



HAL
open science

Impact of stress on aged immune system compartments: Overview from fundamental to clinical data

Tinhinane Fali, H el ene Vallet, Delphine Sauce

► To cite this version:

Tinhinane Fali, H el ene Vallet, Delphine Sauce. Impact of stress on aged immune system compartments: Overview from fundamental to clinical data. *Experimental Gerontology*, 2018, 105, pp.19-26. 10.1016/j.exger.2018.02.007 . hal-02352184

HAL Id: hal-02352184

<https://hal.sorbonne-universite.fr/hal-02352184v1>

Submitted on 6 Nov 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destin ee au d ep ot et  a la diffusion de documents scientifiques de niveau recherche, publi es ou non,  emanant des  tablissements d'enseignement et de recherche fran ais ou  trangers, des laboratoires publics ou priv es.

Impact of Stress on aged immune system compartments:

Overview from fundamental to clinical data

Tinhinane FALI ¹, H el ene VALLET ^{1,2,3}, Delphine SAUCE ^{1,2*}

1. *INSERM, Centre d'Immunologie et des Maladies Infectieuses (CIMI-Paris U1135), Paris, France.*
2. *DHU Fighting Aging and Stress (FAST). Sorbonne Universit es, UPMC Univ Paris 06, Paris, France.*
3. *Piti -Salp tri re Hospital, Unit of Peri-Operative Geriatric care (UPOG), Geriatric Department, Paris, France.*

*To whom correspondence should be addressed:

Delphine Sauce, Infections and Immunity, INSERM U1135, H opital Piti -Salp tri re, 75013

Paris, France. Fax: +33-1-42-17-74-90. Telephone: +33-1-40-77-98-89. Email:

delphine.sauce@upmc.fr

Abstract :

Life expectancy is continuously increasing due to major progress in preventing, delaying or curing various pathologies normally encountered in old age. However, both scientific and medical advances are still required to understand underlying cause of the disparate comorbidities occurrence with aging. In one hand, aging profoundly impairs the immune system; it is characterized by many changes in haematopoiesis, adaptive and innate systems, associated with pro-inflammatory environment. In another hand, stressful events (acute or chronic) can also impact the immune system through the secretion of hormones, which are also altered with aging. The field of psychoneuroimmunology is now providing evidences that in acute medical conditions, elderly people are not equal in their responses to stressors depending on many extrinsic and intrinsic factors. These parameters could interfere with elderly's ability to mount an effective immune response.

The objective of this review is to provide an overview of the literature (from fundamental to clinical observations) to draw a parallel between immune dysregulation caused by stress or by aging. Understanding this entanglement could enable us to target fundamental age-related pathways and thus open new avenues in improving both lifespan and health span.

Key words: Stress, Immunity, Aging

1. Introduction

Around the world, elderly population is growing. The Department of economic and social affair estimated that the over-60s has tripled since 50 years and will be tripled again in 2050. In 2000, it has been estimated in the report titled “World population ageing: 1950-2050” that 69.2 millions of people were aged of 80 years old and over. In 2050, they will be 379.2 millions. Moreover, in 2050, the number of centenarians will be eighteen times higher than in 2000 with 3.2 millions of people [1].

This population aging asks many questions in scientific, medical, societal or ethic areas. A better comprehension of fundamental mechanisms of aging is necessary to prevent and treat age-related diseases. The objective is to develop new therapeutics targeting aging, which involve a close collaboration between scientists and practitioners in the field of Geroscience [2].

Aging can be defined as a progressive decrease of reserve capacities that are specific of each individual. This process, called “frailty” by geriatricians, leads to a gradual loss of physical and cognitive capacities, with an alteration of functional autonomy and quality of life [3]. Frailty is associated with higher mortality and medical complications as falls, swallowing disorder, hospitalizations or institutionalizations. Moreover, aging is the main factor risk for chronic diseases [3] and in acute medical conditions, elderly people are not equal to respond to unexpected threat in case of stress. The capacity to overcome an acute stress is depending on reserve capacities that are impacted by many factors such as the degree of physiological aging and chronic medical condition. These two factors are profoundly dependent on genetic

background, epigenetic, immunological, biological and environmental factors [4, 5].

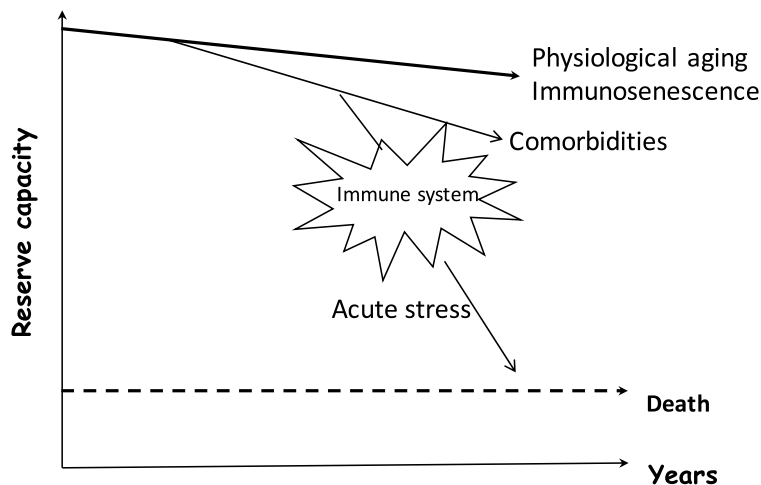


Figure: Aging is a complex process with many inter-individual variations. Physiological modifications including immunosenescence and comorbidities contribute to the decrease of individual reserve capacities. Acute stress drives an important break in patient's evolution and can lead rapidly to death. The immune system is affected by this stress which participates to the bad evolution of elderly patients (Adapted from [6])

Knowledge in the area of human's immunosenescence improved these last decades, but mechanisms implicated in the impact of stress on immune system in the elderly are still poorly understood. Actors involved in resilience capacity need therefore to be better characterized to warrant not only an increased lifespan to the elderly population, but also and importantly to improve its health span.

The objective of this review is to provide an overview of the literature about immunosenescence and stress.

2. Immunological changes with aging

Aging is associated with a decline of the immune system competence termed immunosenescence. It's outlined by several characteristics that affect the adaptive and innate immune compartment [7], as well as the hematopoietic compartment. It is also associated with of a high level of pro-inflammatory cytokines secretion at baseline, called “inflamm-aging”, resulting in a decreased ability to mount an effective immune response to antigens.

2.1 Aging of adaptive immune system

T-cells

Age-related changes in T cell compartment are characterized by 3 main hallmarks: (i) decrease of naïve T cells numbers related to thymic involution [8, 9]. The thymus is the primary lymphoid organ where lymphoid precursors mature into naïve T cells. With aging, the thymus changes in structuration with a progressive decreased mass of functional tissues, progressively replaced by fat accumulation. (ii) Shrinking of the TCR repertoire that determines antigenic diversity broadness and thus preconditions the successful elimination of pathogens from the system [10, 11]. (iii) Increased proportion of terminally differentiated oligoclonal effector memory T-cell populations, particularly encountered with the control of persistent viral infections such as cytomegalovirus [12]. Additionally, T cells switch to a pro-inflammatory cytokine profile with an increase production of IL-6, TNF- α and IFN- γ implicated in the ‘inflamm-aging’ process. Furthermore, frequency of FOXP3⁺ CD4⁺ regulatory T cells increases with age [13], and their capacity in regulating IL-10 production from target CD4⁺ T cells increases in humans [14].

Global gene-expression profiles have been analysed in T cell subpopulations during aging. Based on their known functions, altered genes expression is observed with increased lifespan: (i) the cell-surface receptor expression, exemplified by the loss of CD28 expression on aged memory CD8⁺ T cell who switch to the accumulation of effector/senescent CD57⁺ T cells

[15] with low level of proliferative capacity [16] and higher level of NK cell markers (CD16); (ii) high level expression of chemokine and cytokine receptors in both CD4⁺ and CD8⁺ aged T cells (CX3CR1, CCRL1 [17]), (iii) altered expression of effector molecules (reduced expression of IL-7R and IL-12R on memory CD8⁺ T cells and reduced expression of IL-13, CCL4 and Granzyme B) (iv) altered transcription factors in memory T cells (elevated expression of T-bet related to TH1 lineage development and of EOMES which induces production of IFN γ , perforin and Granzyme B). Reduced expression of MYC, an important regulator of cell proliferation, differentiation and apoptosis, is also found in memory T cells from elderly.

B-cells

It has been reported that age-associated changes in the distribution of the peripheral B cells reflect both decreased B cell generation from the bone marrow and increased B cell longevity. Effectively, the number of B cells in the periphery decreases in old humans. As a consequence of decreased generation of early progenitor B cells, the output of new naïve B cells is reduced [18, 19], and consequently antigen-experienced memory B cells are expanded [19]. This causes a altered antigen-recognition repertoire of B cells and optimal pro-inflammatory cytokines production in old humans [20]. Moreover, class switch recombination is impaired in memory B cells with aging [21, 22]; this may also participate in the decline of the quality of humoral response [23]. It has been reported that both, the enzyme for class switching, activation-induced cytidine deaminase (AID) and E47 proteins, the transcription factor that controls it expression, are down regulated in B cell from elderly individuals [24, 25]. This leads to impaired production of higher affinity protective antibody [26]. In addition, the incidence of B cell malignancy in older adults with oligoclonally expanded B cells is increased [27].

The fact that higher level of autoantibodies and increased frequency of autoimmune diseases are observed in older individuals suggests a failure in B-cell tolerance mechanisms during the aging process. It is probably during transitional B-cell development in elderly, where the reduced production of early B cell progenitor impacts on the peripheral B cells distribution that leads to the emergence of a unique auto-inflammatory B cell subset. This age-associated B cells (ABC) are defined in human by high expression of the transcription factor T-bet and surface marker CD11c [28, 29].

2.2 Aging of innate immune system

The innate immune system of older individuals appears also to be affected with aging. Despite a constant number of polynuclear neutrophils (PNN) [30], their functions are altered [31, 32] with a decrease capacity of LPS activation, phagocytosis [33], chemotactism [34], oxidative burst [35] and antioxidant shield. Changes in the elderlies' functions of PNNs are reflected in decreased signalling transduction cascades and pathways [30, 36, 37], altered Toll-like receptors (TLRs) signal transduction, skewed granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced signal transduction, alterations in the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) and p38 mitogen-activated protein kinase (p38 MAPK) signalling pathways.

In the elderly population, number of monocytes and macrophages is comparable to young population. Nevertheless, aging is associated with a redistribution of the different subsets in favor of pro-inflammatory subsets. There is an increase of pro-inflammatory ($CD14^{++(high)}/CD16^+$) and non classical ($CD14^{+(low)}/CD16^+$) monocytes and a decrease of conventional ($CD14^+/CD16^-$) monocytes in human elderly [38]. Moreover, compared to young population, elderly human monocytes express more CD11b (integrin involved in migration) and less L-selectin (involved in rolling and adhesion to endothelial cells) that

could affect monocytes functions in elderly [39, 40]. Finally, age is associated with an impaired pro-inflammatory response of monocytes to TLR1/ 2 [38] but an increased pro-inflammatory response of monocytes to TLR4 stimulation with a high level of TNF α production [39].

2.3 Hematopoietic Stem cells aging

Aging affects all immune cells including hematopoietic stem cells (HSCs). The maintenance of effective immunity overtime is dependent on the capacity of HSCs to sustain the pool of immunocompetent mature cells. Self-renewal and differentiation potential of stem cells, along with their immune cell reconstitution capacity, have long been considered as infinite. Increasing evidence indicate that is not the case. Aged HSCs exhibit several functional defects, including a diminished regenerative and self-renewal potential [41]. Along with functional decline, number of stem cells also decreases with aging. Despite their self-renewal capability, the most reliable aging effect is the shift in balance from the lymphoid lineage observed in young adults to the myeloid lineage found in the elderly [42-45]. Transfer experiments (reviewed in [46]) demonstrate that HSC from aged mice to young mice are less effective to generate both B and T cells compartments. Clinical evidence in human come from bone marrow transplantation where an older age of the donor seems associated with a poorer success prognosis. Indeed, human BMT from old donors exhibit a high mortality level compared to young donors (five-year overall and diseases-free survival rates of the recipients is 25%) with an increased incidence of GvHD [47].

Nowadays, there are several postulates of stem cell aging: DNA damage due to ROS accumulation along with a decline in the activity of DNA repair gene expression and error accumulation in genetic material is always a problem for systems regardless of the age [48]. Of note, oxidative stress and reduced telomerase activity are other two factors that affect the

function of HSCs in the aged population [49, 50]. An accumulation of defects in HSCs over the lifetime might lead immune system's aging. Altogether, these observations (decrease of stem cell number, function, accumulation of DNA damage and replicative errors) demonstrate that, aging is not only a matter of the increase of damage, but also a matter of failure to replace HSC due to reduced production capacity of stem cells.

2.4 Inflamm-aging

Elderly frequently present a systemic chronic low-grade inflammation that has been coined 'inflammaging' [51], which is characterized by increased levels of pro-inflammatory cytokines (IL-1, IL-6, IL-8, tumor necrosis factor (TNF)- α and C-reactive protein (CRP)) [52, 53].

However, the cellular sources of these cytokines are still unknown. The increased inflammatory cytokines has been proposed to be a driver of less successful aging (increased morbidity, sarcopenia or frailty) and shortened healthspan [53]. The inflammatory scenario is highly complex and occurs in response to various internal and environmental stimuli mediated mainly, but not exclusively, by the high levels of pro-inflammatory cytokines. Indeed, in healthy aging, increased production of anti-inflammatory factors, such as transforming growth factor-beta (TGF- β) and IL-10, may regulate the pro-inflammatory state. Research into inflamm-aging is still at an early stage and the mechanisms involved are not yet completely understood. Several hypotheses were developed to explain this chronic low-grade inflammation: increase of stress [54] and oxidative stress [55] with aging, persistent DNA damage in senescent cells [56], stem cell aging [57]. All these mechanisms are likely interdependent. This results in the generation of Reactive Oxygen Species (ROS) causing both oxidative damage and amplification of the cytokines secretion, thus perpetuating a vicious circle of chronic systemic pro-inflammatory environment where tissue injury and

healing mechanisms proceed in parallel while damages accumulate slowly and asymptotically over decades. Furthermore, endocrine and metabolic alterations are linked to the shift of cytokine production toward a pro-inflammatory profile [58], which could explain some age-related pathologies (Alzheimer disease, Parkinson disease, osteoporosis, diabetes, cancer and Frailty cancer [59-62]).

3. Stress-induced Immune modification

Emerging evidences suggest that cross talk signals between the central nervous system (CNS), the endocrine system and the immune system are required for optimal responses to acute stress events. Indeed, these complex systems interact with each other. Various stressors can affect the circulation and activity of the cells of the immune system via direct neural interventions of the sympathetic, parasympathetic and peptidergic system or through the release of neuroendocrine mediators. The major neuronal pathways, from which stress can affect peripheral immune functions, are the hypothalamic-pituitary-adrenal (HPA) and the sympathetic-adrenal medullary (SAM) that induce the release of major mediators, such as stress hormones. The production of adrenocorticotrophic hormone by the pituitary gland results in the production of glucocorticoid hormones and catecholamines. As leukocytes have receptors for these stress hormones (acetylcholine, norepinephrine and cortisol...), cells can be modulated by the binding of these hormones to their respective receptors. Moreover, nerves can produce noradrenaline that can also modulate immune cell function by binding its receptor at the surface of immune cells within lymphoid organs. These interactions are bidirectional: cytokines produced by immune cells, such as IL-1, can modulate the production of corticotropin-releasing hormone (CRH) by the hypothalamus. Therefore, dysregulation of CNS-endocrine interplay can impact on the immune responses.

In medicine and biology, stress could be defined as physiological responses of an organism submitted to constrain. Stress could be driven by psychological or physical factors, coined stressors that are categorized by the duration and course of the stimulus (discrete versus continuous).

3.1. Animal models of stress

Studying impact of stress on human immune aging is a challenging task, both for ethical reasons in testing hypotheses experimentally and due to delays involved in any longitudinal study. In order to understand how stress impacts immune aging at the cellular and molecular levels, the use of animal model is necessary. In rodents, this includes rotational stress, footshock, restraint stress and social disruption stress.

For rotational stress the animal's cage is slowly rotated to induce spatial disorientation [63], which leads to plasmatic increases of corticosterone and epinephrine levels but has no effect on norepinephrine [64, 65]. Footshock implies a mild electric shock to the foot pads [66] and leads to an increased plasmatic corticosterone and a decrease hypothalamic norepinephrine [67]. An increased plasma corticosterone is observed in physically restraint animals [68], as well as in social disruption stress condition [69]. This involves social reorganization following addition of an "aggressor" to a group of mice.

Metabolic regulation in old mice shows that caloric restriction leads to remarkable increase in lifespan [70]. Follow-up studies including pharmacological intervention showed that mTORC1 pathway and probably the sirtuins are involved in the lifespan-boosting effects of caloric restriction (reviewed in [71]). Animal models of environmental stress show a reduction in the B1/B2-AR ratio and activation of the Beta2-AR-Gi-PI3K-Akt signalling pathway and of downstream molecules such as p53, Akt, HIF1alpha and NF- κ B, a cellular stress responses associated with heart failure [72].

Restraint stress alters immune parameters and induces oxidative stress in the mouse uterus during embryo implantation [73]. In this study, authors showed an increase in maternal plasma cortisone (CORT) secretion and reduced number of implantation site of embryos. They observed also a decreased density of uterus NK cells in the endometrium contrasted by an increased density of mast cell in the myometrium. CD4⁺/CD8⁺ T cell ratio was also decreased with less proliferative capacity of the uterine lymphocytes and cytokine production (IL-2, IL-4) associated with high level of ROS production. Oxidative stress has been linked to aging and senescence through the tumor-suppressor p53 and transcriptional responses, mediated by p44/p53 and p66 [74]. Mice models protected against oxidative stress (adenylyl cyclase type 5 KO), exhibit an increased healthspan. They are also protected against diabetes, obesity, and the cardiomyopathy induced by aging (reviewed in [75]).

3.2. Human stress

In human, models of stress have included laboratory-induced stressors such as a speech stress test and mental arithmetic stress test [76]. Life stressors (such as marital conflict, medical students undergoing examination stress [77, 78], caregivers of Alzheimer's or dementia patients [79, 80], pain following surgery [81, 82], and psychological stressors (such as depression, loneliness) are the most commonly studied. In this context, it is interesting to notice the parallel between immune dysregulation observed with aging or with stress (Table). Therefore, it is conceivable that external stressor may synergize the immune defect of a system already senescent. This has been proven through the comparative study of telomer attrition, which is the gold marker of replicative senescence. This work reveals that telomere length is shorter in mothers caring for severely disabled children (experiencing chronic psychological stress), compared to age-matched women without the caring stress [83].

Thus, since aging is associated with a natural dysregulation of immune cells, chronic stress may amplified immunosenescence (Table), and may be consider as one factor leading to the vulnerability of older individuals to age-related diseases [84]. Briefly, it has been shown that chronic stressors can influence responses to infectious pathogens (reactivation of latent herpesviruses [85, 86]), can limit the efficacy of immune responses to vaccination overtime [87, 88], and can slow wound healing [89]. Moreover, stressful events and the related immune distress lead also to the increased production of pro-inflammatory cytokines [79, 90] that are associated with a spectrum of age-related diseases (frailty, cardiovascular diseases, osteoporosis [91]).

	stress	aging
Total lymphocytes number	∨[92]	∨[93]
CD4/CD8 ratio	∨[94]	∨[95]
Lymphocyte proliferation	∨[92]	∨[16]
T-cell memory response	∨[86]	∨[96]
NK cell activity	∨[97-99]	∨[100]
Viral reactivation (herpes)	↗[86, 101]	↗[102]
Ab titers	∨[103]	∨[24]
IL-10 secretion	↗[104]	∨[105]
Plasma IL-6 concentration	↗[79]	↗[106]
Plasma IFN-g & TNF-a concentration	∨[107], [108]	↗[109]
Plasma CRP concentration	↗[84]	↗[110]
Influenza Vaccination responses	∨[111]	∨[112]
Wound healing	∨[89]	∨[113]
Telomere length	∨[114]	∨[115, 116]

Table: immune dysregulation related to stress or aging

Levels of immunomodulatory stress hormones, cortisol and DHEA, are altered with aging; circadian rhythm changes in hormone levels have recently been followed clinically to maximise immune competence to flu vaccination in the elderly [117]. Human emotions can also impact on rates of aging, and various studies have shown that optimistic personality traits predispose to greater longevity [118], while depression increases the risk of death e.g. after falls in the elderly [119].

It is noteworthy that many clinical events could be considered as acute stressors like sepsis, hip fracture, or acute cardiac failure. All these events are frequent and represent an assault, which is associated with poor prognosis in the elderly population by accelerating abruptly their progressive decline [6].

Hip Fracture

Worldwide 1.6 million patients suffer a hip fracture each year [120]. Hip fracture is a typical pathology linked to aging and its incidence drastically increased after 75 years old [120]. Prognosis of hip fracture is poor with around 30% of death at one year. Furthermore, many survivors will lose their functional autonomy [121]. Many factors such as fall, fracture itself, pain and surgery contribute to consider hip fracture as a good model of acute stress. Several studies highlight modifications of immune system after hip fracture, suggesting an important role of the immune system in hip fracture patient's evolution. In particular, the innate immune system is profoundly affected. Neutrophils undergo a transitory decrease of their chemotaxis and phagocytosis function as well as a decrease of CD16 expression, an activation of NF κ B and PI3K signaling pathways and an inhibition of NADPH oxydase that could impact the clinical evolution of patients [122]. Moreover, the 3 subtypes of monocytes (conventional, intermediate and non conventional) undergo several alterations of their phenotypes and functions, notably non conventional monocytes. Their phagocytosis function and superoxide

production are impaired, their production of TNF- α is increase and their production of IL-10 is decreased [122] compared to healthy controls. These results suggest an intense and transitional pro-inflammatory state after hip fracture where pro and anti-inflammatory markers including cytokines (IL-6, TNF- α , IL-10) [123] and procalcitonin [124] are associated with a short and long term mortality. Furthermore, patients who develop delirium present higher level of CFS and/or serum pro-inflammatory cytokines than patients without delirium after hip fracture such as IL-6 [125], IL-1 β [126]. Noteworthy, one recent publication showed that plasmatic neopterin levels, a molecule released by IFN- γ -activated macrophages or monocytes, is predictive of one-year mortality post hip-fracture in elderly. Moreover, neopterin, measured at arrival to the hospital, correlated negatively with the time of survival after hip fracture surgery [127]. Of interest, pathway leading to the production of neopterin is commonly used for 5,6,7,8-Tetrahydrobiopterin (BH4) synthesis, which is essential for the synthesis of dopamine and serotonin, two hormones involved in stress responses.

Sepsis

Sepsis is thirteen times more frequent in the elderly population and associated with twice more mortality compared to young population [128, 129]. Two immune mechanisms are described in sepsis including a first pro-inflammatory stage with cytokines storm and a second immunosuppressive to allow the return to homeostatic equilibrium [130]. Innate and adaptive immunity alterations are occurring in the course of immunosuppressive stage including monocytes functional alteration, increase of regulatory T cells, increase of inhibitor immune checkpoint expression and decrease of activator immune checkpoint expression on T cells, increase of suppressive cytokines such as interleukin 10 (IL-10) and transforming growth factor-Beta (TGF- β) [130, 131]. The persistence of this suppressive stage is associated

with a poorer prognosis, mainly death and secondary infections. Several pre-clinical studies have tested immunomodulatory agents such as interleukin 7 or anti-programmed cell death 1 antibody (anti-PD1) on septic mice models, with a significant improvement in survival [132, 133]. However, impact of sepsis on the human senescent immune system is still poorly understood and needs further investigation.

Cardiac Failure

One year after a first event of acute cardiac failure, 49% of patients older than 75 years old and 57% of patients older than 85 years old die. Moreover, risk of death after a first event of acute cardiac failure is 2.5 to 3.5 higher after 75 years old compared to young patients (<55 years old) [134]. Acute cardiac injury leads to a sustained inflammatory response. Cardiac pattern recognition receptors (PRRs) recognize some molecules released by dying or injured myocardial cells. Neutrophils and monocytes migrate into the area of tissue injury inducing a « sterile » inflammatory response with production of pro-inflammatory agents (TNF- α , histamine). PRRs also activate inflammasomes that generate a high production of interleukin 1 (IL-1) and 18 (IL-18) [135]. Moreover, histology performed on myocardial infarction shows an infiltration of activated T cells in the per-infarction regions [136], which remain trapped in the coronary wall [137-139].

4. From basic sciences to clinical trials to improve healthy aging

One interesting model of successful aging is the centenarians from who targets in favor of extended lifespan could be identified with the emergence of advanced technologies. In 2008, the study on centenarians from Ashkenazi Jewish cohort showed appearance of genetics variants in the coding sequence of IGF-1R leading to defective IGF signalling pathway,

implicated in their longevity [140]. Another study on German centenarians confirmed the appearance of polymorphisms in FOXO3a gene associated with extreme age [141]. Recently, in 2016 using SNP Genotyping, authors identified SIRT6 polymorphisms associated with human longevity [142]. The whole exom sequencing is improving rapidly the characterisation and identification of the genes linked to extend life span in a healthy way [143]. Except from their genetic specificities, human centenarians exhibit a particular immune phenotype. Italian centenarians cohort revealed a highly conserved immune profile (higher number of naive T cells and of functional memory cells with a preserved T- cell repertoire diversity). Their number of B-cells is maintained with an increased IgM titer, suggesting a better capacity to response to new antigenic challenge. Moreover, their metabolic activity is favorable with an effective insulin pathway [144] and resistance of oxidative stress [145]. One of the other immune hallmark of centenarian individuals is their ability to maintain equilibrium between pro and anti-inflammatory environment [145].

Nowadays, there is none specific biomarkers of aging or “inflamm-aging” [146] and no specific medical intervention targeting inflamm-aging. Among the anti-aging intervention, the caloric restriction (CR) was proposed because of its beneficial effect on oxidative stress and its anti-inflammatory effect. In animal models, several studies concluded to a positive effect of CR on mortality, functional autonomy, and several diseases like Alzheimer disease, Parkinson or cardiomyopathy [147]. In human elderly, results are still lacking. Although, CALERIE study shows a positive effect of CR on 2 biological algorithms of aging, their population are young (mean age: 38 years old) [148]. Furthermore malnutrition is a frequent medical condition in elderly population and associated to mortality and frailty [149, 150]. Impact of CR in this population needs to be evaluated.

Recently, interventional study targeting human aging process and age-related diseases is increasing. We can list in non-exhaustive way, the use in elderly cohort of a rapamycin analogue (known agent used in transplant and cancer), which leads to improved immune flu vaccine responses [151]. In other trials, the uses of metformin in adults at high risk of type 2 diabetes exhibit a reduced incidence of age-related disease such as cardiovascular disease [152, 153] and cancers [154, 155]. Based on these observations, FDA has just approved that Metformin could be tested on global health span in elderly and the first ongoing trial named TAME (Targeting Aging with Metformin) may be the first step towards the development of effective anti-aging drugs [156].

5. Conclusion

Physiological aging is associated with several immune alterations within hematopoietic stem cells, innate and adaptive system. Furthermore, many entanglements exist between stress and immunity, leading to high level of pro and anti-inflammatory stage necessary to defend the system while keeping the immune balance. Elderly people are not equal in their response to stress notably because of immune reserve, which may be different from one individual to another. More investigations are necessary to improve our knowledge of the immune system impact on resilience after an acute stress in the elderly. Additional mechanistic evidences would help to better foresee the link between immunity and neuroendocrine pathway in chronic stress, in particular to investigate if factors of resilience could dampen the deleterious impact of chronic stress on health.

Some behavioural interventions, such as relaxation or Tai Chi may attenuate the stress-induced immune dysregulation. In addition, some nutritional interventions have been suggested as promising anti-inflammatory agents, and may even play on inflammatory responses to stress [157, 158]. However, it remains to elucidate if those interventions are

sufficient to modulate health span. In the future, immunomodulation could be an interesting therapeutic approach to improve the prognosis of elderly patients undergoing acute stress phase but benefit/risk balance for the older individuals needs first to be assessed.

References

1. Department of Economic and Social Affairs. Population Division. World population ageing: 1950-2050. In: <http://www.un.org/esa/population/publications/worldageing19502050/index.htm>; 2001.
2. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, *et al.* Geroscience: linking aging to chronic disease. *Cell* 2014,**159**:709-713.
3. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004,**59**:255-263.
4. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell* 2013,**153**:1194-1217.
5. El Assar M, Angulo J, Carnicero JA, Walter S, Garcia-Garcia FJ, Lopez-Hernandez E, *et al.* Frailty Is Associated With Lower Expression of Genes Involved in Cellular Response to Stress: Results From the Toledo Study for Healthy Aging. *J Am Med Dir Assoc* 2017,**18**:734 e731-734 e737.
6. Bouchon JP. 1+2+3 ou comment tenter d'être efficace en gériatrie?. *Rev. Prat.* 1984,**34**:888-892.
7. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. *Nat Immunol* 2013,**14**:428-436.
8. Sauce D, Larsen M, Fastenackels S, Duperrier A, Keller M, Grubeck-Loebenstien B, *et al.* Evidence of premature immune aging in patients thymectomized during early childhood. *J Clin Invest* 2009,**119**:3070-3078.
9. Zlamy M, Almanzar G, Parson W, Schmidt C, Leierer J, Weinberger B, *et al.* Efforts of the human immune system to maintain the peripheral CD8+ T cell compartment after childhood thymectomy. *Immun Ageing* 2016,**13**:3.
10. Naylor K, Li G, Vallejo AN, Lee WW, Koetz K, Bryl E, *et al.* The influence of age on T cell generation and TCR diversity. *J Immunol* 2005,**174**:7446-7452.
11. Britanova OV, Putintseva EV, Shugay M, Merzlyak EM, Turchaninova MA, Staroverov DB, *et al.* Age-related decrease in TCR repertoire diversity measured with deep and normalized sequence profiling. *J Immunol* 2014,**192**:2689-2698.
12. Sansoni P, Vescovini R, Fagnoni F, Biasini C, Zanni F, Zanlari L, *et al.* The immune system in extreme longevity. *Exp Gerontol* 2008,**43**:61-65.
13. Raynor J, Lages CS, Shehata H, Hildeman DA, Chougnet CA. Homeostasis and function of regulatory T cells in aging. *Curr Opin Immunol* 2012,**24**:482-487.
14. Hwang KA, Kim HR, Kang I. Aging and human CD4(+) regulatory T cells. *Mech Ageing Dev* 2009,**130**:509-517.
15. Tarazona R, DelaRosa O, Alonso C, Ostos B, Espejo J, Pena J, *et al.* Increased expression of NK cell markers on T lymphocytes in aging and chronic activation of the immune system reflects the accumulation of effector/senescent T cells. *Mech Ageing Dev* 2000,**121**:77-88.
16. Nikolich-Zugich J. Ageing and life-long maintenance of T-cell subsets in the face of latent persistent infections. *Nat Rev Immunol* 2008,**8**:512-522.

17. Fann M, Chiu WK, Wood WH, 3rd, Levine BL, Becker KG, Weng NP. Gene expression characteristics of CD28null memory phenotype CD8+ T cells and its implication in T-cell aging. *Immunol Rev* 2005,**205**:190-206.
18. Allman D, Miller JP. B cell development and receptor diversity during aging. *Curr Opin Immunol* 2005,**17**:463-467.
19. Frasca D, Diaz A, Romero M, Blomberg BB. Human peripheral late/exhausted memory B cells express a senescent-associated secretory phenotype and preferentially utilize metabolic signaling pathways. *Exp Gerontol* 2017,**87**:113-120.
20. Johnson SA, Cambier JC. Ageing, autoimmunity and arthritis: senescence of the B cell compartment - implications for humoral immunity. *Arthritis Res Ther* 2004,**6**:131-139.
21. Frasca D, Landin AM, Lechner SC, Ryan JG, Schwartz R, Riley RL, *et al.* Aging down-regulates the transcription factor E2A, activation-induced cytidine deaminase, and Ig class switch in human B cells. *J Immunol* 2008,**180**:5283-5290.
22. Frasca D, Diaz A, Romero M, Phillips M, Mendez NV, Landin AM, *et al.* Unique biomarkers for B-cell function predict the serum response to pandemic H1N1 influenza vaccine. *Int Immunol* 2012,**24**:175-182.
23. Shi Y, Yamazaki T, Okubo Y, Uehara Y, Sugane K, Agematsu K. Regulation of aged humoral immune defense against pneumococcal bacteria by IgM memory B cell. *J Immunol* 2005,**175**:3262-3267.
24. Frasca D, Landin AM, Alvarez JP, Blackshear PJ, Riley RL, Blomberg BB. Tristetraprolin, a negative regulator of mRNA stability, is increased in old B cells and is involved in the degradation of E47 mRNA. *J Immunol* 2007,**179**:918-927.
25. Muramatsu M, Nagaoka H, Shinkura R, Begum NA, Honjo T. Discovery of activation-induced cytidine deaminase, the engraver of antibody memory. *Adv Immunol* 2007,**94**:1-36.
26. Khurana S, Frasca D, Blomberg B, Golding H. AID activity in B cells strongly correlates with polyclonal antibody affinity maturation in-vivo following pandemic 2009-H1N1 vaccination in humans. *PLoS Pathog* 2012,**8**:e1002920.
27. Henry CJ, Casas-Selves M, Kim J, Zaberezhnyy V, Aghili L, Daniel AE, *et al.* Aging-associated inflammation promotes selection for adaptive oncogenic events in B cell progenitors. *J Clin Invest* 2015,**125**:4666-4680.
28. Hao Y, O'Neill P, Naradikian MS, Scholz JL, Cancro MP. A B-cell subset uniquely responsive to innate stimuli accumulates in aged mice. *Blood* 2011,**118**:1294-1304.
29. Naradikian MS, Hao Y, Cancro MP. Age-associated B cells: key mediators of both protective and autoreactive humoral responses. *Immunol Rev* 2016,**269**:118-129.
30. Fortin CF, McDonald PP, Lesur O, Fulop T, Jr. Aging and neutrophils: there is still much to do. *Rejuvenation Res* 2008,**11**:873-882.
31. Angelis P, Scharf S, Christophidis N. Effects of age on neutrophil function and its relevance to bacterial infections in the elderly. *J Clin Lab Immunol* 1997,**49**:33-40.
32. Corberand J, Ngyen F, Laharrague P, Fontanilles AM, Gleyzes B, Gyrard E, *et al.* Polymorphonuclear functions and aging in humans. *J Am Geriatr Soc* 1981,**29**:391-397.
33. Butcher SK, Chahal H, Nayak L, Sinclair A, Henriquez NV, Sapey E, *et al.* Senescence in innate immune responses: reduced neutrophil phagocytic capacity and CD16 expression in elderly humans. *J Leukoc Biol* 2001,**70**:881-886.

34. Fulop T, Larbi A, Douziech N, Fortin C, Guerard KP, Lesur O, *et al.* Signal transduction and functional changes in neutrophils with aging. *Aging Cell* 2004,**3**:217-226.
35. Braga PC, Sala MT, Dal Sasso M, Pecile A, Annoni G, Vergani C. Age-associated differences in neutrophil oxidative burst (chemiluminescence). *Exp Gerontol* 1998,**33**:477-484.
36. Fortin CF, Larbi A, Dupuis G, Lesur O, Fulop T, Jr. GM-CSF activates the Jak/STAT pathway to rescue polymorphonuclear neutrophils from spontaneous apoptosis in young but not elderly individuals. *Biogerontology* 2007,**8**:173-187.
37. Tortorella C, Stella I, Piazzolla G, Simone O, Cappiello V, Antonaci S. Role of defective ERK phosphorylation in the impaired GM-CSF-induced oxidative response of neutrophils in elderly humans. *Mech Ageing Dev* 2004,**125**:539-546.
38. Fehlings MG, Nguyen DH. Immunoglobulin G: a potential treatment to attenuate neuroinflammation following spinal cord injury. *J Clin Immunol* 2010,**30 Suppl 1**:S109-112.
39. Hearps AC, Martin GE, Angelovich TA, Cheng WJ, Maisa A, Landay AL, *et al.* Aging is associated with chronic innate immune activation and dysregulation of monocyte phenotype and function. *Aging Cell* 2012,**11**:867-875.
40. De Martinis M, Modesti M, Ginaldi L. Phenotypic and functional changes of circulating monocytes and polymorphonuclear leucocytes from elderly persons. *Immunol Cell Biol* 2004,**82**:415-420.
41. Geiger H, de Haan G, Florian MC. The ageing haematopoietic stem cell compartment. *Nat Rev Immunol* 2013,**13**:376-389.
42. Rossi DJ, Bryder D, Zahn JM, Ahlenius H, Sonu R, Wagers AJ, *et al.* Cell intrinsic alterations underlie hematopoietic stem cell aging. *Proc Natl Acad Sci U S A* 2005,**102**:9194-9199.
43. Sudo K, Ema H, Morita Y, Nakauchi H. Age-associated characteristics of murine hematopoietic stem cells. *J Exp Med* 2000,**192**:1273-1280.
44. Sauce D, Larsen M, Fastenackels S, Pauchard M, Ait-Mohand H, Schneider L, *et al.* HIV disease progression despite suppression of viral replication is associated with exhaustion of lymphopoiesis. *Blood* 2011,**117**:5142-5151.
45. Grover A, Sanjuan-Pla A, Thongjuea S, Carrelha J, Giustacchini A, Gambardella A, *et al.* Single-cell RNA sequencing reveals molecular and functional platelet bias of aged haematopoietic stem cells. *Nat Commun* 2016,**7**:11075.
46. Linton PJ, Dorshkind K. Age-related changes in lymphocyte development and function. *Nat Immunol* 2004,**5**:133-139.
47. Kollman C, Howe CW, Anasetti C, Antin JH, Davies SM, Filipovich AH, *et al.* Donor characteristics as risk factors in recipients after transplantation of bone marrow from unrelated donors: the effect of donor age. *Blood* 2001,**98**:2043-2051.
48. Behrens A, van Deursen JM, Rudolph KL, Schumacher B. Impact of genomic damage and ageing on stem cell function. *Nat Cell Biol* 2014,**16**:201-207.
49. Ito K, Hirao A, Arai F, Takubo K, Matsuoka S, Miyamoto K, *et al.* Reactive oxygen species act through p38 MAPK to limit the lifespan of hematopoietic stem cells. *Nat Med* 2006,**12**:446-451.
50. Rossi DJ, Bryder D, Weissman IL. Hematopoietic stem cell aging: mechanism and consequence. *Exp Gerontol* 2007,**42**:385-390.

51. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci* 2014,**69 Suppl 1**:S4-9.
52. Fagiolo U, Cossarizza A, Scala E, Fanales-Belasio E, Ortolani C, Cozzi E, *et al.* Increased cytokine production in mononuclear cells of healthy elderly people. *Eur J Immunol* 1993,**23**:2375-2378.
53. Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, *et al.* Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev* 2007,**128**:92-105.
54. Butcher SK, Lord JM. Stress responses and innate immunity: aging as a contributory factor. *Aging Cell* 2004,**3**:151-160.
55. Cannizzo ES, Clement CC, Sahu R, Follo C, Santambrogio L. Oxidative stress, inflammaging and immunosenescence. *J Proteomics* 2011,**74**:2313-2323.
56. Olivieri F, Albertini MC, Orciani M, Ceka A, Cricca M, Procopio AD, *et al.* DNA damage response (DDR) and senescence: shuttled inflamma-miRNAs on the stage of inflammaging. *Oncotarget* 2015,**6**:35509-35521.
57. Jones DL, Rando TA. Emerging models and paradigms for stem cell ageing. *Nat Cell Biol* 2011,**13**:506-512.
58. Paolisso G, Barbieri M, Bonafe M, Franceschi C. Metabolic age modelling: the lesson from centenarians. *Eur J Clin Invest* 2000,**30**:888-894.
59. Calabrese V, Santoro A, Monti D, Crupi R, Di Paola R, Latteri S, *et al.* Aging and Parkinson's Disease: Inflammaging, neuroinflammation and biological remodeling as key factors in pathogenesis. *Free Radic Biol Med* 2018,**115**:80-91.
60. Fulop T, Dupuis G, Witkowski JM, Larbi A. The Role of Immunosenescence in the Development of Age-Related Diseases. *Rev Invest Clin* 2016,**68**:84-91.
61. Lencel P, Magne D. Inflammaging: the driving force in osteoporosis? *Med Hypotheses* 2011,**76**:317-321.
62. Hubbard RE, O'Mahony MS, Savva GM, Calver BL, Woodhouse KW. Inflammation and frailty measures in older people. *J Cell Mol Med* 2009,**13**:3103-3109.
63. Glaser R, Thorn BE, Tarr KL, Kiecolt-Glaser JK, D'Ambrosio SM. Effects of stress on methyltransferase synthesis: an important DNA repair enzyme. *Health Psychol* 1985,**4**:403-412.
64. Hu J, Chen Z, Gorczyński CP, Gorczyński LY, Kai Y, Lee L, *et al.* Sleep-deprived mice show altered cytokine production manifest by perturbations in serum IL-1ra, TNFa, and IL-6 levels. *Brain Behav Immun* 2003,**17**:498-504.
65. McCarty R, Eisen G, Bartholow CL. Plasma catecholamine responses to acute motion stress in laboratory rats. *Physiol Behav* 1991,**49**:653-656.
66. Kusnecov AV, Grotta LJ, Schmidt SG, Bonneau RH, Sheridan JF, Glaser R, *et al.* Decreased herpes simplex viral immunity and enhanced pathogenesis following stressor administration in mice. *J Neuroimmunol* 1992,**38**:129-137.
67. Shanks N, Zalcman S, Zacharko RM, Anisman H. Alterations of central norepinephrine, dopamine and serotonin in several strains of mice following acute stressor exposure. *Pharmacol Biochem Behav* 1991,**38**:69-75.
68. Dobbs CM, Vasquez M, Glaser R, Sheridan JF. Mechanisms of stress-induced modulation of viral pathogenesis and immunity. *J Neuroimmunol* 1993,**48**:151-160.

69. Padgett DA, Sheridan JF, Dorne J, Berntson GG, Candelora J, Glaser R. Social stress and the reactivation of latent herpes simplex virus type 1. *Proc Natl Acad Sci U S A* 1998,**95**:7231-7235.
70. Kitada M, Koya D. The use of calorie restriction mimetics to study aging. *Methods Mol Biol* 2013,**1048**:95-107.
71. Ruetenik A, Barrientos A. Dietary restriction, mitochondrial function and aging: from yeast to humans. *Biochim Biophys Acta* 2015,**1847**:1434-1447.
72. Spadari RC, Cavadas C, de Carvalho A, Ortolani D, de Moura AL, Vassalo PF. Role of Beta-adrenergic Receptors and Sirtuin Signaling in the Heart During Aging, Heart Failure, and Adaptation to Stress. *Cell Mol Neurobiol* 2017.
73. Liu G, Dong Y, Wang Z, Cao J, Chen Y. Restraint stress alters immune parameters and induces oxidative stress in the mouse uterus during embryo implantation. *Stress* 2014,**17**:494-503.
74. Gambino V, De Michele G, Venezia O, Migliaccio P, Dall'Olio V, Bernard L, *et al.* Oxidative stress activates a specific p53 transcriptional response that regulates cellular senescence and aging. *Aging Cell* 2013,**12**:435-445.
75. Vatner SF, Pachon RE, Vatner DE. Inhibition of adenylyl cyclase type 5 increases longevity and healthful aging through oxidative stress protection. *Oxid Med Cell Longev* 2015,**2015**:250310.
76. Burleson MH, Poehlmann KM, Hawkley LC, Ernst JM, Berntson GG, Malarkey WB, *et al.* Neuroendocrine and cardiovascular reactivity to stress in mid-aged and older women: long-term temporal consistency of individual differences. *Psychophysiology* 2003,**40**:358-369.
77. Kiecolt-Glaser JK, Page GG, Marucha PT, MacCallum RC, Glaser R. Psychological influences on surgical recovery. Perspectives from psychoneuroimmunology. *Am Psychol* 1998,**53**:1209-1218.
78. Marshall GD, Jr., Agarwal SK, Lloyd C, Cohen L, Henninger EM, Morris GJ. Cytokine dysregulation associated with exam stress in healthy medical students. *Brain Behav Immun* 1998,**12**:297-307.
79. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A* 2003,**100**:9090-9095.
80. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 2004,**130**:601-630.
81. Lutgendorf SK, Logan H, Costanzo E, Lubaroff D. Effects of acute stress, relaxation, and a neurogenic inflammatory stimulus on interleukin-6 in humans. *Brain Behav Immun* 2004,**18**:55-64.
82. McGuire L, Heffner K, Glaser R, Needleman B, Malarkey W, Dickinson S, *et al.* Pain and wound healing in surgical patients. *Ann Behav Med* 2006,**31**:165-172.
83. Chen X, Velez JC, Barbosa C, Pepper M, Andrade A, Stoner L, *et al.* Smoking and perceived stress in relation to short salivary telomere length among caregivers of children with disabilities. *Stress* 2015,**18**:20-28.
84. Graham JE, Christian LM, Kiecolt-Glaser JK. Stress, age, and immune function: toward a lifespan approach. *J Behav Med* 2006,**29**:389-400.
85. Pariante CM, Carpiniello B, Orru MG, Sitzia R, Piras A, Farci AM, *et al.* Chronic caregiving stress alters peripheral blood immune parameters: the role of age and severity of stress. *Psychother Psychosom* 1997,**66**:199-207.

86. Glaser R, Kiecolt-Glaser JK. Chronic stress modulates the virus-specific immune response to latent herpes simplex virus type 1. *Ann Behav Med* 1997,**19**:78-82.
87. Li J, Cowden LG, King JD, Briles DA, Schroeder HW, Jr., Stevens AB, *et al.* Effects of chronic stress and interleukin-10 gene polymorphisms on antibody response to tetanus vaccine in family caregivers of patients with Alzheimer's disease. *Psychosom Med* 2007,**69**:551-559.
88. Glaser R, Sheridan J, Malarkey WB, MacCallum RC, Kiecolt-Glaser JK. Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. *Psychosom Med* 2000,**62**:804-807.
89. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. *Lancet* 1995,**346**:1194-1196.
90. von Kanel R, Dimsdale JE, Mills PJ, Ancoli-Israel S, Patterson TL, Mausbach BT, *et al.* Effect of Alzheimer caregiving stress and age on frailty markers interleukin-6, C-reactive protein, and D-dimer. *J Gerontol A Biol Sci Med Sci* 2006,**61**:963-969.
91. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annu Rev Med* 2000,**51**:245-270.
92. Glaser R, Kiecolt-Glaser JK, Stout JC, Tarr KL, Speicher CE, Holliday JE. Stress-related impairments in cellular immunity. *Psychiatry Res* 1985,**16**:233-239.
93. Sauce D, Appay V. Altered thymic activity in early life: how does it affect the immune system in young adults? *Curr Opin Immunol*,**23**:543-548.
94. Kiecolt-Glaser JK, Glaser R, Strain EC, Stout JC, Tarr KL, Holliday JE, *et al.* Modulation of cellular immunity in medical students. *J Behav Med* 1986,**9**:5-21.
95. Wikby A, Maxson P, Olsson J, Johansson B, Ferguson FG. Changes in CD8 and CD4 lymphocyte subsets, T cell proliferation responses and non-survival in the very old: the Swedish longitudinal OCTO-immune study. *Mech Ageing Dev* 1998,**102**:187-198.
96. Olsson J, Wikby A, Johansson B, Lofgren S, Nilsson BO, Ferguson FG. Age-related change in peripheral blood T-lymphocyte subpopulations and cytomegalovirus infection in the very old: the Swedish longitudinal OCTO immune study. *Mech Ageing Dev* 2000,**121**:187-201.
97. Esterling BA, Kiecolt-Glaser JK, Glaser R. Psychosocial modulation of cytokine-induced natural killer cell activity in older adults. *Psychosom Med* 1996,**58**:264-272.
98. Irwin M, Lacher U, Caldwell C. Depression and reduced natural killer cytotoxicity: a longitudinal study of depressed patients and control subjects. *Psychol Med* 1992,**22**:1045-1050.
99. Kiecolt-Glaser JK, Garner W, Speicher C, Penn GM, Holliday J, Glaser R. Psychosocial modifiers of immunocompetence in medical students. *Psychosom Med* 1984,**46**:7-14.
100. Solana R, Tarazona R, Gayoso I, Lesur O, Dupuis G, Fulop T. Innate immunosenescence: effect of aging on cells and receptors of the innate immune system in humans. *Semin Immunol* 2012,**24**:331-341.
101. Glaser R, Kiecolt-Glaser J. Stress-associated depression in cellular immunity: implications for acquired immune deficiency syndrome (AIDS). *Brain Behav Immun* 1987,**1**:107-112.
102. Thomasini RL, Pereira DS, Pereira FSM, Mateo EC, Mota TN, Guimaraes GG, *et al.* Aged-associated cytomegalovirus and Epstein-Barr virus reactivation and cytomegalovirus relationship with the frailty syndrome in older women. *PLoS One* 2017,**12**:e0180841.

103. Glaser R, Mehl VS, Penn G, Speicher CE, Kiecolt-Glaser JK. Stress-associated changes in plasma immunoglobulin levels. *Int J Psychosom* 1986,**33**:41-42.
104. Glaser R, MacCallum RC, Laskowski BF, Malarkey WB, Sheridan JF, Kiecolt-Glaser JK. Evidence for a shift in the Th-1 to Th-2 cytokine response associated with chronic stress and aging. *J Gerontol A Biol Sci Med Sci* 2001,**56**:M477-482.
105. Castaneda-Delgado JE, Frausto-Lujan I, Gonzalez-Curiel I, Montoya-Rosales A, Serrano CJ, Torres-Juarez F, *et al.* Differences in Cytokine Production during Aging and Its Relationship with Antimicrobial Peptides Production. *Immunol Invest* 2017,**46**:48-58.
106. Ershler WB, Sun WH, Binkley N, Gravenstein S, Volk MJ, Kamoske G, *et al.* Interleukin-6 and aging: blood levels and mononuclear cell production increase with advancing age and in vitro production is modifiable by dietary restriction. *Lymphokine Cytokine Res* 1993,**12**:225-230.
107. Glaser R, Rice J, Sheridan J, Fertel R, Stout J, Speicher C, *et al.* Stress-related immune suppression: health implications. *Brain Behav Immun* 1987,**1**:7-20.
108. Kiecolt-Glaser JK, Loving TJ, Stowell JR, Malarkey WB, Lemeshow S, Dickinson SL, *et al.* Hostile marital interactions, proinflammatory cytokine production, and wound healing. *Arch Gen Psychiatry* 2005,**62**:1377-1384.
109. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. *Exp Gerontol* 2004,**39**:687-699.
110. Ballou SP, Lozanski FB, Hodder S, Rzewnicki DL, Mion LC, Sipe JD, *et al.* Quantitative and qualitative alterations of acute-phase proteins in healthy elderly persons. *Age Ageing* 1996,**25**:224-230.
111. Kiecolt-Glaser JK, Glaser R, Gravenstein S, Malarkey WB, Sheridan J. Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proc Natl Acad Sci U S A* 1996,**93**:3043-3047.
112. Castle SC. Clinical relevance of age-related immune dysfunction. *Clin Infect Dis* 2000,**31**:578-585.
113. Gomez CR, Boehmer ED, Kovacs EJ. The aging innate immune system. *Curr Opin Immunol* 2005,**17**:457-462.
114. Damjanovic AK, Yang Y, Glaser R, Kiecolt-Glaser JK, Nguyen H, Laskowski B, *et al.* Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. *J Immunol* 2007,**179**:4249-4254.
115. Blackburn EH, Epel ES, Lin J. Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. *Science* 2015,**350**:1193-1198.
116. Aubert G. Telomere dynamics and aging. *Prog Mol Biol Transl Sci* 2014,**125**:89-111.
117. Long JE, Drayson MT, Taylor AE, Toellner KM, Lord JM, Phillips AC. Morning vaccination enhances antibody response over afternoon vaccination: A cluster-randomised trial. *Vaccine* 2016,**34**:2679-2685.
118. Danner DD, Snowdon DA, Friesen WV. Positive emotions in early life and longevity: findings from the nun study. *J Pers Soc Psychol* 2001,**80**:804-813.
119. Phillips AC, Upton J, Duggal NA, Carroll D, Lord JM. Depression following hip fracture is associated with increased physical frailty in older adults: the role of the cortisol: dehydroepiandrosterone sulphate ratio. *BMC Geriatr* 2013,**13**:60.
120. Borgstrom F, Johnell O, Kanis JA, Jonsson B, Rehnberg C. At what hip fracture risk is it cost-effective to treat? International intervention thresholds for the treatment of osteoporosis. *Osteoporos Int* 2006,**17**:1459-1471.

121. Boddaert J, Raux M, Khiami F, Riou B. Perioperative management of elderly patients with hip fracture. *Anesthesiology* 2014,**121**:1336-1341.
122. Baehl S, Garneau H, Le Page A, Lorrain D, Viens I, Svtelis A, *et al.* Altered neutrophil functions in elderly patients during a 6-month follow-up period after a hip fracture. *Exp Gerontol* 2015,**65**:58-68.
123. Sun T, Wang X, Liu Z, Chen X, Zhang J. Plasma concentrations of pro- and anti-inflammatory cytokines and outcome prediction in elderly hip fracture patients. *Injury* 2011,**42**:707-713.
124. Vallet H, Chenevier-Gobeaux C, Villain C, Cohen-Bittan J, Ray P, Epelboin L, *et al.* Prognostic Value of Serum Procalcitonin After Orthopedic Surgery in the Elderly Population. *J Gerontol A Biol Sci Med Sci* 2017,**72**:438-443.
125. Neerland BE, Hall RJ, Seljeflot I, Frihagen F, MacLulich AM, Raeder J, *et al.* Associations Between Delirium and Preoperative Cerebrospinal Fluid C-Reactive Protein, Interleukin-6, and Interleukin-6 Receptor in Individuals with Acute Hip Fracture. *J Am Geriatr Soc* 2016,**64**:1456-1463.
126. Cape E, Hall RJ, van Munster BC, de Vries A, Howie SE, Pearson A, *et al.* Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1beta in delirium after hip fracture. *J Psychosom Res* 2014,**77**:219-225.
127. Larsen M, Bayard C, Lepetitcorps H, Cohen-Bittan J, Appay V, Boddaert J, *et al.* Elevated Neopterin Levels Predict Early Death in Older Hip-fracture Patients. *EBioMedicine* 2017,**26**:157-164.
128. Martin GS. Sepsis: the future is bright. *Crit Care Med* 2006,**34**:2484-2485.
129. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med* 2006,**34**:15-21.
130. Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. *Immunol Rev* 2016,**274**:330-353.
131. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. *Nat Rev Immunol* 2008,**8**:776-787.
132. Unsinger J, McGlynn M, Kasten KR, Hoekzema AS, Watanabe E, Muenzer JT, *et al.* IL-7 promotes T cell viability, trafficking, and functionality and improves survival in sepsis. *J Immunol* 2010,**184**:3768-3779.
133. Brahmamdam P, Inoue S, Unsinger J, Chang KC, McDunn JE, Hotchkiss RS. Delayed administration of anti-PD-1 antibody reverses immune dysfunction and improves survival during sepsis. *J Leukoc Biol* 2010,**88**:233-240.
134. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, *et al.* Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation* 2009,**119**:515-523.
135. Epelman S, Liu PP, Mann DL. Role of innate and adaptive immune mechanisms in cardiac injury and repair. *Nat Rev Immunol* 2015,**15**:117-129.
136. Abbate A, Bussani R, Liuzzo G, Biondi-Zoccai GG, Barresi E, Mellone P, *et al.* Sudden coronary death, fatal acute myocardial infarction and widespread coronary and myocardial inflammation. *Heart* 2008,**94**:737-742.
137. Boag SE, Das R, Shmeleva EV, Bagnall A, Egred M, Howard N, *et al.* T lymphocytes and fractalkine contribute to myocardial ischemia/reperfusion injury in patients. *J Clin Invest* 2015,**125**:3063-3076.

138. Hoffmann J, Fiser K, Weaver J, Dimmick I, Loeher M, Pircher H, *et al.* High-throughput 13-parameter immunophenotyping identifies shifts in the circulating T-cell compartment following reperfusion in patients with acute myocardial infarction. *PLoS One* 2012,**7**:e47155.
139. Ferencik M, Hoffmann U, Bamberg F, Januzzi JL. Highly sensitive troponin and coronary computed tomography angiography in the evaluation of suspected acute coronary syndrome in the emergency department. *Eur Heart J* 2016,**37**:2397-2405.
140. Suh Y, Atzmon G, Cho MO, Hwang D, Liu B, Leahy DJ, *et al.* Functionally significant insulin-like growth factor I receptor mutations in centenarians. *Proc Natl Acad Sci U S A* 2008,**105**:3438-3442.
141. Flachsbarth F, Caliebe A, Kleindorff R, Blanche H, von Eller-Eberstein H, Nikolaus S, *et al.* Association of FOXO3A variation with human longevity confirmed in German centenarians. *Proc Natl Acad Sci U S A* 2009,**106**:2700-2705.
142. Li Y, Qin J, Wei X, Liang G, Shi L, Jiang M, *et al.* Association of SIRT6 Gene Polymorphisms with Human Longevity. *Iran J Public Health* 2016,**45**:1420-1426.
143. Dewey FE, Murray MF, Overton JD, Habegger L, Leader JB, Fetterolf SN, *et al.* Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study. *Science* 2016,**354**.
144. Bucci L, Ostan R, Giampieri E, Cevenini E, Pini E, Scurti M, *et al.* Immune parameters identify Italian centenarians with a longer five-year survival independent of their health and functional status. *Exp Gerontol* 2014,**54**:14-20.
145. Franceschi C, Monti D, Sansoni P, Cossarizza A. The immunology of exceptional individuals: the lesson of centenarians. *Immunol Today* 1995,**16**:12-16.
146. Xia S, Zhang X, Zheng S, Khanabdali R, Kalionis B, Wu J, *et al.* An Update on Inflamm-Aging: Mechanisms, Prevention, and Treatment. *J Immunol Res* 2016,**2016**:8426874.
147. Chung KW, Kim DH, Park MH, Choi YJ, Kim ND, Lee J, *et al.* Recent advances in calorie restriction research on aging. *Exp Gerontol* 2013,**48**:1049-1053.
148. Belsky DW, Huffman KM, Pieper CF, Shalev I, Kraus WE. Change in the Rate of Biological Aging in Response to Caloric Restriction: CALERIE Biobank Analysis. *J Gerontol A Biol Sci Med Sci* 2017,**73**:4-10.
149. Harris D, Haboubi N. Malnutrition screening in the elderly population. *J R Soc Med* 2005,**98**:411-414.
150. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, *et al.* Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001,**56**:M146-156.
151. Mannick JB, Del Giudice G, Lattanzi M, Valiante NM, Praestgaard J, Huang B, *et al.* mTOR inhibition improves immune function in the elderly. *Sci Transl Med* 2014,**6**:268ra179.
152. Abbasi F, Chu JW, McLaughlin T, Lamendola C, Leary ET, Reaven GM. Effect of metformin treatment on multiple cardiovascular disease risk factors in patients with type 2 diabetes mellitus. *Metabolism* 2004,**53**:159-164.
153. Pryor R, Cabreiro F. Repurposing metformin: an old drug with new tricks in its binding pockets. *Biochem J* 2015,**471**:307-322.
154. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. *BMJ* 2005,**330**:1304-1305.
155. Anisimov VN. Metformin for aging and cancer prevention. *Aging (Albany NY)* 2010,**2**:760-774.

156. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a Tool to Target Aging. *Cell Metab* 2016,**23**:1060-1065.
157. Maes M, Lin A, Kenis G, Egyed B, Bosmans E. The effects of noradrenaline and alpha-2 adrenoceptor agents on the production of monocytic products. *Psychiatry Res* 2000,**96**:245-253.
158. Kiecolt-Glaser JK, Belury MA, Porter K, Beversdorf DQ, Lemeshow S, Glaser R. Depressive symptoms, omega-6:omega-3 fatty acids, and inflammation in older adults. *Psychosom Med* 2007,**69**:217-224.