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Metabolic Syndrome, Hormones, and Maintenance of T Cells during Aging

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Summary

Although the phenotype of T-cell senescence has been extensively investigated, few studies have analyzed the factors that promote the generation and maintenance of naïve and memory T cells that exist throughout the lifespan of the individuals. Unlike senescent T cells, naïve and memory T cells are able to participate in useful immune responses as well as respond to new activation. Hormones such as leptin, ghrelin, IGF-1, IGFBP3, and cytokines, including IL-7, regulate both thymopoiesis and maintenance of naïve T cells in the periphery. Although chronic viruses such as cytomegalovirus (CMV) are thought to drive T cell senescence, other microbes may be important for maintenance of non-senescent T cells. Microbiota of the gut can induce metabolic syndrome as well as modulate T cell development into specific subpopulations of effector cells. Finally, T-cell generation, maintenance, and apoptosis depend upon pathways of energy utilization within the T cells, which parallel those that regulate overall metabolism. Therefore, better understanding of metabolic syndrome, T cell metabolism, hormones, and microbiota may lead to new insights into the maintenance of proper immune responses in old age.

Prevention of Immune Senescence by Hormones and Apoptosis

Although it is known that there is an increase in senescent T cells with a limited T-cell receptor (TCR) repertoire in old age, much less attention has been focused on the maintenance of useful naïve or early memory T cells. Naïve T cells produced decades earlier can persist into late adulthood and provide an important source of T cells capable of entering into the younger memory pool or responding to new antigens [1]. The two main genetically controlled processes that regulate the size of the naïve T cell and young memory pools are the initial thymic output and subsequent maintenance [2]. Specific factors that regulate both thymopoiesis and maintenance include IL-7, peptide hormones, and sex steroids [3**,4**]. T-cell maintenance is also affected by appropriate T cell activation and activation-induced cell death (AICD) [5**–7]. Functional T-cell apoptosis signaling, which can best be analyzed by *in vivo* analysis, is necessary to remove cells that have become exhausted by replicative senescence or have accumulated oxidative DNA damage [8,9]. Hsu *et al* have shown that successful immune aging is associated with normal AICD in nonagenarians [5]. This review will discuss key factors

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Conflicts of Interest

The authors declare no potential conflicts of interest with the materials described in this manuscript.

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related to hormones that regulate thymocyte production, even into late life, as well as factors that maintain apoptosis, prevent accumulation of senescent cells, and provide necessary immunologic “space” for functional naïve and memory T cells.

1. Maintenance of naïve T cells through the metabolic pathway

1.1 Leptin, an adipokine that may regulate thymopoiesis—Leptin is a 16-kDa hormone derived from adipose tissue that acts on specific regions of the brain to regulate food intake, energy expenditure, and neuroendocrine function [10–12**]. Leptin is structurally related to cytokines and acts on receptors that belong to the cytokine receptor superfamily [13**]. Therefore, leptin is also considered to be an adipokine [14]. Interestingly, recent findings suggest that leptin might also play a role in regulating thymopoiesis. Gruver *et al* [3, 15] have shown that the leptin receptor is expressed in the thymic medulla and that leptin protects against stress-induced thymic atrophy. Leptin has a beneficial effect on thymopoiesis as determined by analysis of T cell receptor recombination excision circles (TRECs). Nonagenarians exhibiting higher levels of circulating leptin also exhibited a higher percentage of TREC⁺ CD28⁺CD95[−] CD8 T cells in peripheral blood mononuclear cells (PBMCs) [16**]. Thus, leptin may have a beneficial effect on thymopoiesis and maintenance of naïve T cells throughout the lifespan of an individual (Fig. 1).

1.2. Growth hormone (GH) and insulin-like growth factor (IGF)-1—There is extensive evidence that GH deficiency and deficiencies of GH signaling can prolong both lifespan and immune response in aged mice [17,18]. GH signaling is regulated at multiple levels, including the level of growth hormone itself, the level of growth hormone signaling, as well as the levels of IGF-1 and insulin-like growth factor binding proteins (IGFBPs) (Fig. 1) [19]. On the other hand, IGFBP, in addition to binding IGF-1, exhibits autocrine and paracrine actions that affect cell mobility, adhesion, apoptosis, survival, and the cell cycle [20]. Low levels of leptin, IGF-1 and IGFBP3 and high TNF were associated with high mortality among centenarians [21**].

We have recently shown that there is a significant positive correlation between GH and senescent T cells as well as a positive correlation between IGFBP3 and the percentage of naïve CD8 T cells in nonagenarians [16**]. These results suggest that higher levels of IGFBP3 can act to suppress the action of IGF-1 to promote and sustain the levels of naïve T cells during late old age. In addition, lower levels of GH and IGF-1 also play a key role in promoting higher levels of naïve T cells and limiting the percentage of terminally differentiated or senescent T cells.

1.3. Metabolic syndrome and T-cell senescence—The metabolic theory of aging implies that caloric restriction can limit immune senescence in animals, including primates and possibly humans [22**]. This is consistent with new results showing that inhibition of the mammalian target of rapamycin (mTOR) signaling pathway can mimic certain aspects of caloric restriction and can also inhibit immune senescence (Fig. 1) [23**,24]. Rapamycin can extend lifespan through mechanisms similar to caloric restriction [25].

More recently, there has been increased attention focused on the role of metabolic syndrome in immune responses. Metabolic syndrome alters T cell development and T-cells derived from adipose tissue exhibit pro-inflammatory properties [26**,27,28]. Adipose tissue promotes the production and release of high levels of IL-6, TNF- α , and CRP [29**–32] (Fig 2). Although hormones such as leptin and adiponectin [33] are major regulators of metabolic syndrome, other factors include the amount of visceral fat. Visceral or mesenteric fat, but not subcutaneous fat, have a major deleterious effect related to inflammation in metabolic syndrome [31].

One important link between visceral fat and immune response that has only recently been appreciated is that different innate immune response defects can alter the presence of different species of gut microbiota that promote metabolic syndrome [34**,35] and indirectly or directly affect T cell development [36]. Changes in intestinal microbiota are an essential factor in numerous disorders that promote chronic inflammation. In contrast, germ-free mice exhibit lower levels of T cell stimulation and decreased accumulation of CD44⁺CD62L⁺ T cells, while certain gut microbiota, such as the Cytophaga-Flavobacter-Bacteroidetes phylum, promote development of IL-17 producing Th17 T cells [37]. Other bacteria, such as γ -proteobacteria, exhibit a low correlation with Th17 cells [37]. Toll-like receptors expression and genetic manipulation in mice have been shown to alter the gut microbiota and promote chronic inflammation [38]. Thus, the altered innate responses and gut microflora can cause metabolic syndrome [39], which promotes systemic chronic inflammation and T cell senescence [40]. Regulation of gut microflora with, for example, probiotics, may be an effective way to control both metabolic syndrome and the accumulation of senescent T cells.

1.4. T cell metabolism and longevity of T cells—How does organismal metabolism relate to T-cell metabolism? It is worthwhile to note that the maintenance and generation of T cells from older individuals may both be regulated through the PI-3K/AKT/FOXO signaling axis in that T cells use a similar pathway as IGF-1 for regulation of their activation (Fig. 3). Studies by Thompson and colleagues indicate that T cells utilize CD28, which is the homologue of IGF-1R, to trigger its signaling event [41**]. The significance of CD28 in regulating T cells through the PI-3K/AKT/inhibition of FOXO signaling axis has critical biologic implications since this signaling event also increases glucose uptake and glycolytic rate to maintain cellular ATP/ADP levels or macromolecular synthesis in response to T-cell activation [41**]. It is possible that the CD28/PI-3K/AKT and resulting inhibition of the FOXO signaling axis is a unique mechanism developed to separate T cells from the major glucose metabolic system operated by the liver. This would confer an evolutionary advantage for the organism, because the signal that triggers T-cell co-stimulation by CD28 also triggers the energy utilization of the T cell (Fig. 3). In the absence of foreign pathogenic antigens, T cells are maintained in a quiescent state similar to the lower metabolic state of the whole organism to not only conserve energy, but also prevent unnecessary expansion and the necessity for subsequent massive apoptosis of T cells. Both events require very tight regulation to prevent pathogenic consequences to the whole organism. During an immune response, the T cell rapidly regains its ability to respond upon encountering a foreign antigen presented by the antigen-presenting cells. On completion of the T-cell response, down-modulation of the CD28/PI-3K/AKT/inhibition of FOXO signaling axis is a critical event in returning the T cell to its quiescent state. In the periphery, the loss of CD28 expression and altered CD28 signaling are predominant features of T-cell senescence [5,16,42**]. These features are very similar to the life-long enhancement of the IGF-1 signal and its association with shortened lifespan of the organism.

2. Maintenance of naïve T cells through proper regulation of T-cell apoptosis

2.1. Increased activation-induced cell death (AICD) increases thymopoiesis and maintains the naïve T cell repertoire—Zhou *et al* [43**] showed that enforced expression of CD95 (Fas) during thymocyte development and on peripheral T cells can increase thymopoiesis, thymic output, prolong maintenance of naïve or memory T cells in the periphery, and limit development of senescent cells. The mechanism for this was proposed to be heightened sensitivity to apoptosis *in vivo*, which leads to more efficient elimination of pre-senescent cells before development of a senescent apoptosis-resistant phenotype. This enables immunologic space to be available for subsequent immune responses. Murasko and coworkers [44**] showed that Poly(I:C) activation and induction of interferons (IFNs) led to the depletion of T cells in young, but not aged mice. Therefore, appropriate regulation of apoptosis and

removal of cells at the earliest stage of senescence can limit immune senescence and an improved immune response.

Although apoptosis resistance is a property common to all senescent cells, there have been conflicting results between *in vivo* and *in vitro* studies of immune cells from aged humans and mice. Studies *in vitro* show that cells from aged humans and mice are more susceptible to genotoxin-induced cell death [8,9]. However, T-cell death induced by DNA damage and stress is different from AICD during T cell maintenance. Hsu *et al* [6,7] have shown that there is decreased apoptosis after transfer of senescent CD8 T cells from a T cell receptor transgenic (Tg) mouse into a stimulating environment *in vivo*, resulting in lower induction of apoptosis and expansion/infiltration of CD8 T cells in aged mice. Ahmed and colleagues have demonstrated that although generation of T-cell responses is compromised in old mice, homeostatic maintenance, which requires IL-7/IL-7R interaction, was not affected in lymphocytic-choriomeningitis-virus – (LCMV-) specific CD8⁺ T cells in 22-month-old mice [45**]. Recently, Swain and colleagues [46] found that with increasing organismal age, naïve CD4 T cells become progressively longer-lived. Newly generated naïve T cells derived from aged stem cells have a shorter lifespan like that of young naïve T cells. Conversely, naïve CD4 T cells derived from middle-aged thymectomized mice were longer-lived *in vivo* and their development of functional defects was accelerated. These findings suggested a connection between the accumulation of AICD-resistant T cells from aged mice and the molecular mechanisms associated with the generation of these cells. Because the expression of T-cell AICD inducers, Fas ligand and Bim, are directly down-stream of the FOXO transcription regulator, loss of the FOXO effects may be one mechanism leading to a decline in T-cell AICD in older individuals (Fig. 3).

2.2. The PI-3K/AKT/FOXO signaling during DNA damage-induced apoptosis—

The PI-3K/AKT/FOXO signaling axis is involved in control of cell-cycle entry and exit [47]. These events are not only critical during T-cell activation/AICD, but are also an important mechanism for inducing cell cycle arrest and apoptosis during growth factor withdrawal and oxidative stress. A relatively low concentration of reactive oxygen species (ROS) such as H₂O₂ and O₂⁻ induces cell proliferation by ERK and PI-3K/AKT pathways largely through stimulation of receptor-ligand interactions [48]. In contrast, a large amount of ROS induces deleterious damage and apoptosis in cells by a specific signaling pathway that includes activation of the mitogen-activated protein kinase (MAPK) pathway that ultimately activates the FOXO signaling triggering apoptosis pathway [49]. Thus, the redox status of cells provides a signal for either survival and proliferation or damage and apoptosis. Deficiency of FOXO3 has been shown to be associated with increased induction of the cell-cycle-arrest protein *p21^{CIP1/WAF1/Sdi1}* and lower expression of several ROS-scavenging enzymes in FOXO3-deficient cells after oxidative stress [50].

The DNA damage-associated cellular senescence also can be connected to the cellular metabolic pathway via a p53-dependent mechanism (Figure 4). ROS, UV light or other genotoxic stresses, that induce DNA damage, principally, double-stranded breaks (DSBs), is detected by the MRE11-RAD50-NBS1 complex, which in turn activates ATM [51]. A key substrate of ATM is p53. ATM phosphorylates p53 leading to its stabilization and activation [52]. P53 has several functions that can regulate T-cell senescence. First, p53 can promote apoptosis of damaged naïve and pre-senescent T cells, creating immunologic space for development of functional T cells [53]. Secondly, p53 can decrease IGF signaling by down-regulation of IGF-1R as well as upregulation of IGFBP-3 [54]. This function would serve to limit further genotoxic stress by lowering the metabolic rate of the cell. Third, it can promote cell cycle arrest and repair of DNA damage [55]. However, prolonged cell cycle arrest is a feature of senescent T cells, and over-activity of this function of p53 may be deleterious to successful immune aging [56]. Lower rate of metabolism is postulated to be associated with

decreased ROS and may be decreased DSBs. Low metabolism also is associated with lower induction of AKT, which physically associates with MDM2 and phosphorylates it at the Ser166 and Ser186 residues to block the effect of ATM phosphorylation of p53 [57]. However, it is likely that for optimum longevity, even at low metabolic rates, the preferential activity of p53 during genotoxic stress is to induce apoptosis and to decrease metabolism of injured cells rather than to induction of cell cycle arrest for the purpose of promoting DNA repair, since this latter function might eventually lead to T-cell senescence [58].

Conclusions

The regulation of the IGF/CD28 signaling pathway, which functions primarily in regulating growth and metabolism of the overall organism, plays a similar role in regulating naïve T cells and T cell senescence. Leptin and gut microbiota that can regulate metabolic syndrome can also affect thymopoiesis and maintenance of peripheral T cells. Life-long high stimulation of T cells may become an important mechanism for acceleration of T-cell senescence. The challenge will be to determine whether leptin, IGFBP3, and rapamycin directly regulate the CD28 signaling pathway in the periphery or indirectly regulate this pathway through the enhancement of thymic output or the proper regulation of apoptosis to help preserve naïve T cells during aging.

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Abbreviations

FOXO	Forkhead box O transcription factor
GH	Growth hormone
IGF-1	Insulin-like growth factor 1
IGFBP	Insulin-like growth factor binding protein
mTOR	Mammalian target of rapamycin
TRECs	T cell receptor recombination excision circles
PDK1	Phosphoinositide dependent kinase
PI-3K	Phosphatidylinositol 3-kinase
PIP3	Phosphatidylinositol 3,4,5-triphosphate
ROS	Reactive oxygen species
Th17	IL-17 producing CD4 T-helper cells
TLR	Toll-like receptor

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Dorshkind K, Montecino-Rodriguez E, Signer RA. The ageing immune system: is it ever too old to become young again? *Nat Rev Immunol* 2009;9:57–62. [PubMed: 19104499]
2. Hsu HC, Zhang HG, Li L, Yi N, Yang PA, Wu Q, Zhou J, Sun S, Xu X, Yang X, et al. Age-related thymic involution in C57BL/6J x DBA/2J recombinant-inbred mice maps to mouse chromosomes 9 and 10. *Genes Immun* 2003;4:402–410. [PubMed: 12944977]
- **3. Gruver AL, Ventevogel MS, Sempowski GD. Leptin receptor is expressed in thymus medulla and leptin protects against thymic remodeling during endotoxemia-induced thymus involution. *J Endocrinol* 2009;203:75–85. Leptin-deficient *ob/ob* mice, and leptin-receptor *db/db* mice have been observed to exhibit increased thymic atrophy and suppressed immune response for 1–3 decades. After the identification of leptin and leptin receptor as being defective in *ob/ob* and *db/db* mice, Gruver and Sempowski investigated defects in leptin and leptin receptor during thymic involution. Using the LPS-induced thymic atrophy model for age-related stress, leptin was shown to protect endotoxemia-induced thymic involution in both thymic stroma and lymphoid compartments. This present paper reports that leptin receptor expression is restricted to medullary epithelial cells and describes novel intra-thymic effects of leptin on thymic epithelial cells (TEC subset and thymopoiesis). The results suggest that intrathymic leptin signaling regulate thymic epithelium and T-cell development during an acute stress-induced thymic involution. [PubMed: 19587263]
- **4. Dixit VD, Yang H, Sun Y, Weeraratna AT, Youm YH, Smith RG, Taub DD. Ghrelin promotes thymopoiesis during aging. *J Clin Invest* 2007;117:2778–2790. Ghrelin, produced primarily by cells in the stomach acts on ghrelin receptor expressed in the pituitary, CNS and also on immune cells. Ghrelin can have proinflammatory cytokines. This paper provides evidence that signaling through the ghrelin receptor can promote generation of naïve T cells and inhibit age-associated thymic involution. [PubMed: 17823656]
- **5. Hsu HC, Scott DK, Zhang P, Zhou J, Yang P, Wu Q, Schroeder HW Jr, Gerald LB, Ravussin E, Jazwinski SM, et al. CD8 T-cell immune phenotype of successful aging. *Mech Ageing Dev* 2006;127:231–239. This study shows that the percent of CD28⁺CD95[−] CD8⁺ naïve peripheral blood T cells exhibit the best correlation to the chronologic age of an individual. There is an increase in both activation and activation-induced cell death (AICD) in nonagenarians. The results suggest that increased AICD can result in enhanced rejuvenation capacity of T cells and limit the impact of aging on T cell senescence in nonagenarians. [PubMed: 16313945]
6. Hsu HC, Shi J, Yang P, Xu X, Dodd C, Matsuki Y, Zhang HG, Mountz JD. Activated CD8(+) T cells from aged mice exhibit decreased activation-induced cell death. *Mech Ageing Dev* 2001;122:1663–1684. [PubMed: 11557272]
7. Hsu HC, Zhou T, Shi J, Yang PA, Liu D, Zhang HG, Bluethmann H, Mountz JD. Aged mice exhibit in vivo defective peripheral clonal deletion of D(b)/HY reactive CD8(+) T cells. *Mech Ageing Dev* 2001;122:305–326. [PubMed: 11311318]
8. Weyand CM, Fujii H, Shao L, Goronzy JJ. Rejuvenating the immune system in rheumatoid arthritis. *Nat Rev Rheumatol* 2009;5:583–8. [PubMed: 19798035]
9. Pawelec G, Wagner W, Adibzadeh M, Engel A. T cell immunosenescence in vitro and in vivo. *Exp Gerontol* 1999;34:419–429. [PubMed: 10433396]
10. Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science* 1995;269:546–549. [PubMed: 7624778]
11. Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, Collins F. Effects of the obese gene product on body weight regulation in *ob/ob* mice. *Science* 1995;269:540–543. [PubMed: 7624776]
- **12. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;372:425–432. Leptin was first identified by positional cloning of the mouse obesity (*Ob*) gene. The human homologue gene was also identified. [PubMed: 7984236]
- **13. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richards GJ, Campfield LA, Clark FT, Deeds J, et al. Identification and expression cloning of a leptin receptor, OB-R. *Cell* 1995;83:1263–1271. The leptin receptor was identified by producing an alkaline-phosphatase fusion protein with leptin and was identified to be highly expressed in mouse choroid plexus. The cDNA expression library produced from the mouse choroid plexus was screened with the leptin-

AP fusion protein to identify the leptin receptor which was also found to be closely related to the signal transducer component of the IL-6 receptor, G-CSF receptor and the LIF receptor. Genetic mapping of the leptin receptor showed it mapped closely to the diabetic (*db*) locus on chromosome 4 of mouse. [PubMed: 8548812]

14. Unger RH. Minireview: weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. *Endocrinology* 2003;144:5159–5165. [PubMed: 12960011]
15. Gruver AL, Sempowski GD. Cytokines, leptin, and stress-induced thymic atrophy. *J Leukoc Biol* 2008;84:915–923. [PubMed: 18495786]
- **16. Chen J, Li J, Lim FC, Wu Q, Douek DC, Scott DK, Ravussin E, Hsu HC, Jazwinski SM, Mountz JD. Maintenance of naïve CD8 T cells in nonagenarians by leptin, IGFBP3 and T3. *Mech Ageing Dev* 131:29–37. The CD28⁺CD95[−] CD8 T cells were shown to have the highest level of T cell receptor recombination excision circle (TRECs) in individuals of all ages including nonagenarians. These naïve CD8 T cells were shown to be positively correlated with high levels of leptin and IGFBP3, whereas senescent T cells were correlated with GH levels. These results suggest these hormones play an important role in maintenance of naïve CD8 T cells by acting on peripheral T cells or by acting on the thymus. [PubMed: 19941883]
17. Holland AM, van den Brink MR. Rejuvenation of the aging T cell compartment. *Curr Opin Immunol* 2009;21:454–459. [PubMed: 19608394]
18. Bartke A. Minireview: role of the growth hormone/insulin-like growth factor system in mammalian aging. *Endocrinology* 2005;146:3718–3723. [PubMed: 15919742]
19. Bartke A. Impact of reduced insulin-like growth factor-1/insulin signaling on aging in mammals: novel findings. *Aging Cell* 2008;7:285–290. [PubMed: 18346217]
20. Jogie-Brahim S, Feldman D, Oh Y. Unraveling insulin-like growth factor binding protein-3 actions in human disease. *Endocr Rev* 2009;30:417–437. [PubMed: 19477944]
- **21. Arai Y, Takayama M, Gondo Y, Inagaki H, Yamamura K, Nakazawa S, Kojima T, Ebihara Y, Shimizu K, Masui Y, et al. Adipose endocrine function, insulin-like growth factor-1 axis, and exceptional survival beyond 100 years of age. *J Gerontol A Biol Sci Med Sci* 2008;63:1209–1218. Observational studies of 252 centenarians for adipose endocrine function and IGF-1 was carried out. Low levels of leptin and high TNF were associated with high mortality among centenarians. Low levels of IGF-1 and IGFBP3 were also associated with increased mortality and adipose risk score, indicating cumulative effects of adipokine dysregulation. This regulation was strongly associated with mortality. [PubMed: 19038836]
- **22. Fontana L, Partridge L, Longo VD. Extending Healthy Life Span From Yeast to Humans. *Science* 2010;328:321–328. This is a concise and outstanding review of mechanisms of calorie restriction. This review brings together information gathered from different species and different signaling pathways including the mammalian target of rapamycin (mTOR), FOXO, GH, and IGF-1. This review also discusses dietary restriction in humans. [PubMed: 20395504]
- **23. Kaeblerlein M, Powers RW 3rd, Steffen KK, Westman EA, Hu D, Dang N, Kerr EO, Kirkland KT, Fields S, Kennedy BK. Regulation of yeast replicative life span by TOR and Sch9 in response to nutrients. *Science* 2005;310:1193–1196. The mechanism of lifespan extension in yeast was investigated in 564 single-gene deletion strains leading to identification of the nutrient-responsive TOR and Sch9 pathways as defining a primary conduit through which excess nutrient intake limits longevity in yeast. [PubMed: 16293764]
24. Madsen MA, Hsieh CC, Boylston WH, Flurkey K, Harrison D, Papaconstantinou J. Altered oxidative stress response of the long-lived Snell dwarf mouse. *Biochem Biophys Res Commun* 2004;318:998–1005. [PubMed: 15147972]
25. Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, Carter CS, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature* 2009;460:392–395. [PubMed: 19587680]
- **26. Feuerer M. Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat Med* 2009;15:930–939. Foxp3⁺ Treg cells were found distributed in fat tissue between adipocytes. Fat tissue from obese individuals also contains macrophages which were in close proximity to the Foxp3⁺ T cells. A unique population of Treg cells was enriched in abdominal adipose tissue of normal but not obese mice. [PubMed: 19633656]

27. Lumeng CN, Maillard I, Saltiel AR. T-ing up inflammation in fat. *Nat Med* 2009;15:846–847. [PubMed: 19661987]
28. Sepe A, Tchkonian T, Thomou T, Zamboni M, Kirkland JL. Aging and Regional Differences in Fat Cell Progenitors - A Mini-Review. *Gerontology*.
- **29. Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;444:860–867. This is an outstanding review of mechanisms of inflammation related to metabolic syndromes. Innate immune responses in TLR signaling that are increased with obesity are reviewed. The various mechanisms of suppression of insulin receptor signaling through inflammatory responses including suppressor of cytokine signaling (SOCS) protein and other signaling pathways that connect insulin receptor signaling and TNF receptor signaling are nicely illustrated. [PubMed: 17167474]
30. Nijhuis J. Neutrophil activation in morbid obesity, chronic activation of acute inflammation. *Obesity* 2009;17:2014–2018. [PubMed: 19390527]
31. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology* 2007;132:2169–2180. [PubMed: 17498510]
32. Sutherland JP, McKinley B, Eckel RH. The metabolic syndrome and inflammation. *Metab Syndr Relat Disord* 2004;2:82–104. [PubMed: 18370640]
33. Stenholm S, Koster A, Alley DE, Visser M, Maggio M, Harris TB, Egan JM, Bandinelli S, Guralnik JM, Ferrucci L. Adipocytokines and the metabolic syndrome among older persons with and without obesity - the InCHIANTI Study. *Clin Endocrinol (Oxf)*. 2009
- **34. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A* 2004;101:15718–15723. Introduction of gut microbiota into adult germ-free mice was shown to produce a rapid increase in body fat content. Despite reduced chow consumption, the metabolic rate was shown to be higher in conventional mice compared to the germ-free counterparts. Therefore, a novel mechanism was identified in which microbiota directs the host to increase hepatic production of triglycerides and promote storage of triglycerides and adipocytes by suppression of intestinal expression of circulating LPL inhibitor through a mechanism of suppression of FIAF in gut epithelium. There was also increased processing of dietary polysaccharides resulting in increased hepatic lipogenesis. This paper was the first to suggest that different microbiota can function as an “environmental” factor that affects predisposition toward energy storage and obesity. [PubMed: 15505215]
35. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature* 2006;444:1022–1023. [PubMed: 17183309]
36. Iyer A, Fairlie DP, Prins JB, Hammock BD, Brown L. Inflammatory lipid mediators in adipocyte function and obesity. *Nat Rev Endocrinol* 6:71–82. [PubMed: 20098448]
37. Ivanov II, Frutos Rde L, Manel N, Yoshinaga K, Rifkin DB, Sartor RB, Finlay BB, Littman DR. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. *Cell Host Microbe* 2008;4:337–349. [PubMed: 18854238]
38. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* 328:228–231. [PubMed: 20203013]
39. Cani PD. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008;57:1470–1481. [PubMed: 18305141]
40. Lawler DF, Larson BT, Ballam JM, Smith GK, Biery DN, Evans RH, Greeley EH, Segre M, Stowe HD, Kealy RD. Diet restriction and ageing in the dog: major observations over two decades. *Br J Nutr* 2008;99:793–805. [PubMed: 18062831]
- **41. Frauwirth KA, Riley JL, Harris MH, Parry RV, Rathmell JC, Plas DR, Elstrom RL, June CH, Thompson CB. The CD28 signaling pathway regulates glucose metabolism. *Immunity* 2002;16:769–777. CD28 signaling and T cells were shown to exhibit actions similar to insulin receptor to upregulate glucose utilization and control T cell activation and metabolism. CD28 co-stimulation enhances expression of glucose transporters, glucose uptake and glycolysis, which is dependent on PI-3K activation. [PubMed: 12121659]
- **42. Vallejo AN, Nestel AR, Schirmer M, Weyand CM, 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* 1998;273:8119–8129. This manuscript analyzed the CD28 promoter to define

potential mechanisms for down regulation of CD28 with T cell senescence. There was down regulation of CD28 promoter binding activity in senescent cells possibly related to decreased activity of several transcription factors including STAT4. [PubMed: 9525915]

- **43. Zhou T, Edwards CK 3rd, Mountz JD. Prevention of age-related T cell apoptosis defect in CD2-fas-transgenic mice. *J Exp Med* 1995;182:129–137. A CD2-fas transgene was constitutively expressed in T cells throughout the lifespan of mice. This resulted in decreased thymic involution and maintenance of naïve T cells. This is the first study that proposes that the mechanism for inhibition of T cell senescence is associated with increased Fas apoptosis and removal of cells at the pre-senescent stage of development. [PubMed: 7540646]
- **44. Jiang J, Anaraki F, Blank KJ, Murasko DM. Cuttine edge: T cells from aged mice are resistant to depletion early during virus infection. *J Immunol* 2003;171:3353–3357. There was transient depletion of T cells following infection of young mice with the E55 murine leukemia virus. On days 1–3 after infection, 50% of CD8 T cells and 25% – 50% of CD4 T cells were depleted. However, there was no depletion of either CD4 or CD8 T cells in aged mice. This depletion was shown to be due to increased apoptosis rather than altered traffic and migration. The depletion was dependent on environment since noted depletion of donor CD8 T cells from young or aged mice were observed in aged recipients. The depletion was proposed to be due to innate responses including interferon- α . The results suggest that for an optimal immune response, initial depletion of resident T cells provide space for a subsequent response to an infectious agent, and both the age of the T cell and the innate immune environment are important regulators. [PubMed: 14500628]
- **45. Kapasi ZF, Murali-Krishna K, McRae ML, Ahmed R. Defective generation but normal maintenance of memory T cells in old mice. *Eur J Immunol* 2002;32:1567–1573. Young and aged (23/24 mo) mice were infected with LCMV. There is decreased generation of T cells in aged mice compared to young mice. However, once generated memory CD8 T cells were maintained at stable levels in both young and aged mice for more than 5 months. These results suggest that viral specific cytotoxic CD8 T-cell responses, once generated, are not subject to increased deletion or apoptosis in aged mice compared to young mice. [PubMed: 12115639]
46. Tsukamoto H, Clise-Dwyer K, Huston GE, Duso DK, Buck AL, Johnson LL, Haynes L, Swain SL. Age-associated increase in lifespan of naïve CD4 T cells contributes to T-cell homeostasis but facilitates development of functional defects. *Proc Natl Acad Sci U S A* 2009;106:18333–18338. [PubMed: 19815516]
47. Chang F, Lee JT, Navolanic PM, Steelman LS, Shelton JG, Blalock WL, Franklin RA, McCubrey JA. Involvement of PI3K/Akt pathway in cell cycle progression, apoptosis, and neoplastic transformation: a target for cancer chemotherapy. *Leukemia* 2003;17:590–603. [PubMed: 12646949]
48. Torres M. Mitogen-activated protein kinase pathways in redox signaling. *Front Biosci* 2003;8:d369–391. [PubMed: 12456373]
49. Luo X, Puig O, Hyun J, Bohmann D, Jasper H. Foxo and Fos regulate the decision between cell death and survival in response to UV irradiation. *EMBO J* 2007;26:380–390. [PubMed: 17183370]
50. Marinkovic D, Zhang X, Yalcin S, Luciano JP, Brugnara C, Huber T, Ghaffari S. Foxo3 is required for the regulation of oxidative stress in erythropoiesis. *J Clin Invest* 2007;117:2133–2144. [PubMed: 17671650]
51. Williams RS, Moncalian G, Williams JS, Yamada Y, Limbo O, Shin DS, Grocock LM, Cahill D, Hitomi C, Guenther G, Moiani D, Carney JP, Russell P, Tainer JA. Mre11 dimers coordinate DNA end bridging and nuclease processing in double-strand-break repair. *Cell* 2008;135:97–109. [PubMed: 18854158]
52. Chehab NH, Malikzay A, Stavridi ES, Halazonetis TD. Phosphorylation of Ser-20 mediates stabilization of human p53 in response to DNA damage. *Proc Natl Acad Sci U S A* 1999;96:13777–82. [PubMed: 10570149]
53. Ohkusu-Tsukada K, Tsukada T, Isobe K. Accelerated development and aging of the immune system in p53-deficient mice. *J Immunol* 1999;163:1966–72. [PubMed: 10438933]
54. Grimberg A. P53 and IGFBP-3: apoptosis and cancer protection. *Mol Genet Metab* 2000;70:85–98. [PubMed: 10873390]
55. Beneke R, Möröy T. Inhibition of poly(ADP-ribose) polymerase activity accelerates T-cell lymphomagenesis in p53 deficient mice. *Oncogene* 2001;20:8136–41. [PubMed: 11781827]

56. Tyner SD, Venkatachalam S, Choi J, Jones S, Ghebranious N, Igelmann H, Lu X, Soron G, Cooper B, Brayton C, Park SH, Thompson T, Karsenty G, Bradley A, Donehower LA. p53 mutant mice that display early ageing-associated phenotypes. *Nature* 2002;415:45–53. [PubMed: 11780111]
57. Zhou BP, Liao Y, Xia W, Zou Y, Spohn B, Hung MC. HER-2/neu induces p53 ubiquitination via Akt-mediated MDM2 phosphorylation. *Nat Cell Biol* 2001;3:973–82. [PubMed: 11715018]
58. Van Nguyen T, Puebla-Orsorio N, Pang H, Dujka ME, Zhu C. DNA damage-induced cellular senescence is sufficient to suppress tumorigenesis: a mouse model. *J Exp Med* 2007;204:1453–61. [PubMed: 17535972]

Figure 1.

Leptin, IGFBP3, and rapamycin suppress the IGF-1 signaling pathway to preserve naïve T cells and promote longevity. IGF-1 signaling through the IRS proteins, which bind to the p110 subunit of phosphatidylinositol 3-kinase (PI-3K), leads to the generation of phosphatidylinositol 3,4,5-triphosphate (PIP3) and phosphorylation of AKT by phosphoinositide dependent kinase (PDK1). Phosphorylation of AKT leads to subsequent activation of mTOR and phosphorylates or inactivates a family of apoptosis-inducing forkhead transcription factors, including forkhead box O1 (FOXO1 or FKHR), forkhead box O3 (FOXO3, or FKHRL1), and forkhead box O4 (MLLT-7, FOXO4 or AFX). Life-long enhanced IGF-1 signaling pathway is associated with shortening of lifespan. In contrast, inhibition of mTOR by dietary restriction or rapamycin has been shown to be associated with longevity in mammals. It has recently been shown that increased levels of factors such as leptin and IGFBP3 that can inhibit the IGF-1 signaling pathway, are also associated with preservation of naïve CD8 T cells in human nonagenarians.

Figure 2.

Potential mechanisms of metabolic syndrome/obesity leading to T-cell senescence. This figure illustrates how obesity, inflammatory factors, and thymic involution might work synergistically to promote T-cell senescence. Excessive amount of visceral fat not only prohibits thymic output but also triggers chronic inflammatory responses that can further promote T-cell senescence. Leptin exhibits a unique effect to suppress obesity and has been shown to be effective in enhancing naïve T cells in the periphery.

Figure 3.

The CD28 signaling pathway in T cells is equivalent to the IGF-1 pathway in the whole organism. Stimulation of the CD28/PI-3K/AKT pathway and thereby inhibition of the FOXO signaling axis is a unique mechanism developed to separate T cells from the major glucose metabolic system. This would confer a great evolutionary advantage on the organism, because the signal that triggers T-cell co-stimulation by CD28 also triggers the energy utilization of T cells. However, life-long over-utilization of this pathway is associated with acceleration of T-cell senescence, including loss of CD28 expression and development of AICD-resistant T cells.

Figure 4.

Reactive oxygen species, UV light or other genotoxic stresses, that induce DNA damage, principally, double-stranded breaks, is detected by the MRE11-RAD50-NBS1 complex, which in turn activates ATM. A key substrate of ATM is p53. ATM phosphorylates p53 leading to its stabilization and activation. ATM also phosphorylates the E3 ubiquitin ligase MDM2 at the Ser³⁹⁵ residue, which inhibits ubiquitination and degradation of p53. One key function of p53 is to inhibit cell cycle and promote apoptosis. A second key function is p53 can inhibit expression of an IGF-1 receptor (IGF-1R), while at the same time increasing expression of IGFBP-3, which decreases IGF-1 signaling. A third key function is to induce cell cycle arrest to enable DNA repair. AKT can also phosphorylate MDM2 at the Ser¹⁶⁶ and Ser¹⁸⁶ residue which blocks the effect of ATM phosphorylation of p53, resulting in inhibition of apoptosis. Thus, appropriate regulation of DNA damage can lead to inhibition of the growth hormone signaling pathway and this leads to lower oxidative stress. Thus, limitation of DNA damage by low ROS and control of DNA repair by several mechanisms can promote healthy immune aging.