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Gain and Loss of T cell subsets in old age –

Age-related reshaping of the T cell repertoire

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Abstract

The immune system is affected by the aging process and undergoes significant age-related changes, termed immunosenescence. Different T cell subsets are affected by this process. Alterations within the bone marrow and thymus lead to a shift in the composition of the T cell repertoire from naïve to antigen-experienced T cells, thereby compromising the diversity of the T cell pool. Additional infection with latent pathogens such as Cytomegalovirus aggravates this process. In this review we focus on the major age-related changes that occur in the naïve and the antigen-experienced T cell population. We discuss the mechanisms responsible for the generation and maintenance of these subsets and how age-related changes can be delayed or prevented by clinical interventions.

Key words:

Immunosenescence, T cells, aging, human

Introduction

Worldwide the mean life expectancy is increasing and thereby leading to dramatic demographic changes. To ensure longevity and healthy aging the maintenance of appropriate immunity is necessary. However, as individuals age numerous physiological functions are decreased and the immune system undergoes profound age-related changes, termed immunosenescence. Changes of the aging immune system are of particular importance as they contribute to a higher incidence and severity of infectious diseases, decreased efficacy of vaccinations and possibly autoimmunity and cancer [1-3]. Although immunosenescence affects many components of both, the innate as well as the adaptive immunity, the latter is more severely affected by aging. These changes are numerous and affect a wide range of cell types, ranging from hematopoietic stem cells and lymphoid progenitors to mature lymphocytes in secondary lymphoid organs and the periphery [4]. However one of the most prominent features of immunosenescence and therefore mainly associated with the decline of immunological responsiveness in elderly persons are changes in the composition of the T cell compartment. The most substantial age-related changes within the T cell compartment are a decrease in the number of antigen-inexperienced naïve T lymphocytes combined with an increase in antigen-experienced memory and effector T cells. The initial trigger responsible for the dysbalance within the composition of the T cell pool observed in elderly persons is the involution of the T cell maturation organ, the thymus gland. Along with a decrease in functional thymic mass with age and the consequent reduction in naïve T cell output comes the necessity of homeostatic forces to take more responsibility assuming survival and in keeping T cell numbers constant. For the regulation of the maintenance of the T cell compartment apoptosis is another key player since it controls the selection of the

T cell repertoire in the thymus, the deletion of self-reactive lymphocytes, the regulation of immunological memory and the deletion of effector T cells [5]. Further effects of aging on the immune system are telomere shortening, changes in T cell signaling, impaired DNA repair and antioxidant mechanisms, which may all contribute in regulating T cell survival and shaping of the repertoire. Additionally, pathogens themselves may accelerate age-related changes. One prominent example that has been extensively studied in the context of immunosenescence is the cytomegalovirus (CMV) [6].

In this review we describe the major age-related changes that occur in naïve versus antigen-experienced T cells. Specifically we review the literature on the origin and fate of these subsets. Finally we discuss modes of intervention potentially suitable to counteract deleterious changes.

Naïve T cells

Age-related changes in the generation of naïve T cells

All circulating blood cells of an individual including the mature lymphocytes originate from common pluripotent hematopoietic stem cells (HSCs), which are maintained in specialized niches within the bone marrow. Common T lymphoid progenitors leave the bone marrow in an immature state and migrate to the thymus, a central lymphoid organ, responsible for the development, selection and output of mature naïve T cells, referred to as recent thymic emigrants (RTE), into the periphery [7, 8]. One of the major changes in the aged immune system is a decline in the naïve T cell number. This has mainly two reasons: With age the function of HSCs decreases due to deficiencies in DNA damage repair [9] and the shortening of telomeres [10], leading to a reduced capacity to generate lymphoid progenitors. It has also been suggested that age-related changes of the stem cell niche, e.g. the decline of the overall amount of hematopoietic tissue, can contribute to the declined HSC function in elderly persons [11]. Secondly, the thymus is severely affected. At birth the thymus is fully developed, but its involution and the replacement of functional tissue by fat starts soon after birth, continues throughout life and is almost complete at the age of 50 [12-14]. Thus in young persons naïve T cells are continuously generated and regenerate the T cell pool to retain the capability of the adaptive immune system to respond to a variety of different pathogens.

As a result of thymic involution the output of peripheral naïve T cells is dramatically reduced (up to -80%) with age, which leads to a reduced ability of the host to respond to new antigens. Low naïve T cell numbers have been described in the periphery as well as lymphoid tissue [15, 16]. Recent striking evidence from young adults thymectomized

as infants in the course of cardiac surgery who have decreased naïve T cell counts further emphasizes the role of the thymus for the maintenance of the naïve T cell repertoire [17, 18]. Similar results as in humans are reported in studies on mice. After thymectomy the functionality of the already existing naïve $CD4^+$ T cells is decreased, suggesting premature immune aging [19].

Maintenance of naïve T cells in old age

Aging affects the naïve $CD4^+$ and $CD8^+$ T cell compartments in slightly different ways [14, 20-22]. Although the diversity and number of the naïve $CD4^+$ T cell compartment is maintained stable for a long time, a dramatic and sudden collapse of diversity occurs after the age of 70, leading to a more restricted repertoire [23, 24]. Similar changes occur earlier in life and more gradually in the naïve $CD8^+$ T cell compartment. In contrast to naïve $CD4^+$ T cells, naïve $CD8^+$ T cells of aged humans seem to be more susceptible to death receptor-mediated apoptosis, triggered by TNF-α or Fas [25, 26]. It is therefore suggested that Fas and TNF-α mediated apoptosis might contribute to the gradual disappearance of naïve, and also of memory, $CD8^+$ T cells. Generally the $CD8^+$ T cell pool is more affected by age-related changes than the $CD4^+$ T cell pool. This suggests that $CD4^+$ T cells may be more prone to respond to survival assuring mechanisms than $CD8^+$ T cells.

The reduced thymic output of newly generated naïve T cells is compensated by several mechanisms. Homeostatic proliferation has been identified to play a key role for the maintenance and restoration of the size of the naïve T cell pool. Thus it has been shown that IL-7 plays a essential role in controlling homeostatic proliferation of naïve $CD4^+$ and $CD8^+$ T cells and supports the survival of naïve $CD8^+$ T cells [27]. For the survival of

naïve $CD4^+$ T cells IL-7 and IL-4 are both essential [28]. It has been proposed that IL-7 acts in conjunction with TCR signals from contact with self-MHC/peptide ligands, which sustains the expression of anti-apoptotic molecules (e.g. Bcl-2). Naïve T cells are thus kept alive in a resting state and have a long lifespan [29, 30]. However this extended lifespan is associated with a prolonged exposure of naïve T cells to unfavorable environmental factors, which cause DNA damage, which contribute to decreased function in old age [31]. If the naïve T cell numbers drop below 4% of total T cells, homeostatic proliferation increases exponentially. This accelerates telomere shorting and may lead to a memory-like phenotype [32, 33]. Naïve T cell survival may differ between subsets, as $CD31^+$ (PECAM-1) thymic-naïve T cells decline during aging, but still display a polyclonal TCR repertoire, while central-naïve $CD4^+$ $CD31^-$ T cell numbers remain constant during aging, but exhibit increased TCR-mediated signaling and a dramatically restricted TCR repertoire [34].

Age-related functional changes of naïve T cells

In humans naïve T cells are defined on the basis of their surface expression of CD45RA, CD28, CD62L or CCR7 [22, 35]. This population undergoes functional alterations during aging. For example $CD45RA^+CD28^+CD8^+$ T cells from elderly persons produce larger amounts of the pro-inflammatory cytokine IFN-γ after their stimulation with OKT3 and IL-2 than those cells of young persons [36]. They also have shorter telomeres and a highly restricted TCR repertoire compared with a corresponding population from young persons, suggesting increased homeostatic proliferation [37]. The loss of TCR diversity in the naïve T cell compartment has also been demonstrated in aged mice [38]. Studies in mice have also demonstrated that aged mice accumulate various intrinsic defects of

naïve T cells related to TCR-mediated signaling, IL-2 production and generation of long-term memory cells [39]. Thus low IL-2 production leads for instance to reduced expansion and thereby to inefficient generation of effector T cells. This age-related defect can be reversed by the addition of exogenous IL-2 [39-41]. Additionally it has been shown that naïve $CD4^+$ T cells do not form immunologic synapses upon stimulation with peptide antigen and antigen presenting cells [42]. This may be due to an altered cholesterol/phospholipid ratio in the lymphocyte membrane, leading to an impaired TCR-dependent recruitment of signal molecules to the immunological synapses [43, 44]. Impaired T cell surface glycosylation [45] and phosphorylation [46-48] of key signaling molecules have also been suggested to contribute to age-associated defects in TCR signaling. Age-related defects in naïve T cell activation, expansion and differentiation may affect their cognate helper function to B cells and lead to reduced humoral immune responses [49, 50].

Naïve T cells in vitro - precautions

We and others have shown that the level of oxygen to which T cells are exposed is a critical parameter. Normally cells in *ex vivo* and *in vitro* experiments are cultured in air supplemented with 20% O_2, but indeed the oxygen level in the *in vivo* environment of T cells is lower than in the air and varies from 1 to 10 %, depending on the localization of the T cells [51, 52]. Recent studies have shown that different oxygen levels can influence the responsiveness of human T cells *in vitro*. *Ex vivo* T cell studies by Larbi et al. [53] showed a decreased proliferation and higher susceptibility to apoptosis at low oxygen levels following activation. These data could be confirmed by our group. We demonstrated that CD3/CD28-stimulated naïve T cells from young and elderly persons

cultivated at 3% have a significantly increased rate of apoptosis (Figure 1A) and reduced proliferation (Figure 1B). It is therefore important to consider the oxygen levels in which naïve T cells are cultured *in vitro* when interpreting data from such experiments.

In conclusion naïve T cells display remarkable changes during aging, in number as well as in functionality.

Antigen-experienced T cells

Generation of memory T cells

Immunological T cell memory is a key feature of the adaptive immune system in all vertebrates to ensure protection against previously encountered pathogens. Two models have been proposed for the generation of memory T cells following a primary infection. A linear model which postulates a consecutive activation of a naïve T cell, its subsequent expansion into an effector population that can potently eliminate the pathogen and the development of T cell memory following a contraction phase [54]. The integration of various factors and environmental parameters, such as signal strength, costimulatory signals and the surrounding cytokine milieu determines the outcome of the differentiation of an effector to a memory T cell. In stark contrast, the model of the asymmetric T cell division favors a more practical approach and a division of labor [55]. While a naïve T cell is primed by an antigen presenting cell, cytosolic and membrane components of the T cell shift and aggregate towards/away from the contact zone and remain throughout the first cell division. Unequal inheritance of those components to the progeny ensures the simultaneous generation of an effector cell, fully equipped with cytotoxic mediators at the proximal site of the immunological synapse, and a distal daughter cell that becomes the first memory T cell to that particular antigen.

Age-related changes within the memory T cell compartment

During the course of healthy aging the peripheral T cell compartment is populated by increasing numbers of memory T cells. This is due to the age-dependent decline in the output of naïve T cells (see above) and results in the filling of the resulting

immunological space with naïve and memory T cells by homeostatic means. In contrast to naïve T cells memory T cells rely on IL-7 in concert with IL-15, cycle and self-renew *in vivo* three- to fourfold faster than naïve T cells and are capable of vigorous proliferation under lymphopenic conditions [56]. Additionally, homeostatic turnover of naïve $CD8^+$ T cells may induce a memory-like phenotype [57, 58], thereby complicating the quantitative analysis of naïve, antigen-inexperienced T cells in elderly persons [22, 59]. In addition to the decrease in naïve T cell numbers, antigenic stimulation by persistent viral infections can challenge the tightly regulated orchestra of clonal expansion, contraction and homeostasis of memory T cell and may thus lead to the massive accumulation of clones of certain specificities [60, 61]. This culminates in a dramatically reduced diversity of the memory T cell pool in elderly individuals [20, 24]. Similar to the situation in naïve T cells, this age-related effect is more pronounced within the $CD8^+$ T cell compartment [62]. It is also of interest that new T cell subsets appear in the aged $CD8^+$ memory compartment, such as a population of $CD25^+$ T cells [59, 63]. These memory T cells, which are neither regulatory, nor recently activated, produce IL-2 and IL-4 and represent an early stage in the differentiation of $CD8^+$ T cells, with longer telomeres (indicating a shorter replicative history) and a polyclonal TCR repertoire. Elderly persons with a high frequency of $CD8^+CD25^+$ memory T cells seem to have a better functioning immune system as indicated by an intact humoral immune response after influenza vaccination.

Function and maintenance of memory T cells

Similar to naïve T cells, where it has been shown that naïve T cells from young mice exhibit a better functional profile than naïve T cells from aged animals [40, 41], the

functionality of memory T cells strongly depends on the age of the host at the time the antigen is encountered. Studies in mice have shown that $CD4^+$ memory T cells generated during youth function well into old age, *in vivo* as well as *in vitro*, in terms of proliferation, cytokine production and cognate helper function, compared to memory T cells generated later in life [64]. Once generated memory T cells have different possible destinies: they can either survive as memory T cells, go into apoptosis or differentiate into effector T cells. The homeostatic maintenance of memory T cells throughout lifetime is tightly regulated and preserves T cell repertoire diversity to combat new pathogens as well as the host's ability to mount vigorous recall responses to recurrent infections [65]. Only recently have we begun to understand how and where memory T cells are maintained and sheltered in times of serenity. In this respect, the bone marrow and its mesenchymal stromal cells (MSCs) have been paid particular attention. Among other proteins, MSCs express proteoglycan ligands to CD44 which is present on memory T cells and mediates their local retention in the bone marrow. They furthermore produce IL-7 and IL-15 for the homeostatic maintenance of memory T cells [66]. It has been proposed that memory T cells, when in contact with stromal cells in the bone marrow, are suppressed and display reduced allogenic and mitogenic proliferation, a state of T cell anergy and reduced apoptosis as well as modulated cytokine production [66]. As for today, we only know little about the aged bone marrow and its role as survival niche for memory T cells. Recent data from our laboratory suggests that the bone marrow of elderly persons seems still intact as a frontline defense against recurrent infections (Herndler-Brandstetter *et al*., in preparation). Further sites of residence include the gut and other mucosal surfaces, which are not well characterized in terms of age-related changes in the harboring potential of memory T cells. Further

studies will have to shed light on how memory T cells are maintained throughout a lifetime, with special respect to these sites.

Generation of terminally differentiated T cells

Over the last decade, scientific evidence has accumulated that persistent viral infections play a major role in driving the T cell compartment into exhaustion [6] with highest rates of exhausted T cells observed in elderly persons. Persistent infection with HCV [67], HIV [68-73] and CMV [20, 74] but not EBV or VZV have been shown to cause inflation of exhausted T cells already early in life. Depending on the type of persistent viral infection, T cells are repeatedly stimulated by viral antigens thereby contributing to the massive accumulation of virus-specific $CD4^+$ and $CD8^+$ T cell clones in both, mice [75] and humans [76, 77]. Although persistent CMV-infection is systemically controlled by the immune system and viral particles are detectable only in times of reactivation, life-long exposure to CMV has been demonstrated to severely impair the T cell system. It increases the number of highly differentiated, exhausted $CD4^+$ and $CD8^+$ T cells [74, 78] with an average of 10% – in the elderly up to 50% – of the overall T cell pool being specific for CMV [77]. One of the most robust markers in describing these exhausted T cells is the lack of the costimulatory molecule CD28, a member of the tumor necrosis factor receptor (TNFR) family that interacts with CD80 and/or CD86 expressed on activated antigen presenting cells. Along with an appropriate TCR/MHC engagement, CD28 signaling provides the obligatory second stimulus to achieve full T cell activation and differentiation. Recently, it has been shown that signaling via the CD28 receptor overcomes the T cells auto-inhibitory pathway to sustain full T cell activation and IL-2 production [79]. The loss of CD28-mediated Akt (Ser473) signaling has also been

associated with decreased telomerase activity [80] further contributing to the exhaustion of $CD28^-$ T cells. In general, the $CD8^+$ T cell compartment is more affected by the accumulation of terminally differentiated T cells than the $CD4^+$ T cell compartment [81, 82]. Exceptions represent rheumatoid arthritis and inflammatory bowel diseases, where the expansion of $CD28^-$ T cells is predominant in the $CD4^+$ T cell compartment [83, 84].

Maintenance of terminally differentiated T cells

The persistence and accumulation of exhausted T cells is still a matter of debate. Some reports using heavy glucose favor an extended lifespan rather than accelerated proliferation [85]. Along this line other reports suggest a certain resistance to apoptosis [25, 26, 86]. Contrariwise, different authors stress their susceptibility to apoptosis [87-89] and are therefore in favor of a more continuous production model, either antigenic derived or homeostatically.

Functional changes in terminally differentiated T cells

The gene expression profile of $CD8^+CD28^-$ T cells fundamentally differs from $CD8^+CD28^+$ T cells, both at the mRNA level as well as in microRNA usage, which in part explains the differences observed in apoptosis and the modulation of the activation threshold [90-95]. The loss of CD28 is associated with a change of cellular function in T cells including decreased TCR-mediated activation and proliferation as well as a diminished ability to secrete IL-2 but high levels of cytotoxic mediators (perforin and granzymes) that enable them to exhibit immediate effector functions. The finding that $CD28^-$ T cells have shorter telomeres than their $CD28^+$ counterparts [96, 97] completed the dogma of the ‘senescent’ $CD28^-$ T cell arising from chronic TCR stimulation with no

further proliferative capacity. Only recently have we begun to understand the complex processes taking place during the aging of the human immune system. It has been shown that $CD28^-$ T cells are not truly senescent as they can still proliferate if provided appropriate costimulation, especially by 4-1BBL and OX40L [98] and/or cytokines, such as IL-2 and IL-15 [87, 99].

Consequences of the accumulation of terminally differentiated T cells

The age-dependent accumulation of exhausted $CD28^-$ T cells, which preferentially produce the pro-inflammatory cytokines IFN-γ and TNF-α, is thought to contribute – together with components of the innate immune system – to the low-grade pro-inflammatory background observed in elderly persons (inflamm-aging) [100]. The enhanced prevalence of $CD28^-$ T cells in elderly persons, together with other parameters, such as a disturbed CD4:CD8 ratio and CMV-seropositivity, has led to the definition of the so-called 'immune risk phenotype' (IRP) predicting a higher 2-year mortality in a longitudinal study of octa- and nonagenarians [101]. The efficacy of booster vaccinations is severely decreased in the elderly [1, 102] and an insufficient antibody response following influenza vaccination in elderly persons has been correlated with a high frequency of $CD8^+CD28^-$ T cells [103]. Persistent infection with CMV and the consequent accumulation of pro-inflammatory $CD8^+CD28^-$ T cells have also been associated with an enhanced risk of coronary heart disease and impaired vascular function [104-106]. In particular, vascular inflammation caused by vessel wall injury and endothelial cell (EC) dysfunction is triggered by persistent infection with CMV [107, 108] and leads to increased arterial blood pressure, consequently contributing to the development of atherosclerosis [109]. An accumulation of $CD28^-$ T cells was also

identified in persons suffering from rheumatoid arthritis and ankylosing spondylitis [83, 110]. In conclusion, persistent infection with CMV and/or the accumulation of $CD28^-$ T cells may thus be involved in the pathogenesis of a broad variety of age-associated diseases.

Interventions to decelerate age-related changes of the T cell repertoire

Strategies to counteract age-related defects in naïve T cells

Experiments in mice [40] and studies in humans [111] indicate some promising approaches for the rejuvenation of naïve T cells leading to the production of new naïve T cells that function as well as young cells and better than those from aged individuals. Thus it has been shown that the defects of old naïve T cells can be restored when IL-2 treated cells or naïve T cells from young mice are reimplanted into aged mice [49]. The production of rejuvenated naïve T cells can also be achieved by increasing immunological space by whole body irradiation [112]. Another strategy aims at restoring thymopoiesis in the elderly. Factors such as IL-7, growth hormone and sex hormone ablation have thereby been tried (reviewed by [113]).

Caloric restriction

Increasing lifespan of cells and organisms has long been of great interest for the scientific community. Caloric restriction (CR) is today the only known method to prolong median as well as maximal lifespan in all tested animals, from invertebrates to rodents and even vertebrates including non-human primates. While it is not fully understood how CR fulfills this life prolonging effect, several probably concerted hypotheses have been postulated, one including the mTOR signaling pathway which we will discuss shortly hereafter. CR not only increases the median and maximal lifespan of a variety of organisms, but also improves specific functions that seem to acquire failures with age, for instance the immune system. Nikolich-Zugich reviewed the impact of CR on the immune system and showed, that in rodents and non-human primates CR was able to

attenuate the natural shift from naïve to memory-phenotype T cells and maintain a higher number of naïve T cells in aged animals while decreasing the total number of peripheral lymphocytes [114]. Still it remains unclear whether this is due to an increased thymic production of naïve T cells, improved maintenance of naïve T cells in the periphery or reduced T cell activation. Furthermore the age-related increase of pro-inflammatory cytokines, such as IL-6, IFN-γ and TNF-α, and the resulting pro-inflammatory state of an aged immune system (inflamm-aging) can be reversed by CR. Finally, the decreased proliferative capacity of T cells in an aged immune system due to the shift from naïve to memory-phenotype T cells can be avoided and even retracted by CR.

mTOR, autophagy and aging

The mammalian target of rapamycin (mTOR), a central integrator of diverse intra- and extracellular signals such as growth factors, nutrients, energy status or stress signals [115] could be an explanation for the life-prolonging effect of CR. In case of sufficient nutrients and other positive signals and/or in the absence of stress signals, in other words, if the cell is doing fine, mTOR is active and thereby inhibits the catabolic process of autophagy while promoting anabolic processes important for growth and proliferation via different downstream molecules. Two of the best characterized ones are S6 kinase 1 (S6K1) and the 4E binding protein 1 (4EBP1) [116]. In the course of CR, nutrients are rare and the enzymatic activity of mTOR is inhibited, leading to an upregulation of autophagy while cell growth and proliferation cease. This is reasonable for the cell since autophagy describes amongst other things the recycling of cellular components to gain new building blocks for critical proteins by degrading momentarily not needed proteins

and even organelles [117]. It has been shown that autophagy can be induced in all somatic cells of an organism by fasting or CR which represents mTOR inhibition in the course of nutrient withdrawal [118]. It is known that chronological aging of cells leads to malfunctions in various cellular mechanisms and autophagy is not an exception. It has been shown that with the aging of an organism autophagic capacity declines, leading to the accumulation of already quantitatively increased potentially harmful protein aggregates that are normally degraded via autophagy [118]. When in other somatic cells the autophagic efficiency declines with chronological aging, the same is certainly true for T cells. Interestingly, it has been found that in T cells that display replicative senescence characteristics, autophagic capacity is also decreased [119]. One might conclude, that the higher the differentiation stage of a T cell is, the lower its autophagic capacity is and therefore its probability to survive stress situations.

Pharmacological interventions

Besides CR, there are other methods to prolong lifespan via autophagy. Recently we have shown that the natural polyamine spermidine promotes longevity in yeast, flies, worms and human PBMCs in an autophagy dependent fashion [120]. Furthermore mice fed with a spermidine rich diet have an increased lifespan [121]. Along the line of mTOR inhibiting autophagy, rapamycin, a well known inhibitor of mTOR and immunosuppressive drug, prolongs lifespan in various organisms in a mTOR dependent fashion [122-124]. Interestingly, autophagy not only prolongs the lifespan but also increases the resistance to disadvantageous environmental circumstances [125]. In the immune system, mTOR is additionally responsible for the differentiation of $CD8^+$ T cells. Araki et al have recently shown, that in mice inhibition of mTOR by rapamycin shortly

after an acute lymphocytic choriomeningitis virus infection improved not only the quantity but also the quality of virus-specific $CD8^+$ T cells [126]. Therefore they propose that treatment with rapamycin after vaccination could enhance memory T cell formation.

Conclusion

Immunosenescence describes the wide range of changes within the immune system that occur with increasing age. In this review we summarize the most prominent alterations in naïve and antigen-experienced T cells. Special emphasis is placed on terminally differentiated T cells that accumulate in the elderly, display a decayed functionality and contribute to a low-grade pro-inflammatory background, a phenomenon called inflamm-aging. These age-associated dysfunctions within T cells have a strong clinical impact, the most important being reduced efficacy of vaccination and decreased resistance to infections. Our continuously improving comprehension of the aged immune system reveals strategies to overcome the detrimental effects of immunosenescence, some of which are discussed in this review.

1. Grubeck-Loebenstein B, Berger P, Saurwein-Teissl M, Zisterer K and Wick G: No immunity for the elderly. Nat Med. 4(8): 870, 1998

2. Weinberger B, Herndler-Brandstetter D, Schwanninger A, Weiskopf D and Grubeck-Loebenstein B: Biology of immune responses to vaccines in elderly persons. Clin Infect Dis. 46(7): 1078-84, 2008

3. Targonski PV, Jacobson RM and Poland GA: Immunosenescence: role and measurement in influenza vaccine response among the elderly. Vaccine. 25(16): 3066-9, 2007

4. Linton PJ and Dorshkind K: Age-related changes in lymphocyte development and function. Nat Immunol. 5(2): 133-9, 2004

5. Gupta S, Su H, Bi R, Agrawal S and Gollapudi S: Life and death of lymphocytes: a role in immunesenescence. Immun Ageing. 2: 12, 2005

6. Brunner S, Herndler-Brandstetter D, Weinberger B and Grubeck-Loebenstein B: Persistent viral infections and immune aging. Ageing Res Rev. 2010

7. Kohler S and Thiel A: Life after the thymus: CD31+ and CD31- human naive CD4+ T-cell subsets. Blood. 113(4): 769-74, 2009

8. Douek DC, McFarland RD, Keiser PH, Gage EA, Massey JM, Haynes BF, Polis MA, Haase AT, Feinberg MB, Sullivan JL, Jamieson BD, Zack JA, Picker LJ, and Koup RA: Changes in thymic function with age and during the treatment of HIV infection. Nature. 396(6712): 690-5, 1998

9. Rossi DJ, Bryder D, Seita J, Nussenzweig A, Hoeijmakers J and Weissman IL: Deficiencies in DNA damage repair limit the function of haematopoietic stem cells with age. Nature. 447(7145): 725-9, 2007

10. Ju Z, Jiang H, Jaworski M, Rathinam C, Gompf A, Klein C, Trumpp A and Rudolph KL: Telomere dysfunction induces environmental alterations limiting hematopoietic stem cell function and engraftment. Nat Med. 13(6): 742-7, 2007

11. Wagner W, Horn P, Bork S and Ho AD: Aging of hematopoietic stem cells is regulated by the stem cell niche. Exp Gerontol. 43(11): 974-80, 2008

12. Steinmann GG: Changes in the human thymus during aging. Curr Top Pathol. 75: 43-88, 1986

13. George AJ and Ritter MA: Thymic involution with ageing: obsolescence or good housekeeping? Immunol Today. 17(6): 267-72, 1996

14. Aspinall R and Andrew D: Thymic involution in aging. J Clin Immunol. 20(4): 250-6, 2000

15. Fagnoni FF, Vescovini R, Passeri G, Bologna G, Pedrazzoni M, Lavagetto G, Casti A, Franceschi C, Passeri M and Sansoni P: Shortage of circulating naive CD8(+) T cells provides new insights on immunodeficiency in aging. Blood. 95(9): 2860-8, 2000

16. Lazuardi L, Jenewein B, Wolf AM, Pfister G, Tzankov A and Grubeck-Loebenstein B: Age-related loss of naive T cells and dysregulation of T-cell/B-cell interactions in human lymph nodes. Immunology. 114(1): 37-43, 2005

17. Prelog M, Keller M, Geiger R, Brandstatter A, Wurzner R, Schweigmann U, Zlamy M, Zimmerhackl LB and Grubeck-Loebenstein B: Thymectomy in early childhood: significant alterations of the CD4(+)CD45RA(+)CD62L(+) T cell compartment in later life. Clin Immunol. 130(2): 123-32, 2009

18. Sauce D, Larsen M, Fastenackels S, Duperrier A, Keller M, Grubeck-Loebenstein B, Ferrand C, Debre P, Sidi D and Appay V: Evidence of premature immune aging in patients thymectomized during early childhood. J Clin Invest. 119(10): 3070-8, 2009

19. Swain S, Clise-Dwyer K and Haynes L: Homeostasis and the age-associated defect of CD4 T cells. Semin Immunol. 17(5): 370-7, 2005

20. Weinberger B, Lazuardi L, Weiskirchner I, Keller M, Neuner C, Fischer KH, Neuman B, Wurzner R and Grubeck-Loebenstein B: Healthy aging and latent infection with CMV lead to distinct changes in CD8+ and CD4+ T-cell subsets in the elderly. Hum Immunol. 68(2): 86-90, 2007

21. Effros RB, Cai Z and Linton PJ: CD8 T cells and aging. Crit Rev Immunol. 23(1-2): 45-64, 2003

22. Pfister G, Weiskopf D, Lazuardi L, Kovaiou RD, Cioca DP, Keller M, Lorbeg B, Parson W and Grubeck-Loebenstein B: Naive T cells in the elderly: are they still there? Ann N Y Acad Sci. 1067: 152-7, 2006

23. Goronzy JJ, Lee WW and Weyand CM: Aging and T-cell diversity. Exp Gerontol. 42(5): 400-6, 2007

24. Naylor K, Li G, Vallejo AN, Lee WW, Koetz K, Bryl E, Witkowski J, Fulbright J, Weyand CM and Goronzy JJ: The influence of age on T cell generation and TCR diversity. J Immunol. 174(11): 7446-52, 2005

25. Gupta S and Gollapudi S: TNF-alpha-induced apoptosis in human naive and memory CD8+ T cells in aged humans. Exp Gerontol. 41(1): 69-77, 2006

26. Gupta S and Gollapudi S: CD95-mediated apoptosis in naive, central and effector memory subsets of CD4+ and CD8+ T cells in aged humans. Exp Gerontol. 43(4): 266-74, 2008

27. Schluns KS, Kieper WC, Jameson SC and Lefrancois L: Interleukin-7 mediates the homeostasis of naive and memory CD8 T cells in vivo. Nat Immunol. 1(5): 426-32, 2000

28. Boursalian TE and Bottomly K: Survival of naive CD4 T cells: roles of restricting versus selecting MHC class II and cytokine milieu. J Immunol. 162(7): 3795-801, 1999

29. Caserta S and Zamoyska R: Memories are made of this: synergy of T cell receptor and cytokine signals in CD4(+) central memory cell survival. Trends Immunol. 28(6): 245-8, 2007

30. Tan JT, Dudl E, LeRoy E, Murray R, Sprent J, Weinberg KI and Surh CD: IL-7 is critical for homeostatic proliferation and survival of naive T cells. Proc Natl Acad Sci U S A. 98(15): 8732-7, 2001

31. Barnett YA and Barnett CR: DNA damage and mutation: contributors to the age-related alterations in T cell-mediated immune responses? Mech Ageing Dev. 102(2-3): 165-75, 1998

32. Kilpatrick RD, Rickabaugh T, Hultin LE, Hultin P, Hausner MA, Detels R, Phair J and Jamieson BD: Homeostasis of the naive CD4+ T cell compartment during aging. J Immunol. 180(3): 1499-507, 2008

33. Cicin-Sain L, Messaoudi I, Park B, Currier N, Planer S, Fischer M, Tackitt S, Nikolich-Zugich D, Legasse A, Axthelm MK, Picker LJ, Mori M, and Nikolich-Zugich J: Dramatic increase in naive T cell turnover is linked to loss of naive T cells from old primates. Proc Natl Acad Sci U S A. 104(50): 19960-5, 2007

34. Kohler S, Wagner U, Pierer M, Kimmig S, Oppmann B, Mowes B, Julke K, Romagnani C and Thiel A: Post-thymic in vivo proliferation of naive CD4+ T cells constrains the TCR repertoire in healthy human adults. Eur J Immunol. 35(6): 1987-94, 2005

35. Alves NL, Hooibrink B, Arosa FA and van Lier RA: IL-15 induces antigen-independent expansion and differentiation of human naive CD8+ T cells in vitro. Blood. 102(7): 2541-6, 2003

36. Pfister G and Savino W: Can the immune system still be efficient in the elderly? An immunological and immunoendocrine therapeutic perspective. Neuroimmunomodulation. 15(4-6): 351-64, 2008

37. Pawelec G, Akbar A, Caruso C, Effros R, Grubeck-Loebenstein B and Wikby A: Is immunosenescence infectious? Trends Immunol. 25(8): 406-10, 2004

38. Ahmed M, Lanzer KG, Yager EJ, Adams PS, Johnson LL and Blackman MA: Clonal expansions and loss of receptor diversity in the naive CD8 T cell repertoire of aged mice. J Immunol. 182(2): 784-92, 2009

39. Haynes L and Eaton SM: The effect of age on the cognate function of CD4+ T cells. Immunol Rev. 205: 220-8, 2005

40. Haynes L, Linton PJ, Eaton SM, Tonkonogy SL and Swain SL: Interleukin 2, but not other common gamma chain-binding cytokines, can reverse the defect in generation of CD4 effector T cells from naive T cells of aged mice. J Exp Med. 190(7): 1013-24, 1999

41. Linton PJ, Haynes L, Klinman NR and Swain SL: Antigen-independent changes in naive CD4 T cells with aging. J Exp Med. 184(5): 1891-900, 1996

42. Garcia GG and Miller RA: Age-dependent defects in TCR-triggered cytoskeletal rearrangement in CD4+ T cells. J Immunol. 169(9): 5021-7, 2002

43. Huber LA, Xu QB, Jurgens G, Bock G, Buhler E, Gey KF, Schonitzer D, Traill KN and Wick G: Correlation of lymphocyte lipid composition membrane microviscosity and mitogen response in the aged. Eur J Immunol. 21(11): 2761-5, 1991

44. Stulnig TM, Buhler E, Bock G, Kirchebner C, Schonitzer D and Wick G: Altered switch in lipid composition during T-cell blast transformation in the healthy elderly. J Gerontol A Biol Sci Med Sci. 50(6): B383-90, 1995

45. Garcia GG and Miller RA: Age-related defects in CD4+ T cell activation reversed by glycoprotein endopeptidase. Eur J Immunol. 33(12): 3464-72, 2003

46. Miller RA, Garcia G, Kirk CJ and Witkowski JM: Early activation defects in T lymphocytes from aged mice. Immunol Rev. 160: 79-90, 1997

47. Kirk CJ, Freilich AM and Miller RA: Age-related decline in activation of JNK by TCR- and CD28-mediated signals in murine T-lymphocytes. Cell Immunol. 197(2): 75-82, 1999

48. Kirk CJ and Miller RA: Analysis of Raf-1 activation in response to TCR activation and costimulation in murine T-lymphocytes: effect of age. Cell Immunol. 190(1): 33-42, 1998

49. Eaton SM, Burns EM, Kusser K, Randall TD and Haynes L: Age-related defects in CD4 T cell cognate helper function lead to reductions in humoral responses. J Exp Med. 200(12): 1613-22, 2004

50. Haynes L and Maue AC: Effects of aging on T cell function. Curr Opin Immunol. 21(4): 414-7, 2009

51. Caldwell CC, Kojima H, Lukashev D, Armstrong J, Farber M, Apasov SG and Sitkovsky MV: Differential effects of physiologically relevant hypoxic conditions on T lymphocyte development and effector functions. J Immunol. 167(11): 6140-9, 2001

52. Atkuri KR, Herzenberg LA, Niemi AK and Cowan T: Importance of culturing primary lymphocytes at physiological oxygen levels. Proc Natl Acad Sci U S A. 104(11): 4547-52, 2007

53. Larbi A, Cabreiro F, Zelba H, Marthandan S, Combet E, Friguet B, Petropoulos I, Barnett Y and Pawelec G: Reduced oxygen tension results in reduced human T cell proliferation and increased intracellular oxidative damage and susceptibility to apoptosis upon activation. Free Radic Biol Med. 48(1): 26-34, 2010

54. Seder RA and Ahmed R: Similarities and differences in CD4+ and CD8+ effector and memory T cell generation. Nat Immunol. 4(9): 835-42, 2003

55. Chang JT, Palanivel VR, Kinjyo I, Schambach F, Intlekofer AM, Banerjee A, Longworth SA, Vinup KE, Mrass P, Oliaro J, Killeen N, Orange JS, Russell SM, Weninger W, and Reiner SL: Asymmetric T lymphocyte division in the initiation of adaptive immune responses. Science. 315(5819): 1687-91, 2007

56. Surh CD and Sprent J: Regulation of naive and memory T-cell homeostasis. Microbes Infect. 4(1): 51-6, 2002

57. Ge Q, Hu H, Eisen HN and Chen J: Naive to memory T-cell differentiation during homeostasis-driven proliferation. Microbes Infect. 4(5): 555-8, 2002

58. Hamilton SE, Wolkers MC, Schoenberger SP and Jameson SC: The generation of protective memory-like CD8+ T cells during homeostatic proliferation requires CD4+ T cells. Nat Immunol. 7(5): 475-81, 2006

59. Herndler-Brandstetter D, Veel E, Laschober GT, Pfister G, Brunner S, Walcher S, Parson W, Lepperdinger G and Grubeck-Loebenstein B: Non-regulatory CD8+CD45RO+CD25+ T-lymphocytes may compensate for the loss of antigen-inexperienced CD8+CD45RA+ T-cells in old age. Biol Chem. 389(5): 561-8, 2008

60. Karrer U, Sierro S, Wagner M, Oxenius A, Hengel H, Koszinowski UH, Phillips RE and Klenerman P: Memory inflation: continuous accumulation of antiviral CD8+ T cells over time. J Immunol. 170(4): 2022-9, 2003

61. Snyder CM, Cho KS, Bonnett EL, van Dommelen S, Shellam GR and Hill AB: Memory inflation during chronic viral infection is maintained by continuous production of short-lived, functional T cells. Immunity. 29(4): 650-9, 2008

62. Saule P, Trauet J, Dutriez V, Lekeux V, Dessaint JP and Labalette M: Accumulation of memory T cells from childhood to old age: central and effector memory cells in CD4(+) versus effector memory and terminally differentiated memory cells in CD8(+) compartment. Mech Ageing Dev. 127(3): 274-81, 2006

63. Schwaiger S, Wolf AM, Robatscher P, Jenewein B and Grubeck-Loebenstein B: IL-4-producing CD8+ T cells with a CD62L++(bright) phenotype accumulate in a subgroup of older adults and are associated with the maintenance of intact humoral immunity in old age. J Immunol. 170(1): 613-9, 2003

64. Haynes L, Eaton SM, Burns EM, Randall TD and Swain SL: CD4 T cell memory derived from young naive cells functions well into old age, but memory generated from aged naive cells functions poorly. Proc Natl Acad Sci U S A. 100(25): 15053-8, 2003

65. Nikolich-Zugich J: Ageing and life-long maintenance of T-cell subsets in the face of latent persistent infections. Nat Rev Immunol. 8(7): 512-22, 2008

66. Tokoyoda K, Hauser AE, Nakayama T and Radbruch A: Organization of immunological memory by bone marrow stroma. Nat Rev Immunol. 10(3): 193-200, 2010

67. Gruener NH, Lechner F, Jung MC, Diepolder H, Gerlach T, Lauer G, Walker B, Sullivan J, Phillips R, Pape GR, and Klenerman P: Sustained dysfunction of antiviral CD8+ T lymphocytes after infection with hepatitis C virus. J Virol. 75(12): 5550-8, 2001

68. Pantaleo G, Soudeyns H, Demarest JF, Vaccarezza M, Graziosi C, Paolucci S, Daucher M, Cohen OJ, Denis F, Biddison WE, Sekaly RP, and Fauci AS: Evidence for

rapid disappearance of initially expanded HIV-specific CD8+ T cell clones during primary HIV infection. Proc Natl Acad Sci U S A. 94(18): 9848-53, 1997

69. Sewell AK, Price DA, Oxenius A, Kelleher AD and Phillips RE: Cytotoxic T lymphocyte responses to human immunodeficiency virus: control and escape. Stem Cells. 18(4): 230-44, 2000

70. Shankar P, Russo M, Harnisch B, Patterson M, Skolnik P and Lieberman J: Impaired function of circulating HIV-specific CD8(+) T cells in chronic human immunodeficiency virus infection. Blood. 96(9): 3094-101, 2000

71. Appay V, Dunbar PR, Callan M, Klenerman P, Gillespie GM, Papagno L, Ogg GS, King A, Lechner F, Spina CA, Little S, Havlir DV, Richman DD, Gruener N, Pape G, Waters A, Easterbrook P, Salio M, Cerundolo V, McMichael AJ, and Rowland-Jones SL: Memory CD8+ T cells vary in differentiation phenotype in different persistent virus infections. Nat Med. 8(4): 379-85, 2002

72. Kostense S, Vandenberghe K, Joling J, Van Baarle D, Nanlohy N, Manting E and Miedema F: Persistent numbers of tetramer+ CD8(+) T cells, but loss of interferon-gamma+ HIV-specific T cells during progression to AIDS. Blood. 99(7): 2505-11, 2002

73. Oxenius A, Sewell AK, Dawson SJ, Gunthard HF, Fischer M, Gillespie GM, Rowland-Jones SL, Fagard C, Hirschel B, Phillips RE, and Price DA: Functional discrepancies in HIV-specific CD8+ T-lymphocyte populations are related to plasma virus load. J Clin Immunol. 22(6): 363-74, 2002

74. Almanzar G, Schwaiger S, Jenewein B, Keller M, Herndler-Brandstetter D, Wurzner R, Schonitzer D and Grubeck-Loebenstein B: Long-term cytomegalovirus infection leads to significant changes in the composition of the CD8+ T-cell repertoire, which may be

the basis for an imbalance in the cytokine production profile in elderly persons. J Virol. 79(6): 3675-83, 2005

75. Mueller SN and Ahmed R: High antigen levels are the cause of T cell exhaustion during chronic viral infection. Proc Natl Acad Sci U S A. 106(21): 8623-8, 2009

76. Fletcher JM, Vukmanovic-Stejic M, Dunne PJ, Birch KE, Cook JE, Jackson SE, Salmon M, Rustin MH and Akbar AN: Cytomegalovirus-specific CD4+ T cells in healthy carriers are continuously driven to replicative exhaustion. J Immunol. 175(12): 8218-25, 2005

77. Sylwester AW, Mitchell BL, Edgar JB, Taormina C, Pelte C, Ruchti F, Sleath PR, Grabstein KH, Hosken NA, Kern F, Nelson JA, and Picker LJ: Broadly targeted human cytomegalovirus-specific CD4+ and CD8+ T cells dominate the memory compartments of exposed subjects. J Exp Med. 202(5): 673-85, 2005

78. Ouyang Q, Wagner WM, Zheng W, Wikby A, Remarque EJ and Pawelec G: Dysfunctional CMV-specific CD8(+) T cells accumulate in the elderly. Exp Gerontol. 39(4): 607-13, 2004

79. Bjorgo E and Tasken K: Novel mechanism of signaling by CD28. Immunol Lett. 129(1): 1-6, 2010

80. Plunkett FJ, Franzese O, Finney HM, Fletcher JM, Belaramani LL, Salmon M, Dokal I, Webster D, Lawson AD and Akbar AN: The loss of telomerase activity in highly differentiated CD8+CD28-CD27- T cells is associated with decreased Akt (Ser473) phosphorylation. J Immunol. 178(12): 7710-9, 2007

81. Fagnoni FF, Vescovini R, Mazzola M, Bologna G, Nigro E, Lavagetto G, Franceschi C, Passeri M and Sansoni P: Expansion of cytotoxic CD8+ CD28- T cells in healthy ageing people, including centenarians. Immunology. 88(4): 501-7, 1996

82. Vallejo AN, Nestel AR, Schirmer M, Weyand CM and Goronzy JJ: Aging-related deficiency of CD28 expression in CD4+ T cells is associated with the loss of gene-specific nuclear factor binding activity. J Biol Chem. 273(14): 8119-29, 1998

83. Schmidt D, Goronzy JJ and Weyand CM: CD4+ CD7- CD28- T cells are expanded in rheumatoid arthritis and are characterized by autoreactivity. J Clin Invest. 97(9): 2027-37, 1996

84. Kobayashi T, Okamoto S, Iwakami Y, Nakazawa A, Hisamatsu T, Chinen H, Kamada N, Imai T, Goto H and Hibi T: Exclusive increase of CX3CR1+CD28-CD4+ T cells in inflammatory bowel disease and their recruitment as intraepithelial lymphocytes. Inflamm Bowel Dis. 13(7): 837-46, 2007

85. Wallace DL, Masters JE, de Lara CM, Henson SM, Worth A, Zhang Y, Kumar SR, Beverley PC, Akbar AN and Macallan DC: Human cytomegalovirus-specific CD8(+) T-cell expansions contain long-lived cells that retain functional capacity in both young and elderly subjects. Immunology. 2010

86. Gupta S and Gollapudi S: Susceptibility of naive and subsets of memory T cells to apoptosis via multiple signaling pathways. Autoimmun Rev. 6(7): 476-81, 2007

87. Borthwick NJ, Lowdell M, Salmon M and Akbar AN: Loss of CD28 expression on CD8(+) T cells is induced by IL-2 receptor gamma chain signalling cytokines and type I IFN, and increases susceptibility to activation-induced apoptosis. Int Immunol. 12(7): 1005-13, 2000

88. Geginat J, Lanzavecchia A and Sallusto F: Proliferation and differentiation potential of human CD8+ memory T-cell subsets in response to antigen or homeostatic cytokines. Blood. 101(11): 4260-6, 2003

89. Sallusto F, Geginat J and Lanzavecchia A: Central memory and effector memory T cell subsets: function, generation, and maintenance. Annu Rev Immunol. 22: 745-63, 2004

90. Fann M, Chiu WK, Wood WH, 3rd, Levine BL, Becker KG and Weng NP: Gene expression characteristics of CD28null memory phenotype CD8+ T cells and its implication in T-cell aging. Immunol Rev. 205: 190-206, 2005

91. Lindsay MA: microRNAs and the immune response. Trends Immunol. 29(7): 343-51, 2008

92. Lazuardi L, Herndler-Brandstetter D, Brunner S, Laschober GT, Lepperdinger G and Grubeck-Loebenstein B: Microarray analysis reveals similarity between CD8+CD28- T cells from young and elderly persons, but not of CD8+CD28+ T cells. Biogerontology. 10(2): 191-202, 2009

93. Weng NP, Akbar AN and Goronzy J: CD28(-) T cells: their role in the age-associated decline of immune function. Trends Immunol. 30(7): 306-12, 2009

94. Hackl M, Brunner S, Fortschegger K, Schreiner C, Micutkova L, Muck C, Laschober GT, Lepperdinger G, Sampson N, Berger P, Herndler-Brandstetter D, Wieser M, Kuhnel H, Strasser A, Rinnerthaler M, Breitenbach M, Mildner M, Eckhart L, Tschachler E, Trost A, Bauer JW, Papak C, Trajanoski Z, Scheideler M, Grillari-Voglauer R, Grubeck-Loebenstein B, Jansen-Durr P, and Grillari J: miR-17, miR-19b, miR-20a, and miR-106a are down-regulated in human aging. Aging Cell. 9(2): 291-6, 2010

95. Luo X, Tsai LM, Shen N and Yu D: Evidence for microRNA-mediated regulation in rheumatic diseases. Ann Rheum Dis. 69 Suppl 1: i30-36, 2010

96. Monteiro J, Batliwalla F, Ostrer H and Gregersen PK: Shortened telomeres in clonally expanded CD28-CD8+ T cells imply a replicative history that is distinct from their CD28+CD8+ counterparts. J Immunol. 156(10): 3587-90, 1996

97. Kovaiou RD, Weiskirchner I, Keller M, Pfister G, Cioca DP and Grubeck-Loebenstein B: Age-related differences in phenotype and function of CD4+ T cells are due to a phenotypic shift from naive to memory effector CD4+ T cells. Int Immunol. 17(10): 1359-66, 2005

98. Kober J, Leitner J, Klauser C, Woitek R, Majdic O, Stockl J, Herndler-Brandstetter D, Grubeck-Loebenstein B, Reipert BM, Pickl WF, Pfistershammer K, and Steinberger P: The capacity of the TNF family members 4-1BBL, OX40L, CD70, GITRL, CD30L and LIGHT to costimulate human T cells. Eur J Immunol. 38(10): 2678-88, 2008

99. Chiu WK, Fann M and Weng NP: Generation and growth of CD28nullCD8+ memory T cells mediated by IL-15 and its induced cytokines. J Immunol. 177(11): 7802-10, 2006

100. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E and De Benedictis G: Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 908: 244-54, 2000

101. Wikby A, Ferguson F, Forsey R, Thompson J, Strindhall J, Lofgren S, Nilsson BO, Ernerudh J, Pawelec G and Johansson B: An immune risk phenotype, cognitive impairment, and survival in very late life: impact of allostatic load in Swedish octogenarian and nonagenarian humans. J Gerontol A Biol Sci Med Sci. 60(5): 556-65, 2005

102. Chen WH, Kozlovsky BF, Effros RB, Grubeck-Loebenstein B, Edelman R and Sztein MB: Vaccination in the elderly: an immunological perspective. Trends Immunol. 30(7): 351-9, 2009

103. Saurwein-Teissl M, Lung TL, Marx F, Gschosser C, Asch E, Blasko I, Parson W, Bock G, Schonitzer D, Trannoy E, and Grubeck-Loebenstein B: Lack of antibody production following immunization in old age: association with CD8(+)CD28(-) T cell clonal expansions and an imbalance in the production of Th1 and Th2 cytokines. J Immunol. 168(11): 5893-9, 2002

104. Blankenberg S, Rupprecht HJ, Bickel C, Espinola-Klein C, Rippin G, Hafner G, Ossendorf M, Steinhagen K and Meyer J: Cytomegalovirus infection with interleukin-6 response predicts cardiac mortality in patients with coronary artery disease. Circulation. 103(24): 2915-21, 2001

105. Grahame-Clarke C, Chan NN, Andrew D, Ridgway GL, Betteridge DJ, Emery V, Colhoun HM and Vallance P: Human cytomegalovirus seropositivity is associated with impaired vascular function. Circulation. 108(6): 678-83, 2003

106. Spyridopoulos I, Hoffmann J, Aicher A, Brummendorf TH, Doerr HW, Zeiher AM and Dimmeler S: Accelerated telomere shortening in leukocyte subpopulations of patients with coronary heart disease: role of cytomegalovirus seropositivity. Circulation. 120(14): 1364-72, 2009

107. Fish KN, Soderberg-Naucler C, Mills LK, Stenglein S and Nelson JA: Human cytomegalovirus persistently infects aortic endothelial cells. J Virol. 72(7): 5661-8, 1998

108. Bentz GL and Yurochko AD: Human CMV infection of endothelial cells induces an angiogenic response through viral binding to EGF receptor and beta1 and beta3 integrins. Proc Natl Acad Sci U S A. 105(14): 5531-6, 2008

109. Cheng J, Ke Q, Jin Z, Wang H, Kocher O, Morgan JP, Zhang J and Crumpacker CS: Cytomegalovirus infection causes an increase of arterial blood pressure. PLoS Pathog. 5(5): e1000427, 2009

110. Schirmer M, Goldberger C, Wurzner R, Duftner C, Pfeiffer KP, Clausen J, Neumayr G and Falkenbach A: Circulating cytotoxic CD8(+) CD28(-) T cells in ankylosing spondylitis. Arthritis Res. 4(1): 71-6, 2002

111. Holland AM and van den Brink MR: Rejuvenation of the aging T cell compartment. Curr Opin Immunol. 21(4): 454-9, 2009

112. Haynes L, Eaton SM, Burns EM, Randall TD and Swain SL: Newly generated CD4 T cells in aged animals do not exhibit age-related defects in response to antigen. J Exp Med. 201(6): 845-51, 2005

113. Hollander GA, Krenger W and Blazar BR: Emerging strategies to boost thymic function. Curr Opin Pharmacol. 10(4): 443-53, 2010

114. Nikolich-Zugich J and Messaoudi I: Mice and flies and monkeys too: caloric restriction rejuvenates the aging immune system of non-human primates. Exp Gerontol. 40(11): 884-93, 2005

115. Dunlop EA and Tee AR: Mammalian target of rapamycin complex 1: signalling inputs, substrates and feedback mechanisms. Cell Signal. 21(6): 827-35, 2009

116. Foster KG and Fingar DC: Mammalian target of rapamycin (mTOR): conducting the cellular signaling symphony. J Biol Chem. 285(19): 14071-7, 2010

117. Yang Z and Klionsky DJ: Eaten alive: a history of macroautophagy. Nat Cell Biol. 12(9): 814-22, 2010

118. Cuervo AM, Bergamini E, Brunk UT, Droge W, Ffrench M and Terman A: Autophagy and aging: the importance of maintaining "clean" cells. Autophagy. 1(3): 131-40, 2005

119. Gerland LM, Genestier L, Peyrol S, Michallet MC, Hayette S, Urbanowicz I, Ffrench P, Magaud JP and Ffrench M: Autolysosomes accumulate during in vitro CD8+ T-

lymphocyte aging and may participate in induced death sensitization of senescent cells. Exp Gerontol. 39(5): 789-800, 2004

120. Eisenberg T, Knauer H, Schauer A, Buttner S, Ruckenstuhl C, Carmona-Gutierrez D, Ring J, Schroeder S, Magnes C, Antonacci L, Fussi H, Deszcz L, Hartl R, Schraml E, Criollo A, Megalou E, Weiskopf D, Laun P, Heeren G, Breitenbach M, Grubeck-Loebenstein B, Herker E, Fahrenkrog B, Frohlich KU, Sinner F, Tavernarakis N, Minois N, Kroemer G, and Madeo F: Induction of autophagy by spermidine promotes longevity. Nat Cell Biol. 11(11): 1305-14, 2009

121. Soda K, Dobashi Y, Kano Y, Tsujinaka S and Konishi F: Polyamine-rich food decreases age-associated pathology and mortality in aged mice. Exp Gerontol. 44(11): 727-32, 2009

122. Kaeberlein M, Burtner CR and Kennedy BK: Recent developments in yeast aging. PLoS Genet. 3(5): e84, 2007

123. Kapahi P, Zid BM, Harper T, Koslover D, Sapin V and Benzer S: Regulation of lifespan in Drosophila by modulation of genes in the TOR signaling pathway. Curr Biol. 14(10): 885-90, 2004

124. Bjedov I, Toivonen JM, Kerr F, Slack C, Jacobson J, Foley A and Partridge L: Mechanisms of life span extension by rapamycin in the fruit fly Drosophila melanogaster. Cell Metab. 11(1): 35-46, 2010

125. Vigne P, Tauc M and Frelin C: Strong dietary restrictions protect Drosophila against anoxia/reoxygenation injuries. PLoS One. 4(5): e5422, 2009

126. Araki K, Turner AP, Shaffer VO, Gangappa S, Keller SA, Bachmann MF, Larsen CP and Ahmed R: mTOR regulates memory CD8 T-cell differentiation. Nature. 460(7251): 108-12, 2009

Figure 1

Effect of oxygen level on apoptosis and proliferation of $CD8^+CD45RA^+CD28^+$ T cells from young (n=5) and elderly persons (n=3), stimulated for 5 days with CD3/CD28 DynaBeads

(A) Flow cytometric analysis of Annexin V / 7-AAD of $CD8^+CD45RA^+CD28^+$ T cells at 3% and 20% oxygen after 5 days. A representative contour plot (left) and a bar chart (right; mean ± SEM, *$p<0.05$, student's t-test)

(B) Proliferation of CFSE-labeled $CD8^+CD45RA^+CD28^+$ T cells at 3% and 20% oxygen after 5 days. One representative histogram is shown.

Figure

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