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

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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].

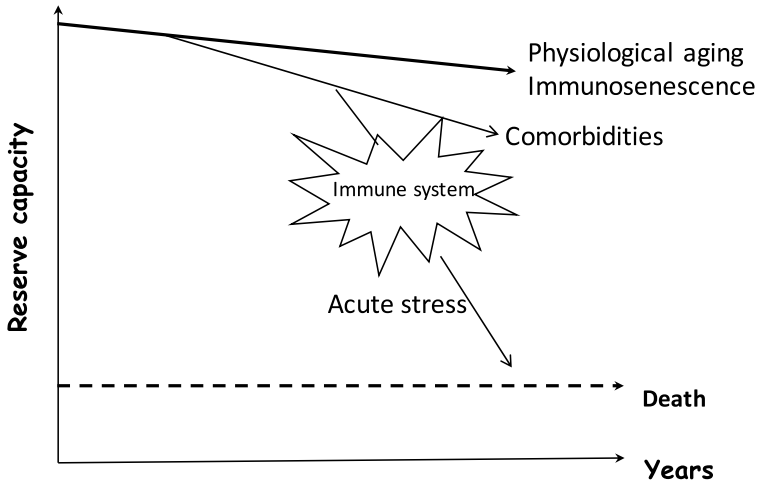

Figure: **Aging is a complex process with many inter-individual variations**. Physiological modifications including immunosenescence and comorbidities contribute to the decrease of individual reserve capacities. Acute stress drives an important break in patient's evolution and can lead rapidly to death. 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 IFNγ, 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 substes 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 TNFα 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 linage 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 asymptomatically 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

Blooming 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 adrenocorticotropic hormone by the pituitary gland results in the production of glucorticoid hormones and catecholamnies. 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-κB, 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 rythm 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 it's 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 NFKB 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-1β [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). PPRs 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.

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