REVIEW ARTICLE

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Growth hormone, inflammation and aging

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Mutant animals characterized by extended longevity provide valuable tools to study the mechanisms of aging. Growth hormone and insulin-like growth factor-1 (IGF-1) constitute one of the well-established pathways involved in the regulation of aging and lifespan. Ames and Snell dwarf mice characterized by GH deficiency as well as growth hormone receptor/growth hormone binding protein knockout (GHRKO) mice characterized by GH resistance live significantly longer than genetically normal animals. During normal aging of rodents and humans there is increased insulin resistance, disruption of metabolic activities and decline of the function of the immune system. All of these age related processes promote inflammatory activity, causing long term tissue damage and systemic chronic inflammation. However, studies of long living mutants and calorie restricted animals show decreased pro-inflammatory activity with increased levels of anti-inflammatory adipokines such as adiponectin. At the same time, these animals have improved insulin signaling and carbohydrate homeostasis that relate to alterations in the secretory profile of adipose tissue including increased production and release of anti-inflammatory adipokines. This suggests that reduced inflammation promoting healthy metabolism may represent one of the major mechanisms of extended longevity in long-lived mutant mice and likely also in the human.

Keywords: *Ghowth hormone*; *obesity*; *inflammation*; *calorie restriction*; *aging*

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Interactions between the somatotropic axis, immune function and aging are complex and not completely understood. Circulating levels of pituitary growth hormone (GH) and insulin-like growth factor-1 (IGF-1), a key mediator of many of the GH actions, decline with age starting soon after attainment of sexual and physical maturation (1, 2). Declining function of the somatotropic axis (GH, IGF-1 and hypothalamic factors which control GH release) has been linked to age-related changes in body composition, various alterations and deficits in physiological functions and, in humans, to an increased risk of cardiovascular disease. Thus, reduced GH levels emerge as a biomarker of aging as well as a suspected causal factor in various symptoms and functional deficits associated with the aging process. In sharp contrast to these findings, mutant mice lacking GH or GH receptors age slowly and outlive their normal siblings by as much as 40–60% (3–6). Moreover, these long-lived GH-deficient and GH-resistant animals exhibit a delayed onset and reduced incidence of cancer, the leading cause of death in laboratory mice (7, 8). In the human, a genetic GH-deficiency resulting from a mutation of the GH releasing hormone (GHRH) receptor gene diminishes atherosclerosis (9) while GH resistance (the Laron syndrome) provides striking protection from diabetes and cancer (10). While the longevity of individuals with these and other dwarfing syndromes is not extended, there is evidence linking exceptional human survival to genetic polymorphisms that reduce somatotropic signaling (11, 12). Moreover, a pathological excess of GH reduces life expectancy in both humans and mice (13). Collectively, these findings imply that GH can accelerate aging and that its physiological actions on growth, development and body composition may be linked to significant 'costs' in terms of longevity and susceptibility to age-related disease.

As discussed in some detail below, aging is associated with numerous symptoms of reduced immune competence and there is considerable interest in elucidating the relationships between inflammatory processes and aging. Chronic low grade inflammation stemming from age-related changes in the distribution and function of

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adipose tissue as well as 'inflammatory load' related to the life-time history of infectious diseases are suspected of being major determinants of human aging and lifespan (14, 15).

In contrast to well-documented links between GH and aging and between aging and inflammation, the impact of GH on immune function and inflammatory processes is relatively unexplored. Moreover, the available evidence is controversial with reported examples of both anti- and pro-inflammatory effects of GH. Growth hormone therapy can reduce the levels of C-reactive protein (CRP), an important marker of inflammation in GH-deficient patients (16), and exert anti-inflammatory effects in different models of experimentally induced sepsis by reducing the levels of TNFα and promoting secretion of IL-10 (17, 18). Perhaps exogenous GH can overcome the effects of sepsis-induced IGF-1 resistance (19). In contrast to these observations, a massive increase in GH levels in GH transgenic mice is associated with increased levels of pro-inflammatory cytokines and enhanced markers of renal inflammation (20, 21).

Aging and inflammation

Aging correlates with increased risk of cancer, diabetes, atherosclerosis, cataracts, metabolic syndrome, sarcopenia and osteoporosis. Another important change associated with aging is decline in immune system function and many aspects of aging involve inflammatory processes (22). There is strong association of aging with chronic low grade inflammatory activity which may progress to long term tissue damage and systemic chronic inflammation (23). This systemic inflammation may cause organ specific illness with increased risk of mortality. With growing elderly populations and extended longevity in developed countries there is increasing interest in elucidating the age-related inflammation processes. Additionally, increasing incidence of obesity in developed countries can intensify this problem, because of known pro-inflammatory action of excess of adipose tissue. On the other hand calorie restriction that is known to extend longevity was repeatedly shown to enhance the immune function and ameliorate inflammation (24–27).

Obesity and inflammation

Accumulation of adipose tissue in obese humans and animals involves adipocyte hypertrophy as well as hyperplasia which promote inflammation by changing the secretory profile of the adipose tissue. This involves stimulation of the production and secretion of pro-inflammatory adipokines including TNF-α and IL-6 (28, 29). TNF-α exerts its effects on metabolism through serine-phosphorylation of IRS-1 which inhibits its interaction with the β-subunit of the insulin receptor and blocks insulin signaling pathway. IL-6 induces the production of hepatic CRP (28). Obesity also suppresses production and causes a decrease in the secretion of adiponectin (30–33), the adipokine known to have anti-inflammatory effects by inhibiting the expression of endothelial adhesion molecules and vascular smooth muscle cells proliferation, suppressing the transformation of macrophages to foam cells and inducing production of anti-inflammatory factors like IL-10 (28, 34). Adiponectin is also known to suppress the secretion of TNF-α (28). During infection with Listeria monocytogen, adiponectin plays important role in upregulating CCL2 in adipocytes, which is necessary for macrophage recruitment in response to bacterial infection (35).

Adipose tissue in obese subjects is infiltrated by a large number of macrophages. The activated macrophages in these fat depots serve as a source of several chemokines that result in the recruitment of even more macrophages leading to the low-grade inflammatory state associated with obesity (28, 29). It has been shown that proliferating preadipocytes behave like macrophages exhibiting phagocytic and microbicide activities (36). Moreover, obesity is associated with an influx of bone-marrow derived monocytes into adipose tissue followed by their differentiation into mature macrophages. Adipocytes produce MCP-1 – a monocyte/macrophage-specific chemoattractant – as well as CSF-1 – the regulator of macrophage differentiation. In obese subjects there is increased release of MCP-1 leading to more monocyte influx which would then differentiate into mature macrophages in the presence of CSF-1 produced by the adipocytes (37). Overall we could conclude that obesity strongly promotes inflammation and there is strong evidence that inflammation promotes the development of type 2 diabetes (38).

Calorie restriction and inflammation

In contrast to obesity and overfeeding, calorie restriction (CR) produces various physiological benefits. It is well established that CR extends longevity in rodents, improves insulin sensitivity and decreases amount of adipose tissue. The function of immune system is also affected by this dietary intervention by retarding immunosenesence by altering cytokines gene expression (26). The levels of TNFα and IL-6 became elevated as the humans or animals age, which can cause autoreactivity and immune dysfunction. However, subjecting mice to CR reduces the levels of these pro-inflammatory cytokines in old animals to the levels characteristic of young mice (39). Calorie restriction also normalizes processes of apoptosis in aged mice (40) which can be important to improve the function of immune system by eliminating non-functional T-cells (40).

Increased longevity and inflammation

The last 200 years of industrial development along with the progress in medicine and in various public health

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measures had significant effect on human life expectancy by doubling the average longevity from 35–40 to 75–80 (41). There is evidence that this great increase of the lifespan during industrial development is largely due to decreased exposure to chronic inflammation throughout life (14, 42). There is strong evidence that exposure of an individual to past infections and the levels of chronic inflammation increase the risk of heart attack, stroke and even cancer. These diseases are known to correlate with CRP levels in serum (43, 44).

Centenarians represent exceptional longevity in human populations and it is already known that many of these individuals are escaping from major common diseases such as cancer, diabetes etc. There is ongoing interest in investigating the mechanisms that allow these individuals to reach this exceptional longevity. There are several animal mutants used to study longevity with hope to determine the mechanism of extended lifespan and more importantly protection from age related diseases. In our laboratory we use animals with disruption of growth hormone (GH) signaling which greatly extend longevity.

Pituitary hormone deficiency

Ames dwarf mice are homozygous for a recessive loss of function mutation at the Prop1 locus ($Prop1^{df/df}$). This mutation causes deficiency in GH, prolactin (PRL) and thyroid-stimulating hormone (TSH). *Snell dwarf* mice are characterized by homozygous loss-of –function mutation at the Pit1 locus and similarly to Ames dwarfs are GH, PRL and TSH deficient and long living. These hormonal deficiencies suppress circulating levels of insulin like growth factor 1 (IGF-1), thyroid hormones, insulin and glucose. Ames dwarf mice have increased insulin sensitivity and glucose tolerance. Beside healthy insulin signaling these mice are long living and are partially protected from cancer. This could suggest that these animals have also well preserved immune system and are protected from inflammation. However, some of the findings regarding immune system and inflammation available in literature present contradictory results in mice lacking GH. Some studies suggested that due to the lack of GH dwarfism compromises the immune system development (45–49). However, other studies reported that immune competence of dwarf mice did not differ from their normal controls (50, 51). Some of these studies indicated decreased peripheral white blood cells and deficiency of B cell progenitor populations in bone marrow (45), decreased splenic T and B lymphocytes (46) as well as decreased number of thymocytes (47). Functional studies have shown that both cell-mediated immunity and humoral immunity were compromised and could be restored by administration of GH (48, 49). However, Schneider and his colleagues showed that T cell dependent zones in peripheral lymphoid tissues were not deficient in lymphocytes with normal thymus composition (51). Microarray analysis of 34,000 genes in peripheral blood leucocytes from Ames dwarf mice indicated direct interactions between 91 probe sets based on Pathway Architect data base and identified 6 main genes which had altered expression in dwarf as compared to normal mice: casp3, bcl2, IL4, mapk14, TGFβ1 and pcrk. These alterations indicated functional changes in apoptosis, B and T cells homeostasis, prostaglandin synthesis, humoral immunity, chemokine activity complement activation, hemostasis and wound healing (52). Overall these results suggested activation of anti-inflammation pathways in long –living Ames dwarf mice. Studies performed by Flurkey and his colleagues showed that Snell dwarf mice have delayed immune and collagen aging (4). The authors showed that the mutation delays tail tendon collagen cross-linking detected by lower resistance of tendons to breaking in a denaturing urea solution when compared to age matched normal littermate controls (4). Additionally the levels of CD4 and CD8 cells expressing CD44 markers in adult Snell dwarf mice were preserved at the lower levels as expected in young animals, while adult normal controls had increased levels of these cells types (4). However, another study reported suppressed development of bone marrow B cells in Snell dwarf mice (53). In this study Snell dwarf mice were treated with either GH, IGF-1 or thyroxine and only thyroxine intervention restored bone marrow cellularity to the level in normal controls (53). This could indicate that in Snell dwarf mice the deficiency of thyroid hormones rather than GH or IGF-1 can negatively affect function of immune system. Deficiency of PRL could also play a role in the development and function of the immune system in these animals. Prolactin-secreting ectopic transplants of normal pituitaries were shown to enhance the number of lymphocytes and their natural killer activity in Ames dwarf mice (54).

However, there is now more emphasis on the role of adipose tissue in inflammation processes in relation to aging and obesity. It was repeatedly reported that Ames dwarf mice have increased levels of adiponectin that can act as anti-inflammatory factor (55–57). Elevated adiponectin levels in these long-living animals correlate with findings observed in studies of centenarians showing that these exceptionally long-living people also have elevated adiponectin. In studies with mice it was shown that replacing GH can suppress circulating adiponectin levels (55). At the same time the levels of pro-inflammatory TNFα and IL-6 are decreased in adipose tissue of Ames dwarf mice (57) which additionally supports lower inflammation in these long-living animals.

Growth hormone resistance

Growth hormone receptor knockout mice (GHRKO) known also as Laron dwarf mice are characterized by lack of GH receptor (GHR) which causes GH resistance

and dramatic suppression of circulating IGF-1 levels. These animals similarly to Ames and Snell dwarf mice have increased insulin sensitivity, glucose tolerance and low levels of insulin and glucose (58–60). In contrast to Ames and Snell dwarf mice these knockouts have normal or elevated levels of PRL and thyroid hormones together with elevated levels of GH which is however not active due to lack of its receptor. Disruption of GH action promotes increased longevity in these animals. Interestingly these long-living and insulin sensitive animals are obese in comparison to their normal siblings (61) and unexpectedly in addition to the massive increase in subcutaneous fat content GHRKO mice also have increased intra-abdominal obesity (62). Despite this these animals have very healthy insulin signaling. Interestingly, these animals do not derive any benefits from CR in terms of either longevity or insulin sensitivity (58, 59, 63). Our recent study showed that surgical removal of both epididymal and perirenal fat from GHRKO male mice did not improve but rather deteriorated insulin signaling (62). Similarly to Ames dwarf mice, GHRKO animals have higher level of circulating adiponectin (60, 62). While adiponectin is believed to be mainly produced and released by subcutaneous adipose tissue, the removal of intra-abdominal adipose tissue in GHRKO animals caused decrease of adiponectin in circulation in these long-living mice with no changes in normal controls (62). This finding suggested that in contrast to intra-abdominal fat in normal mice the same fat from GHRKO animals is one of the suppliers of circulating adiponectin. The analysis of adiponectin level in different fat pads confirmed the fact that adiponectin level is higher in the epididymal fat from GHRKO mice than in either epididymal or subcutaneous fat from normal littermates (62). More importantly, the levels of pro-inflammatory IL-6 are decreased in both epididymal and perinephric adipose tissue from GHRKO mice in comparison to normal littermates (62). There was similar tendency in the content of TNFα in both fat pads. This balance of pro- and anti-inflammatory adipokines clearly shows that the long-lived GHRKO animals have reduced inflammation.

Importantly, the experiments with fat removal indicated that removing the intra-abdominal fat from normal mice improved insulin sensitivity and glucose tolerance while the same procedure reduced insulin sensitivity and glucose tolerance in GHRKO mice (62). This indicates that secretory activity of adipose tissues can have positive or negative effects on regulation of whole body insulin sensitivity and glucose metabolism. Moreover, these findings indicate that the metabolic balance correlates with alterations in the levels of pro- and anti-inflammatory adipokines. It remains to be clarified whether increased inflammation disturbs metabolic activities and causes insulin resistance, or rather increased insulin resistance and imbalanced metabolic activities promote chronic inflammation.

Summary

Studies in long-lived mutant mice with GH deficiency or resistance begin to clarify complex relationships between inflammation, GH and aging. Although GH was reported to suppress as well as promote inflammation in different settings, congenital absence of GH signals is associated with reduced levels of proinflammatory cytokines and increased levels of adiponectin, an antiinflammatory adipokine. Adiponectin levels are positively associated with longevity in GH-related mutant mice, in transgenic mice overexpressing adiponectin, in calorically restricted animals and also in exceptionally long-lived people and their offspring. In contrast to normal (wild type) animals, in GH resistant GHRKO mutants intra-abdominal adipose tissue emerges as an important source of adiponectin. We suggest that the shift of the secretory profile of adipose tissue from pro- to anti-inflammatory importantly contributes to improved insulin sensitivity, delayed onset and reduced occurrence of neoplasms, reduced rate of aging and extended longevity in mice lacking GH signals. These changes decrease also the exposure to constant chronic inflammation that can have important function in life extension in either Ames, Snell or GHRKO dwarf mice.

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