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The metabolic syndrome, IGF-1, and insulin action

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ABSTRACT

Recent studies have shown that insulin and insulin-like growth factor (IGF)-1 signaling are involved in the control of ageing and longevity in model organisms. Based on these studies, genes involved in the insulin/IGF-1 signaling pathway are believed to play a role in longevity throughout evolution and could also be important in determining human longevity. However, human studies have yielded conflicting and controversial results. In human, defects in insulin receptor signaling cause insulin resistance and diabetes, and IGF-1 deficiency is associated with an increased risk of cardiovascular disease and atherosclerosis. Interestingly, insulin sensitivity normally decreases during aging; however, centenarians were reported to maintain greatly increased insulin sensitivity and had a lower prevalence of the metabolic syndrome as compared to younger subjects. Additionally, a longitudinal study revealed that insulin-sensitizing hormones, including leptin and adiponectin, were significantly associated with the survival of centenarians, indicating that an efficient insulin response may influence human longevity.

1. Introduction

Recent studies on model organisms have shown a significant association between mutations in the genes involved in the insulin/insulin-like growth factor-1 (IGF-1) signaling pathway and extension of life span. The first examples of such genes were found in *Caenorhabditis elegans* (Kenyon et al., 1993) and include *daf-2*, an ortholog of the insulin/IGF-1 receptor gene family, and *daf-16*, an ortholog of the forkhead transcription factors, which regulate insulin/IGF-1-induced gene transcription.

Another example is age-1, which is the *C. elegans* ortholog of the gene encoding the catalytic subunit of phosphoinositide-3-kinase (PI3K)—a protein involved in insulin/IGF-1 signal transduction (Morris et al., 1996). A long-lived mutant of the insulin-like receptor gene (InR) was also reported in *Drosophila melanogaster* (Tatar et al., 2001). At almost the same time, the ablation of the *D. melanogaster* gene, namely *chico*, which encodes an insulin receptor substrate, was reported to extend the life span of flies (Clancy et al., 2001). Regulation of the lifespan of mice by the insulin and IGF-1 receptors has also been reported (Bluher et al., 2003; Holzenberger et al., 2003). Based on these studies, the genes involved in the insulin/IGF-1 signaling pathway are believed to play a role in longevity throughout evolution and could be important for human longevity as well. However, the results from human studies have been conflicting and controversial. In humans, defects in insulin receptor signaling cause insulin resistance and diabetes, and the deficiency of GH and/or IGF-1 is associated with growth disorders and increased risk of cardiovascular disease (CVD) and atherosclerosis. On the other hand, polymorphic variations in the genes coding for the insulin-like growth factor-1 receptor (IGF-1R) and phosphoinositide-3-kinase (PI3K) (Bonafe et al., 2003) and a haplotype of the insulin receptor gene (INSR) (Kojima et al., 2004) have been reported to affect longevity, suggesting a possible implication of insulin/IGF-1 signaling in the aging process in humans. Interestingly, precise phenotyping of centenarians has revealed that preservation of insulin sensitivity, which is a key feature of long-lived mutant mice (Bonkowski et al., 2006; Liu et al., 2004), could be one of the physiological peculiarities relevant in exceptional longevity (Paolisso et al., 1996, 1997). In this review, we will focus on the intricate association between the insulin/IGF-1 pathways and aging and attempt to describe some equivalence between long-lived mutant animals and human longevity.

2. IGF-1 signaling and longevity in human

A great deal of our knowledge of the insulin/IGF-1 signaling pathway and lifespan extension originates from experimental models with monogenic mutations, which down-regulates this conserved pathway. In mammals, the association between the GH/IGF-1 system and longevity has been robustly demonstrated in Ames dwarf, Snell dwarf, and GH receptor knockout (GHRKO)

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mice, and several reviews comprehensively summarized this topic (Bartke, 2005; Longo and Finch, 2003, see also Brown-Borg's paper in this issue). These long-lived rodent models have lower levels of IGF-1 signals and reduced growth and body size. The precise mechanism by which reduced somatotropic signaling promotes longevity has not been entirely elucidated; however, decreased generation of reactive oxygen species (ROS) and increased stress resistance may be involved in the delay in aging in these models (Brown-Borg et al., 1999; Murakami et al., 2003; Salmon et al., 2005). The similarities in the GH/IGF-1 signaling pathways between mice and humans suggest a possible implication of this pathway in human longevity; however, the results from human studies have been somewhat conflicting. It was demonstrated that polymorphisms in the IGF-1R gene and the genotype combination of the IGF-1R and PI3K genes, which are associated with low-serum IGF-1 concentrations, were more common in centenarians (Bonafe et al., 2003, see also Bonafe's paper in this issue). Recently, we reported that an insulin receptor haplotype comprising two SNPs in linkage disequilibrium was more frequent in semisupercentenarians (individuals aged ≥105 years) as compared to healthy younger controls (Kojima et al., 2004). On the other hand, in human, loss-of-function mutations in the insulin receptor have been described to cause different degrees of insulin resistance and diabetes, and the deficiency of GH and/or IGF-1 is associated with growth disorders, increased risk of diseases including cardiovascular diseases and diabetes, and reduced life expectancy (Besson et al., 2003).

In human, IGF-1 levels begin to decline with age from the second decade. The mean circulating IGF-1 levels peak during puberty and decrease 2.5-fold by the third decade, while a further 2-fold decrease occurs between the third and eighth decades (Janssen and Lamberts, 2004). The age-associated decline in GH and IGF-1 secretion, known as somatopause, is associated with loss of exercise capacity and sarcopenia—one of the key components of frailty (Lamberts et al., 1997). Indeed, Cappola and colleagues reported that in a cohort of community dwelling women with at least 1 deficit in physical function, the subjects who had the lowest quartile of IGF-1 and the highest quartile of interleukin-6 (IL-6) were at a greater risk of death as well as incident walking limitation, mobility disability, and disability in the activities of daily living (ADL) (Cappola et al., 2003). In cross-sectional observations, the serum IGF-1 concentrations in centenarians were lower than (Arai et al., 2001) or equivalent to (Paolisso et al., 1997) those in younger subjects, and lower IGF-1 concentrations were associated with poor nutrition and cognitive decline in centenarians (Arai et al., 2001). Moreover, in a longitudinal follow-up of 252 centenarians, Arai and colleagues reported that those having the lowest tertile of IGF-1 were at a greater risk of mortality from all causes even after adjustment for age, sex, education, smoking, ADL, cognitive function, and comorbidities (Arai et al., in press). Very recently, Niedernhofer et al. proposed that in a progeroid syndrome caused by an *XPF* mutation, the suppression of the GH/IGF-1 axis is a stress response to unrepaired DNA damage, in which the energy expenditure shifts from growth to somatic maintenance (Niedernhofer et al., 2006). A similar metabolic change was observed in response to genotoxic stress, caloric restriction, or with normal aging. In this context, the higher mortality in frail older adults or centenarians having decreased somatotropic signaling may be a consequence of the accumulation of unrepaired intrinsic damage. Interestingly, even increased IGF-1 levels do not promote longevity because of a greater risk of developing certain cancers including those of the prostate, breast, lung, and colon (Juul, 2003). In humans, the life-long effect of the GH/IGF-1 system on longevity has not been elucidated; nevertheless, a speculation that attainment of the optimal set-point of this system benefits survival (Janssen and Lamberts, 2004) may be plausible.

As mentioned above, accumulating evidence suggests that a deficiency in the GH/IGF-1 axis during aging may not contribute to longevity in human unlike in rodent experimental models. However, it is still possible that low-IGF-1 signaling during development, but preserved IGF-1 activity during aging may be beneficial for longevity. Very recently, Suh and colleagues demonstrated clear evidence that supports this notion. They identified new nonsynonymous mutations in IGF-1R that results in reduced IGF-1 signaling as measured in transformed lymphocytes, and found the enrichment of these mutations in centenarians (Suh et al., 2008). In addition, low levels of plasma glucose and insulin, a hallmark of enhanced insulin sensitivity, was suggested to be one of the key features in both long-lived mutant mice (Dominici et al., 2002; Liu et al., 2004) and healthy centenarians (Paolisso et al., 1996; Paolisso et al., 1997). These findings indicate that at least some aspects of anti-aging mechanisms mediated by reduced somatotropic axis signaling may broadly apply to mammals, including human.

3. The metabolic syndrome, insulin resistance, and aging

3.1. The metabolic syndrome and diabetes in centenarians

The metabolic syndrome (MetS) is characterized by clustering of cardiovascular risk factors: abdominal obesity, hypertriglyceridemia, low-serum high-density lipoprotein (HDL) cholesterol, elevated blood pressure, glucose intolerance, and a prothrombotic and proinflammatory state (Eckel et al., 2005). Insulin resistance is the most consistent platform that explains the various clinical correlates of this syndrome (Reaven, 1988). In humans, insulin sensitivity normally decreases during aging, and the prevalence of MetS as well as insulin resistance substantially increases in older adults (Ford et al., 2002; Kobayashi et al., 2007). People with MetS are at a greater risk for various illnesses that affect the morbidity and mortality among the elderly, including cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Intriguingly, there is increasing evidence that preservation of insulin action might be one of the striking physiological characteristics that maintain health and promote longevity in humans. By a euglycemic glucose clamp method, Paolisso and colleagues first demonstrated that glucose tolerance and insulin sensitivity were better preserved in healthy centenarians as compared to elderly individuals aged >75 years (Paolisso et al., 1996). Moreover, cross-sectional studies have reproducibly demonstrated that the prevalence of T2DM, which is closely associated with age-related insulin resistance, was very low among centenarians. According to a nationwide survey of the prevalence of circulatory diseases in Japanese adults in 2000 (The Ministry of Health, Labor and Welfare), the prevalence of T2DM was 2.6%, 6.3%, 11.6%, 15.3%, and 14.7% in individuals in their 30s, 40s, 50s, 60s, and in those aged >70 years, respectively; however, in the Tokyo Centenarians Study, only 6.0% of centenarians had T2DM (Takayama et al., 2007). The Finnish Centenarians Study (Louhija, 1994) revealed a 10% prevalence of T2DM in Finnish centenarians, which was lower than the prevalence of T2DM in the 65–85-year-old Finnish individuals. Previously, the Italian Multicenter Study on Centenarians (Motta et al., 2005) reported that 4.9% of 602 centenarians had T2DM, and the New England Centenarian Study reported that 4% of 424 centenarians had T2DM (Evert et al., 2003), both of which were lower as compared to the respective aged, but younger populations. In addition, Barzilai and colleagues demonstrated that larger particle sizes of HDL and low-density lipoprotein (LDL) were associated with a lower prevalence of hypertension, cardiovascular disease, MetS, and eventually with longevity (Barzilai et al., 2003). They also found that the offspring of centenarians shared a similar lipoprotein profile with their probands and had a low risk of MetS, suggesting

the substantial genetic component of this phenotype. As mentioned above, accumulating evidence suggests the possibility of the existence of a protective phenotype against MetS that may be relevant in survival to an advanced age.

3.2. Adipose tissue metabolism and longevity

3.2.1. Body composition, adipokines, and aging

Besides insulin resistance, excess adiposity, i.e., visceral fat accumulation, is a fundamental to the etiology of MetS (Matsuzawa, 2006). It is well known that advancing age is associated with changes in body composition including loss of fat free mass and visceral fat accumulation, being frequently accompanied with blunted insulin action. In a cohort of 2336 older adults aged 70–79 years, visceral adipose tissue assessed by computed tomography was significantly associated with MetS (Goodpaster et al., 2005). Adipose tissue synthesizes a number of bioactive molecules termed as adipokines, which are involved in the regulation of insulin action and lipid metabolism. Experimental evidence suggests that (1) dysregulation of adipokines such as tumor-necrosis factor-α (TNF-α) and plasminogen activator inhibitor type 1 (PAI-1) may contribute to the development of insulin resistance and MetS and (2) a reduction in the adipose tissue mass either as a result of caloric restriction or surgical removal restores insulin sensitivity (Gabriely et al., 2002; Xydakis et al., 2004). Epidemiological evidence also suggested crucial roles of adipokines on the progression of MetS not only in the middle age, but also in the very old (Kanaya et al., 2006). On the other hand, healthy centenarians, who had a preserved insulin sensitivity were shown to have a lower waist-hip ratio and a more favorable body fat content as compared to aged subjects (Paolisso et al., 1995). In addition, lifestyle intervention such as diet and exercise decreased abdominal fat and improved various components of MetS in obese older adults (Villareal et al., 2006), suggesting that visceral fat accumulation and insulin resistance is not inescapable aging process, but could be malleable. To what extent genetics, environment, and health behaviors shapes the anthropometric characteristics of centenarians remain unknown, however, uncovering the mechanisms by which centenarians counteract age-related alteration in body composition and insulin action will provide an important clue to understand some component of healthy aging.

3.2.2. Adiponectin: an insulin-sensitizing hormone

As far as adipokines and insulin action are concerned, a great deal of interest has been generated by the discovery of adiponectin (also known as ADIPOQ, apM1, and ACRP30), which is shown to exert anti-diabetic, anti-atherogenic, and anti-inflammatory effects in rodents and humans (Hotta et al., 2000; Trujillo and Scherer, 2006). In cross-sectional studies, plasma adiponectin concentrations were significantly lower in obese individuals (Arita et al., 1999) and in those having diabetes (Hotta et al., 2000), MetS (Santaniemi et al., 2006; Xydakis et al., 2004), and CVD (Efstathiou et al., 2005; Ouchi et al., 1999), being inversely associated with body adiposity and insulin resistance (Stefan et al., 2002). Recently, a possible association between adiponectin and extended lifespan has been indicated in several animal models. First, mice with fat-specific disruption of the insulin receptor gene (FIRKO) have been demonstrated to have reduced adiposity, lower fasting insulin levels, and extended lifespan (Bluher et al., 2003). FIRKO mice was also characterized by elevated serum adiponectin levels, suggesting that the insulin-sensitizing effects of adiponectin might have contributed to longevity in this model. Second, transgenic (Tg) mice expressing human adiponectin was established by Otabe et al. (2007), and when maintained on a high-fat diet, adiponectin Tg mice exhibited lesser fat accumulation and a smaller adipocyte size in both visceral and subcutaneous adipose tissue with lower levels of fasting glucose, insulin, and leptin as compared to the wild-type mice. Moreover, transgenic expression of adiponectin reduced the morbidity and mortality in mice fed a high-fat diet in relation with attenuated oxidative DNA damage. Third, serum adiponectin levels were increased in long-lived GH-resistant and GH-deficient mice but reduced in short-lived mice with GH overexpression (Wang et al., 2006; Wang et al., 2007), suggesting a possible crosstalk between GH/IGF-1 pathways and adipose tissue metabolism in regard to life extension. These experimental evidences share many similarities with observational findings from centenarians (Table 1). Arai and colleagues reported that centenarians had significantly higher plasma adiponectin concentrations as compared to BMI-matched younger adults (Arai et al., 2006). In addition, the high-plasma adiponectin concentration in centenarians was associated with a favorable metabolic phenotype including higher HDL-C and lower glycohemoglobin, C-reactive protein (CRP) and E-selectin concentrations (Arai et al., 2006). Hyperadiponectinemia in centenarians was also reported by Bik et al. (2006). They found an inverse correlation between adiponectin and HOMA-IR, which is a reliable marker of insulin resistance. Adipose tissue now emerges as a pivotal organ controlling lifespan; however, the precise mechanisms by which adipose tissue metabolism regulates insulin action and lifespan remain to be elucidated.

Table 1
Comparison of long-lived mouse models with centenarians

	CR[a]	Dwarf[b]	FIRKO[c]	ADPN Tg[d,e]	Centenarians[f]
Glucose metabolism					
Plasma insulin	↓	↓	↓	↓	↓
Plasma glucose	↓	↓	↓	↓	↓
Insulin sensitivity	↑	↑	↑	↑	↑
Somatotrophic axis					
Plasma IGF-1	↓	↓↓	↓	NA	↓ or →
Adipose tissue metabolism					
Body adiposity	↓	↑ (with aging) or ↓	↓	↓	↓
Plasma leptin	↓	↓	↑	↓	↓ or ↑
Plasma ADPN	↑	↑	↑	↑↑	↑

NA: no available data; CR: calorie restriction; FIRKO: fat-specific insulin receptor knockout; ADPN: adiponectin.

[a] Longo and Finch (2003) and Wang et al. (2006).
[b] Bartke (2005) and Wang et al. (2006).
[c] Kloting and Blüher (2005).
[d] Kept on high-fat diet.
[e] Otabe et al. (2007).
[f] Paolisso et al. (1995, 1997), Arai et al. (2001, 2006).

3.3. The metabolic network for energy homeostasis and longevity: a large picture

Current advances in obesity research have delineated an integrated metabolic system that maintains whole-body energy homeostasis in response to nutritional availability and energy expenditure (Flier, 2004; Kahn et al., 2005; Sethi and Vidal-Puig, 2007). This system comprises the hypothalamus as the central nervous system (CNS) integrator, adipokines as the afferent signals to the CNS, and sympathetic nerves as the connecting link between key tissues including the liver, muscle, pancreas, adipose tissue, and brain (Evans et al., 2004; Uno et al., 2006). In states of overnutrition, leptin plays a critical role as an antiobesity hormone; however, when exposed to chronic nutritional excess, the system becomes overloaded and eventually induces obesity and insulin resistance (Kahn and Flier, 2000). Interestingly, adipose tissue deficiency or lipodystrophy is also associated with

insulin resistance and metabolic dysregulation (Leow et al., 2003). Therefore, insulin sensitivity, one of the peculiarities of healthy centenarians, may be a surrogate marker of the effectiveness of this integrated metabolic system. Very recently, Arai and colleagues followed a cohort of 252 centenarians for a period of 6.2 years and demonstrated an association between increased mortality and the decline in the levels of biomarkers of adipose endocrine function (Arai et al., in press). Additionally, cumulative dysregulation of multiple adipokines including leptin, adiponectin, and TNF-α constitutes a strong marker of poor prognosis among centenarians, independent of conventional risk factors such as low-serum albumin, interleukin-6, and HDL-C concentrations. Moreover, a graded relationship has been shown to exist (1) between the extent of impairment of adipose endocrine function and the decline in the many key pathways responsible for health maintenance, including those for physical and cognitive function, IGF-1 axis, HDL metabolism, and nutrient synthesis and hepatic function and (2) between the extent of impairment of adipose endocrine function and the up-regulation of the inflammatory cascades. These findings suggest the existence of a large interconnected metabolic network that maintains energy homeostasis and orchestrates multiple physiological functions that are indispensable for survival at an extremely old age. The speculation is far from proven; however, current advancements in aging science as well as clinical research aimed at underpinnings of frailty will provide critical information to clarify the entangled metabolic network of aging.

4. Conclusion

In contrast to the findings from long-lived animal models, a number of epidemiological studies indicate that low-IGF-1 activity, at least during the advanced aging process, is not associated with longevity in human. One possible explanation is that age-related wear and tear on the body system and its counteracting mechanisms may mask the association between GH/IGF-1 pathways and longevity, because such a period is much longer and complicated in human compared to laboratory animals. However, recent genetic study on Ashkenazi Jewish centenarians provides striking evidence that shows possible implication of GH/IGF-1 signaling pathway on human longevity. In addition, precise phenotyping and longitudinal studies on centenarians have led to the emergence of preserved insulin sensitivity as the universal pathway to longevity in mammals, including human. In accordance with this speculation, enhanced insulin sensitivity has been suggested to concomitantly contribute to lifespan extension in Ames dwarf, Snell dwarf, and GHRKO mice as well as calorie restricted animals. The mechanism by which centenarians maintain favorable insulin action has been largely unknown; however, current advances in obesity research, particularly in relation to the physiological roles of adipokines, have shed light on certain aspects of geriatric research and could further our understanding of the neuroendocrine adaptive mechanisms during aging.

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