certain changes to immunity are believed to result in an increased susceptibility to, and severity of, infectious disease and to contribute to many or perhaps all non-communicable age-associated diseases, among them neoplasia, cardiovascular disease, and autoimmunity. It is proposed that understanding these events can be best achieved in the context of the exertion of evolutionary pressures. Newborns have a naïve immune system that must rapidly recognize and respond to the myriad of pathogens in the environment, overcome all these challenges and develop protective immunity to those most commonly present in the locality. There is thus an immediate potent selective pressure, reflected in the large investment of resources in immunity throughout childhood. The amount of resources required to develop and maintain efficient immune responses under excessive pathogen pressure may need to be so large to ensure survival that it can result in significant growth retardation (Urlacher et al., 2018). Such negative associations between immunocompetence and growth have been described in a wide range of species and ecological conditions (e.g. in wild populations of vertebrates (Soler et al., 2003; Palacios et al., 2020) as well as modern hunter-gatherers or forager-horticulturists (Urlacher et al., 2018)). Those individuals surviving the local pathogen onslaught will have developed protective adaptive immunity by the time of sexual maturity and are thus better equipped by virtue of the genes that ensured their survival to face the local pathogen environment so that when they reproduce, these genes are enriched in the population. At puberty, the production of new naïve T cells plummets because of the normal developmental (not senescent) process of thymic involution (Thomas et al., 2020), and the individual then relies predominantly on adaptive immune memory for the prevalent local pathogens, with fewer naïve T cells available to respond to new pathogen challenges which the individual might never need to face (Pawelec, 2018). Therefore, after adulthood and reproduction, there is a trade-off between protection against known "tribal" pathogens and the investment of resources in the generation of T cells specific for pathogens that might never be encountered (and which, apart from being resource-intensive also carry the risk of generating autoimmunity). The older individual must therefore rely on a minor pool of residual naïve cells and a major biased reservoir of accumulated memory cells.

Unlike adaptive immunity, innate immunity is conserved in both vertebrate and invertebrates (Muller et al., 2013), and essentially retains functionality or even becomes over-exuberant with age. Within this scenario, we would predict that immunosenescence in older humans would include low amounts of naïve T and B cells, high numbers of memory cells and potentially over-active innate immune cells which would need to be assessed in the context of their long-term residence in an aged host. Here, we will consider how well the available data in humans conform to the expectations of this paradigm. Given the dynamic nature of the immune system, distinguishing between adaptive responses and changes caused by the ageing process are highly problematic. To overcome this difficulty, it is proposed that only those differences between younger and older individuals that have been robustly associated with detrimental health, reproductive and survival outcomes, or those for which this is highly likely but not yet proven, should be considered as indicators of "senescence" in the exact meaning of the word proposed here. There was considerable debate around this issue centered around whether certain properties of the immune system associated with strict immunosenescence might also manifest under other circumstances, analogous to the findings that replicative senescence programs are reported to be essential for tissue remodelling in embryogenesis (Munoz-Espin et al., 2013). We propose overcoming this mostly semantic problem by employing a similar tactic to the useful distinction in population genetics between broad-sense heritability and strict-sense heritability (Visscher et al., 2008). Thus, we would need to distinguish between 1) Changes in the immune system with age that are adaptive for the individual; 2) Changes in the immune system with age that may have positive effects on some aspects of health and negative effects on others; 3) Changes in the immune system with age that may have positive or negative effects under different environmental contexts, or in different individuals, and are thus difficult to classify as adaptive or detrimental; 4) Changes in the immune system with age that may have positive effects at some ages but negative effects at others; 5) Some changes with age that are known to have exclusively negative effects on health and longevity. In all cases, measurement issues are a major factor, and in many instances we do not yet know which age-associated immune changes are assignable to which category. Hence, at this stage, we propose that it might be useful to distinguish between 1) Strict, general immunosenescence in which age-associated changes have been defined as exclusively detrimental; 2) Strict, individual immunosenescence in which changes are detrimental within an individual in their particular context, even if these are not the same as for others, and even if measurement issues preclude establishing exactly what every one of these changes is; 3) Broad immunosenescence (all changes in the immune system with age, regardless of whether they are beneficial or not, which may be hard to ascertain).

This uncertainty about how to define immunosenescence and interpret its significance for health during aging is analogous to a similar uncertainty regarding the significance of sarcopenia, anthropometric changes and cognitive decline associated with age; are they harbingers of frailty and morbidity or not? This part of the argument is being actively pursued by the "Immune Ageing Working Group" formed recently to discuss the possibility of coding senescence as a recognized disease state (Calimport et al., 2019) and currently preparing a position paper on this topic.

2. Where did we stand in 2019?

A the time of the conference referred to above (https://www.fourwav.es/view/1393/info/) it was common to find a dominant paradigm in the literature that "declining function of the immune system, termed "immunosenescence", leads to a higher incidence of infection, cancer, and autoimmune disease related mortalities in the elderly population" to cite one common way of introducing the topic (Stahl and Brown, 2015). This notion has encouraged numerous attempts by companies and academia to find interventions that prevent or reverse it (Faragher et al., 2014; Capri et al., 2006; Aspinall and Lang, 2018; Aiello et al., 2019). First demonstrating which changes of immune ageing are in fact associated with detrimental health outcomes and only then trying to restore them to an appropriate level may indeed be theoretically desirable. However, prior to establishing which are truly detrimental, rather than merely different in aged individuals, such intervention would be premature, and in some cases might be dangerous (Cohen et al., 2019). One has to say that with this in mind most such efforts are indeed premature because we do not know which parameters to take as biomarkers reflecting these changes, and mistakenly attempting to "correct" adaptive changes would be undesirable. Hence, there is an argument in favour of attempts to classify such biomarkers of senescence in ageing in general, and even more challengingly in immunosenescence in particular, in order to generate actionable entities for treatment (Calimport et al., 2019). Hence, ideally, to identify true indicators of immunosenescence, confounding factors should be considered when designing the experiments, including individual health status, adaptive immunity, and ethnic differences, but in practise this is a major challenge in humans.

So, as alluded to above, a clear definition of the term "immunosenescence" is required, if only to distinguish it from the phenomenon that most springs to mind for biologists of ageing who are not immunologists. Thus, we need to be clear that "immunosenescence" does not refer to the cell biological concept of "replicative senescence", describing the "Hayflick Limit" at which somatic human cells cease dividing due to telomere attrition (in vitro) (Hayflick, 1968; Harley et al., 1990). It rather refers to differences between younger and older individuals, sometimes shown to be changes, but most often only assumed to be changes, in the output of immune cells from the bone marrow, the distribution of immune cells in the periphery and their functionality. Within populations of different immune cell types it is likely that some do exhibit signs of replicative senescence, but the term immunosenescence encompasses far more differences. To define immunosenescence, it is proposed that only those differences that have been shown to be associated with a detrimental clinical outcome (e.g. mortality, frailty, poor response to vaccination, etc.) should be included. Thus, it is still the case that the majority of published studies documents differences between older and younger adults but fails to associate these with a measurable poor clinical condition or with mortality. Moreover, most of the reported differences have not formally been shown to be actual changes over time by means of longitudinal studies. Therefore, age-specific changes in immune traits within individuals might be underestimated in cross-sectional analyses if within a population there is a selective disappearance of individuals with low immunocompetence (Froy et al., 2019; Vaupel and Yashin, 1985). In addition, patterns observed from cross-sectional studies might be mostly attributable to numerous differences between birth cohorts from the early-to-mid 20th century who are now being compared in cross-sectional studies with young controls from the early 21st century (Pawelec, 2019). There have been such striking changes in environment, climate, nutrition, education, life style and morbidity profile - not to mention advances in medicine and public health, including vaccination policies and practices (to name but a few factors) in the intervening years, that studies of such cohorts are not comparing like with like. Thus, individual immunocompetence (and associated immunophenotype) will have been driven to differ not only across age strata but also within strata owing to inequities in health care and other social disparities (Mbow et al., 2014; Labuda et al., 2014). It is essentially impossible to control for these confounding factors, and for practical reasons earlier longitudinal studies mostly focused on following up people already very old, say 85 years of age, so that health and immunity changes over a few years will already be informative for mortality. Such approaches were rare, but some pioneering studies including simple immune parameters were already ongoing several decades ago, e.g. the Baltimore Longitudinal Study of Aging [https://www.nia.nih.gov/research/labs/blsa], the Leiden 85-Plus study (von Faber et al., 2001) and the Swedish OCTO and later NONA studies (Wikby et al., 1994). These oldest-old populations were of course not representative of ageing and mortality of the majority of people in those countries' general population, but at least such long-lived selected populations allowed the hypothesis to be tested that the immune parameters identified at baseline, and in some studies their changes over time, are associated with mortality within a relatively short period of time. Since these early studies, several important longitudinal studies have been established using more sophisticated immunological assessments to associate baseline immune parameters, and changes thereof over time, with clinical outcomes including not only mortality but also more granular clinically-relevant outcomes like responses to vaccination and frailty/morbidity. Such results, supplemented with data from cross-sectional studies identifying differences in immune biomarkers between younger and older adults, are finally beginning to define immune signatures determining whether a person is truly "immunosenescent". Do we now know what these immune parameters are and which outcomes we should assess? The following sections consider this question.

3. Where do we stand in 2020?

A consensus from published studies delineates one immune parameter consistently reported to be different between younger and older adults, namely the very low absolute and relative counts of naïve $CD8^+$ T cells in the peripheral blood of older adults (Fagnoni et al., 2000). This is not to say the older adults actually do possess fewer naïve T cells because data on the presence of immune cells in other organs are mostly lacking and most data pertain only to circulating cells. However, the expectation is that the whole-body number of CD8+ naïve T cells is indeed low, due to markedly reduced thymic output and cell mortality owing to a lifetime's exposure to pathogens, agreeing with data from animal models. Reciprocally, it would be expected that because antigen-stimulated naïve cells differentiate into effector and memory cells, the latter would be increased in older adults, as also often reported (Fagnoni et al., 2000). It is thus somewhat surprising that $CD8^+$ memory cell accumulation in the blood of older adults is not universally reported. It has become apparent in the meantime that the accumulations of late-stage memory cells that are seen in older people are driven by persistent infection with human herpesvirus 5 (HHV5; cytomegalovirus [CMV]), but apparently not by other herpesviruses or other pathogens (Derhovanessian et al., 2010; Wertheimer et al., 2014; Derhovanessian et al., 2011). These sometimes disputed findings have been confirmed in systematic reviews, e.g. (Weltevrede et al., 2016). Because the frequency of CMV-infected individuals increases with age (in industrialized countries) (Hecker et al., 2004) and socioeconomic factors influence the number of infected people at any age (Dowd et al., 2009), CMV infection can confound the age-effects on immune and other parameters such as

glucose regulation (Chen et al., 2012) leading to spurious associations with age. Notwithstanding the different living conditions in low- and middle-income countries (LMICs), the universality of these findings is reflected in reports that loss of $CD8^+$ naïve cells may occur at an earlier chronological age in LMICs, presumably due to high pathogen burden and 100 % penetrance of CMV infection (Alam et al., 2013).

Despite differences in many immune parameters between men and women, in the few studies examining this issue, the markedly lower levels of circulating $CD8^+$ naïve T cells have been found in both sexes, further emphasising the universality of these findings (Di Benedetto et al., 2015). Intriguingly, although present, age-associated differences for $CD4^+$ naïve T cells, B cells, and many aspects of innate immunity, especially dendritic cells (DCs) and neutrophils (Stervbo et al., 2015a; Stervbo et al., 2015b), are much less marked than for CD8 + T cells, one of the enduring mysteries in immunosenescence research. Again, it should be emphasized that the majority of immune cells resides in tissues and not in blood, and that the latter most likely does not reflect patterns of cell subset distribution elsewhere (Thome and Farber, 2015). To reflect patterns of cell subset distribution in tissues with aging, ongoing technical developments in single-cell RNA sequencing are becoming a powerful tool, reflecting changes of cell-type composition within a tissue, and also comparing changes between organs. Moreover, this unbiased technology will provide an age-related transcriptomic profile of each cell subset. Combined with immunostaining and lineage tracing, it will also provide information on whether immune cells infiltrate or expand locally in the tissue. These new techniques promise exciting future discoveries, but so far, the few data on immune cell distribution in tissues in younger and older people are still too limited to be able to suggest any firm correlates with ageing, although pioneering work examining the distribution of immune cells in different organs post-mortem has revealed marked differences between blood and tissues (Thome et al., 2014; Dogra et al., 2020; Thome et al., 2016). However, we must still accept that for the bulk of thus-far available data, we have to rely on blood biomarkers, and that any mechanistic interpretations of their biological impact can only be hypothetical. An exception to this statement would be the important pioneering work on skin immune reactions in older adults (Akbar et al., 2013) which is being very informative in illustrating differences between in situ immune reactivity in younger and older adults (Vukmanovic-Stejic et al., 2018). In that study, antigen challenge locally in the skin was employed to investigate differences in tissue-specific mechanisms responsible for lower responses to virus in older adults, showing lower T-cell infiltration and increased sterile inflammation. This excessive inflammation locally in the skin early after antigen challenge inhibited antigen-specific immunity. The application of this type of approach to questions of immune dysfunction in the elderly remains rare so far.

4. Longitudinal studies allow individual changes over time to be mapped

Longitudinal follow-up studies are required to establish change over time and associate immune biomarkers of ageing with robust clinical outcomes. The selection of these outcomes is challenging, with all-cause mortality the most robust but less informative than, for example, response to vaccination. As the latter is most commonly studied for influenza, many confounding factors complicate interpretations. Response to vaccination are considered below (see Section 5). In this section we will consider the clear endpoint of mortality and the less well-defined endpoints of morbidity and age-associated disease as proxies for ageing. Clearly, factors influencing these outcomes are not likely to be exclusively immune-related, and this is reflected in the inclusion of a multitude of variables in more recently-planned longitudinal studies, such the Baltimore Longitudinal Study on Aging, the Stanford cohort, the Berlin BASE-II study, the BELFRAIL study, the Newcastle 85-Plus study, the Leiden 85-Plus study and others. Indeed, the earliest studies were mostly designed to ask questions unrelated to immunology, onto which some immunological assessments were retrospectively bolted – this was the case with the pioneering Swedish OCTO/NONA studies. The latter established that a constellation of simple immunological measurements, but not any single one by itself, was informative for 2-, 4-, and 6-year survival on follow-up of people 85 years old at baseline (Wikby et al., 1994; Ferguson et al., 1995). This so-called "Immune Risk Profile, IRP" (Pawelec et al., 2001) included poor T-cell proliferative responses to mitogens, high CD8 + T cell numbers and percentages, and low CD4 + T cells and CD19 + B cells. The study included resampling at these two-year intervals and tracked changes to the IRP over time, revealing that individuals who acquired the IRP showed increased mortality over the next two-year period (Wikby et al., 1998). The IRP was associated with CMV-seropositivity (Olsson et al., 2000) and the accumulation of late-stage differentiated CD8 + T cells that had lost expression of CD27 and CD28 (positive costimulatory receptors), and gained expression of KLRG-1 (with negative costimulatory function) and CD57, normally expressed by natural killer cells (Ouyang et al., 2003). Many of these cells were specific for CMV antigens, and the number of such clonal CD8 + T expansions was directly related to the survival time at very old age (Hadrup et al., 2006), underlining the importance of these cells with a "senescent" phenotype in facilitating continued survival of these oldest-old subjects. These studies were also important in illustrating that the IRP was in fact a relative weak predictor of survival, compared to higher levels of IL 6 in the blood, which was associated with cognitive impairment as measured by standard tests and formed a cluster more closely associated with mortality (Wikby et al., 2006). Strikingly, individuals with both this "inflammageing" phenotype and the IRP had much worse survival than those with either one or none of them. Therefore, at least in this population, inflammageing and immunosenescence are separable. It was notable, if initially unexpected, that neither absolute values nor percentages of naïve CD8 + T cells were associated with mortality in these Swedish studies. This was also found to be the case in limited analyses in the Leiden 85-Plus study, where a paucity of naïve cells had no effect on 8-year survival – but higher levels of CD8 + T cells reacting to CMV antigens with a predominantly pro-inflammatory response were strongly correlated with survival time (Derhovanessian et al., 2013). Rather than being senescent, such cells may be critical for continued survival, a point reinforced very recently by the description of so-called "inflammescent" cells driven by CMV (Morris et al., 2020). This is yet another clear example of factors which can be associated with either positive or negative outcomes, depending on the circumstances and could be an illustration of the general finding that immunity is a dangerous ally. These results are consistent with the notion that immune control of persistent CMV infection was paramount in these very elderly people, but both the Swedish and the Dutch studies were conducted on very small numbers of people and the generalisability of these findings is uncertain. Larger studies such as the BELFRAIL study revealed that 3-year survival on follow-up of 85-year--old Belgians was greater in women who were CMV-seropositive and showed accumulations of late-stage CD8 + T cells as reflected in a CD4:8 ratio <1. Strikingly, none of these parameters had any relevance for survival of men (Adriaensen et al., 2017). Thus, in marked disagreement to data reported elsewhere, here an IRP was defined in CMV-seronegative women (only) with a CD4:8 ratio >5, which was due to accumulations of CD4+ naïve cells. These data offer a striking illustration of marked differences in different populations, or perhaps more likely, in different birth cohorts (end of the 19th century-vs-first quarter of the 20th). However, these studies were not able to include a survey of other factors which were shown to have a stronger association with mortality in the Swedish studies, namely markers of inflammation such as IL 6, often taken as a surrogate for "inflammageing". Hence, examining immunological (and other) variables with a broader brush may yield less context-sensitive inconsistent results. Such studies are ongoing, including one recently published on the Stanford Clinical and Translational Research Unit Cohort (Alpert et al., 2019). This seminal study took a "multi-omics" approach to analyse immune parameters at

baseline and in younger and older adults who were reanalysed every year over a 9 follow-up. This approach encompassing expression of immune-related genes captured changes over time of a much wider range of parameters which were correlated with overall survival. As with the much more limited protein-level analysis in the Swedish studies (Nilsson et al., 2003), an immune signature ("IMM-AGE") emerged which was surprisingly independent of exact chronological age or health/disease statuses, with the rapidity of its change being independent of age at baseline, and suggesting that it had already been "pre--programmed" at that time (all participants were adults). This is consistent with the notion that the immune system is "programmed" prior to puberty by the local environment, primarily driven by "tribal" pathogen exposure local to the group. The approach taken in this paper by Alpert et al. identified those fixed parameters whose changing trajectories with age may be important for health and survival mostly as those factors already identified in earlier studies. Thus far, the crucial importance of these signatures has been documented by its application to a completely different population, the Framingham Heart Study, where it was able to predict mortality more accurately than other established biomarkers in this extremely well-investigated cohort (Alpert et al., 2019). Moreover, although IMM-AGE did correlate to some extent with the well-established "DNA methylation clock" linked to chronological age (Bocklandt et al., 2011), its association with overall survival was far closer than that of methylation age. In this respect, it would be interesting to test additional DNA methylation clocks, e.g. those trained on age-related phenotypes and mortality.

5. Impact of age on vaccination

As noted, all-cause mortality or even disease-specific mortality is a clear clinical outcome but not very informative otherwise. Morbidity, assessed by frailty, would be an important alternative but is controversial. Alternatively, responses to vaccination, exceedingly important for the elderly who often respond poorly, would be a very valuable endpoint. Increasing the success of infectious disease vaccines for the elderly is of paramount importance, as starkly emphasized by the SARS-CoV-2 pandemic currently raging during the preparation of this paper (Pawelec and Weng, 2020). $CD8^+$ T cells are required for clearing virally-infected cells, but are those most affected in ageing. The $CD4^+$ T helper cells (Czesnikiewicz-Guzik et al., 2008), antibody-producing B cells (Frasca, 2018), DCs that present antigen to T cells (Agrawal and Gupta, 2011), the lymph nodes in which this takes place (Thompson et al., 2017), are all also compromised to some degree in the ageing host. Many studies have focused on seasonal influenza due to its enormous public health impact, and currently of course on SARS-CoV-2. Here, a clear distinction must be made between vaccines intended to protect against neoantigens, which are generally less effective in the elderly, and those that boost waning memory responses, which can be highly effective in the elderly if given with an effective adjuvant. The latter are most impressively illustrated by the success of Shingrix, the Varicella Zoster vaccine against shingles (McElhaney et al., 2019). However, for new exposures, especially to newly-emerged pathogens such as currently SARS-CoV-2, because of the likelihood that most older people possess a narrowed T cell receptor repertoire due to a greatly reduced naïve T cell pool (Naylor et al., 2005; Egorov et al., 2018), it is conceivable that potential "holes in the repertoire" represent one of the biggest problems when the old immune system must face a new challenge. While this is likely to be true, at least in animal models (Yager et al., 2008) there is in fact surprisingly little published data on this in humans, but is likely to apply to us as well (Zhang et al., 2016). One study directly addressed the consequences in terms of clinically-relevant responses to vaccination against yellow fever (YF) and showed that differences in the $CD4^+$ and $CD8^+$ T cell response, and in DC function were associated with lower antibody titers (Schulz et al., 2015). This study measured recent thymic emigrants (RTEs) as a surrogate for the availability of naïve T cells and showed that lower numbers thereof were associated with poorer responses. Importantly, this study not only supports the expected result that fewer naïve cells presents a problem for combatting pathogens to which the individual was not previously exposed, but also points to what might be crucial inter-individual differences (Tosi et al., 1982) in the residual RTE output from the remnant thymus at late life.

The impact of donor immune age on influenza vaccination is complicated to dissect for many reasons, primarily due to the emergence of different seasonal strains of the virus, and the different levels of T cell memory depending on past exposures (McElhaney et al., 2020). Additional complications arise from the manner in which responder or non-responder status is assigned. For practical reasons, this is not usually done by measuring the degree of protection, but by the unreliable surrogate of post-vaccination changes in antibody titer. It may sometimes be the case that the presence of an already-high titer in an individual cannot be further increased and, although it may be protective, this results in the classification of that individual as a "non-responder" (Mosterin Hopping et al., 2016a). This may already account for some of the discrepancies in the literature regarding the ability of the elderly to respond – as pointed out in a recent study concluding that older adults actually responded similarly to younger ones (Mosterin Hopping et al., 2016b). However, T-cell-mediated responses as well as antibody responses are required for protection, and when these are measured instead of solely antibody levels, the common finding is that fewer older adults are able to mount a potentially protective T cell response. Failure to respond may be more likely in those infected with CMV (McElhaney et al., 2016). Moreover, in this respect, many of the accumulated $CD8^+$ memory T cells in elderly people may exert stronger immunopathological effects, possibly as the price to pay for the absolute requirement to maintain CMV-immunosurveillance. At least some of these late-stage differentiated CD27-CD28-CD57+KLRG-1+$CD8^+$ T cells with short telomeres and little clonal proliferative capacity may indeed be maladaptive – or alternatively, they may be a "necessary evil" to keep CMV in check. As "inflammescent" cells (Morris et al., 2020) they may contribute to the senescence-associated secretory profile (SASP), universally reviled as the cause of "inflammageing" (but of course, as with all things in biology, having its pros and cons). As a final point, it may be useful to consider what exactly is meant by "inflammageing" in contradistinction to "immunosenescence" because as mentioned above sometimes the terms seem to be used interchangeably. Inflammageing usually refers to the slightly higher levels of serum inflammatory factors commonly seen in older adults relative to the young, in individuals without overt infectious disease. It must be borne in mind that most data, as with immune cells, are derived from the systemic circulation and therefore represent only a biomarker. Moreover, it is likely the balance of pro- and anti-inflammatory factors that reflects the individual's overall status (Morrisette-Thomas et al., 2014). Associations of higher levels of pre-inflammatory cytokines like IL 6 have been linked to frailty and mortality (Michaud et al., 2013) as well as inhibited immune function, and efforts to block inflammageing without causing global immunosuppression are being actively considered and trialed (Chambers and Akbar, 2020). The relationships of these factors to immunity, however, are not clear. Their origin is not necessarily immune cells or exclusively immune cells, but it is perhaps more likely that they could be part of the SASP produced by senescent non-immune cells (Tchkonia et al., 2013). Hence, focusing on causality consistently places inflammageing in the foreground as the postulated direct agency of degenerative changes in many or most organ systems, including immune systems. The latter also face the compromise imposed by thymic involution which may be a crucial event for conservation of resources under hunter-gatherer conditions. The critical balance between the energetically expensive and potentially unreliable ally of adaptive immunity and its necessity for protecting against infection early in life is exemplified by findings that, for example, growth retardation in Amazonian children paralleled by inflammatory status is the price that must be paid for dealing with high pathogen loads in humans (Urlacher et al., 2018).

Finally, an additional reason for the poorer responses to vaccination in older adults may be the general slowdown in metabolism, proliferation, and information processing with age, a general manifestation of aging processes and not specific to the immune system. Nonetheless, it may contribute to slower immune responses and longer healing process in the old compared to the young, which in turn may contribute to both immunosenescence and decline in the ability to recover (resilience) eventually increasing mortality risk with age and limiting longevity (Ukraintseva et al., 2016).

6. Conclusions

Immune parameters assessed in cross-sectional studies clearly document multiple differences between younger and older populations. Animal studies as well as some more limited longitudinal studies in humans indicate that many of these differences are indeed likely to be intra-individual age- and environment-associated changes. Some immune signatures established as subject to distinct changes with age can be associated with important health outcomes such as frailty and responses to vaccination, and finally, with mortality. Many others are clearly hallmarks of the adaptation to exposures over the lifespan and continue to play a positive role in maintaining organismal integrity. Many may be informative only in the population in which they were assessed, and the search for truly universal age-associated changes in immune markers is ongoing. Whether these exist as reflections of ageing processes *per se* is open to question (Waaijer et al., 2019). Thus far, they mostly seem limited to reductions in numbers, proportions and the antigen receptor repertoire of peripheral blood naïve T cells and other immune cells. In turn, this reflects thymic involution at puberty and the degree of residual thymic function in later life, as well as possibly dysfunctional haematopoiesis (Leins et al., 2018) and the poorly defined detrimental systemic milieu in older individuals which remains mysterious (Ashapkin et al., 2020). Generating multidimensional immune signatures (Alpert et al., 2019) and incorporating multiple additional fields (Belsky et al., 2015) into constellations of markers may eventually lead to the development of an immunosenescence phenotype "IMP" that would be clinically-relevant and generalizable across different birth cohorts in different environments influencing the multiple immune system compensatory mechanisms (e.g. homeostatic proliferation, memory stem cells, anti-inflammatory mechanisms) which are important for counteracting some of the putative age-associated changes.

Declaration of Competing Interest

AAC is founder and CSO at Oken Health.

S.C.C. declares that he has consulted for and has received honoraria, test products and/or research funding from Abitec, Accera, Bulletproof, Servier and Nestlé Health Science, is the founder of Senotec and is co-inventor on a patent for an medium chain triglyceride formulation.

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