Review

Adipokines and Aging

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Dysregulation of adipose tissue-derived bioactive molecules, termed adipokines, is recognized as common ground for insulin resistance and metabolic syndrome associated with obesity. However, adipokine dysregulation is paradoxically associated with lipodystrophy and lipoatrophy with aging. In familial partial lipodystrophic syndromes and Hutchinson-Gilford progeria syndrome, both of which are caused by mutations in the *LMNA* gene, loss of adipose tissue is associated with adipokine dysregulation, insulin resistance, and atherosclerosis, suggesting a critical role of adipose tissue function in controlling whole body energy metabolism, age-related pathologies, and longevity. Centenarians, a model of healthy aging and longevity, are reported to exhibit preserved insulin sensitivity as well as favorable adipokine profiles, particularly high levels of circulating adiponectin. Furthermore, adipose tissue dysfunction indicated by dysregulation of leptin, tumor necrosis factor-α, and adiponectin is associated with poor prognosis in centenarians. In contrast to results obtained for obesity, adipokine dysregulation in centenarians is associated with very low leptin levels, suggesting that age-related lipoatrophy is the major factor for adipose tissue dysfunction at an advanced age. These observations suggest that adipose tissue excess as well as its aging is implicated in the regulation of adipokines, insulin sensitivity, and lifespan in humans.

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Introduction

The current epidemic of obesity has brought to light the role of adipose tissue as an active endocrine organ in the regulation of energy homeostasis. Adipose tissue secretes a large number of bioactive substances, including leptin, tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), and adiponectin, which are collectively termed adipokines[1]. Dysregulation of adipokines is recognized as common ground for insulin resistance, hyperglycemia, dyslipidemia, hypertension, and the metabolic syndrome (MS) associated with obesity[2, 3]. However, accumulating evidence has shown that adipose tissue deficiency and lipodystrophy are also associated with adipokine dysregulation and have adverse metabolic consequences; this suggests that adipose endocrine function is critically important for maintaining whole-body energy homeostasis, which is indispensable for various physiological processes in states of energy excess and energy deprivation[4]. Furthermore, genetic manipulation of adipose tissue has been shown to enhance longevity in mouse models, suggesting a possible role of adipose tissue as a regulator of lifespan[5].

For more than a decade, studies on centenarians have been conducted to identify the healthy aging phenotype and to determine how this phenotype can be achieved[6, 7]. Several key pathways for maintaining health and longevity have been identified, and insulin sensitivity has been considered as a key factor for the healthy aging phenotype in centenarians[8]. We demonstrate here that centenarians are relatively lean and have well-functioning adipose tissue. In this review, we will discuss the possible roles of adipose tissue and

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adipokines in the regulation of lifespan in experimental models and humans and the possibility that this regulation is effected through maintenance of insulin sensitivity and glucose homeostasis.

Experimental Evidence linking Adipokines, Insulin Sensitivity, and Longevity

Among the adipokines identified, TNF-α was the first to be shown to exert substantial effects on insulin resistance associated with obesity. There have been active research on the association between adipokine dysregulation and insulin resistance, and the findings of these studies are summarized in excellent reviews[9, 10]. Here, we will focus on experimental evidence that provides mechanistic insight into the association among adipokines, insulin sensitivity and longevity. In a series of rat models, decreased visceral fat mass, achieved by either caloric restriction or surgical resection, was shown to improve age-related insulin resistance, possibly by altering the secretion of leptin and other adipokines[11, 12]. Ames dwarf mice, which characteristically have an extended lifespan, are homozygous for a mutation in the *Prop1* gene. They exhibit deficiencies in growth hormone, prolactin, and thyroid-stimulating hormone as well as a smaller body size with normal or reduced fat mass[13]. Ames dwarf mice also display enhanced insulin sensitivity, which is closely associated with high adiponectin levels in plasma[14]. In addition, mice with fat-specific disruption of the insulin receptor gene (FIRKO mice) are reported to have decreased adiposity, lower fasting insulin levels, and an extended lifespan[5]. FIRKO mice also have elevated serum adiponectin levels, which are shown to exert antidiabetic, antiatherogenic, and anti-inflammatory effects in rodents and humans[15, 16]. Transgenic (Tg) mice expressing human adiponectin have been established by Otabe *et al.*[17]. When maintained on a high-fat diet, these adiponectin Tg mice exhibit reduced fat accumulation and smaller adipocyte size in both visceral and subcutaneous adipose tissue, as well as lower fasting glucose, insulin, and leptin levels than wild-type mice. Moreover, macrophage infiltration into adipose tissue is markedly decreased in adiponectin Tg mice. These mouse models reveal that reduced adiposity can extend lifespan, and that alterations in adipokine secretion, particularly upregulation of adiponectin and insulin sensitivity, may be the key mediators of this process.

Human Data on the Relationship between Lipodystrophy and Premature Aging to Insulin Resistance

In individuals with excess adiposity, especially visceral adiposity, dysregulation of many adipokines is observed, including overproduction of TNF-α, IL-6, PAI-1, resistin, and leptin, as well as downregulation of adiponectin. This leads to systemic inflammation and insulin resistance, resulting in cardiovascular complications. On the other hand, loss of adipose tissue in various types of lipodystrophies and lipoatrophy with aging also causes adipokine dysregulation and insulin resistance[18]. Human lipodystrophies are far less common than obesity; however, elucidating the mechanistic link between fat loss and metabolic dysregulation would improve our understanding of the physiological roles of adipose tissue and adipokines. Lipodystrophies are a heterogeneous group of diseases characterized by a pathological deficiency in adipose tissue, ranging from localized to generalized, which may be inherited or acquired[19]. The metabolic consequences include fatty liver, dyslipidemia, insulin resistance and type 2 diabetes. The mechanisms underlying insulin resistance in lipodystrophy are not fully elucidated, but in a subgroup of the disease, adipokine dysregulation, including low levels of circulating leptin and adiponectin, is closely linked to metabolic dysregulation[20]. Moreover, recombinant leptin treatment improved glucose and triglyceride metabolism in patients with lipodystrophy, indicating that leptin signaling plays an essential role in metabolic abnormalities associated with lipodystrophy[21].

Recent researches clarified the genetic and molecular basis underlying the metabolic abnormalities of lipodystrophy. Patients with familial partial lipodystrophic syndromes (FPLDs) exhibit peripheral subcutaneous lipodystrophy and central fat accumulation, together with metabolic dysregulation, including insulin resistance, diabetes, and early atherosclerosis[22]. FPLDs are caused by mutations in *LMNA* (FPLD2), which encodes the nuclear protein lamin A/C, or in PPAR-γ (FPLD3), which plays a key role in adipocyte differentiation[23]. Cultured skin fibroblasts from FPLD patients with *LMNA* mutations are reported to exhibit prelamin A accumulation, increased oxidative stress, and cellular senescence[24]. Furthermore, in FPLD2 patients, the expression of prelamin A was enhanced in peripheral subcutaneous adipose tissue, which was associated with reduced expression of several adipogenic genes[25], suggesting that *LMNA* mutations are critical in the disruption of adipose tissue regeneration. Mutations in *LMNA* are also responsible for Hutchinson-Gilford progeria syndrome (HGPS), a rare premature aging disorder characterized by sclerodermatous changes in the skin, alopecia, osteoporosis, generalized lipodystrophy, and severe premature atherosclerosis[26, 27]. In HGPS, defective lamin A processing leads to the accumulation of mutant prelamin A

(progerin), which results in misshapen nuclei, a hallmark of this disease, and accelerated senescence of fibroblasts[28] and vascular smooth muscle cells (VSMCs)[29]. In cell culture models, accumulation of prelamin A was detected in VSMCs from aged individuals and in atherosclerotic lesions, but not in VSMCs from young and healthy individuals[30]. In this study, prelamin A accumulation was caused in part by the downregulation of lamina A processing enzyme FACE1 in response to oxidative stress, indicating that defective lamin A processing is associated with VSMC aging in the normal population[30]. Further research is warranted to investigate the relevance of dysfunctional pathways in HGPS to vascular aging in an epidemiological setting, and whether these pathways are involved in the normal aging process in other organs, including adipose tissue.

Human Data on the Adipose Tissue Phenotype in Centenarians

In humans, insulin sensitivity normally decreases with aging, and the prevalence of MS or type 2 diabetes, both of which share the common pathogenesis of insulin resistance, increases with advancing age[31, 32]. Individuals with MS are at a greater risk for various illnesses, including cardiovascular disease (CVD), which increases morbidity and mortality among the elderly. Intriguingly, there is increasing evidence that preservation of insulin action might be one of the common peculiarities of centenarians that help maintain health and function throughout their extremely long life. Paolisso *et al*. were the first to report that glucose tolerance and insulin sensitivity are better preserved in healthy centenarians in comparison to elderly individuals over 75 years of age[33]. A series of cross-sectional studies have reproducibly demonstrated that the prevalence of type 2 diabetes, which is closely associated with age-related insulin resistance, is very low among Finnish[34], Italian[35], and Japanese centenarians[36]. In addition, Barzilai *et al*. reported a low prevalence of MS among centenarians and their offspring, which was associated with a larger particle size of high-density lipoprotein (HDL) and low-density lipoprotein (LDL)[37]. HDL subclass was also associated with longevity in Japanese centenarians[38]. These findings collectively indicate the existence of a protective phenotype against MS and insulin resistance, which may be relevant to healthy aging.

Epidemiological evidence provides mechanistic insights into insulin sensitivity in centenarians. Healthy centenarians with preserved insulin sensitivity have been shown to have a lower waist-to-hip ratio and a more favorable body fat content than elderly controls[39]. Arai *et al*. reported that centenarians have higher plasma adiponectin concentrations than body mass index (BMI)-matched younger adults[40]. In addition, the high plasma adiponectin concentrations in centenarians are associated with a favorable metabolic phenotype, including higher HDL-C and lower hemoglobin A1c, C-reactive protein (CRP) and E-selectin concentrations[40]. Bik *et al*. reported the occurrence of hyperadiponectinemia in centenarians[41]; they found an inverse correlation between adiponectin and the homeostasis model assessment for insulin resistance (HOMA-IR), which is a reliable marker of insulin resistance. Aztmon *et al*. reported that centenarians have increased adiponectin levels and that adiponectin levels are inversely correlated with BMI, waist circumference, and the percentage of body fat[42]. Furthermore, they found that 2 common variants of the adiponectin gene (*ADIPOQ*) are associated with higher adiponectin levels and longevity. These findings show that reduced adiposity, together with hyperadiponectinemia and insulin sensitivity, may constitute a well-conserved pathway responsible for an extended life span in mammalian species, including humans.

Aging is associated with fat redistribution, which is characterized by loss of peripheral subcutaneous fat and accumulation of central fat. As discussed earlier, lipodystrophies and lipoatrophy associated with premature aging may cause adipokine dysregulation and insulin resistance, and the molecular basis of these pathological conditions may be relevant to understanding the normal aging process of adipose tissue. Interestingly, recent experimental evidence has shown that cellular senescence of adipose tissue also stimulates the inflammatory cascade and causes insulin resistance[43]. These findings suggest that older people are susceptible to adipokine dysregulation caused by visceral obesity and/or lipoatrophy of peripheral subcutaneous fat, and that adipokine dysregulation is more aggravated at an advanced age. To verify this hypothesis, we examined a series of adipokines, including leptin, adiponectin, and TNF-α, and investigated the association between adipokine dysregulation and all-cause mortality in a cohort of 252 centenarians[44]. In general, the centenarians studied were lean, with a mean BMI of 19.4 ± 3.3, and exhibited low plasma levels of leptin, indicating reduced adipose tissue mass. We found that the lowest tertiles of leptin and the highest tertiles of TNF-α were significantly associated with higher all-cause mortality in centenarians[44]. In addition, cumulative dysregulation of multiple adipokines, including leptin, adiponectin, and TNF-α, constituted a strong marker of poor prognosis among centenarians, independent of conventional risk factors

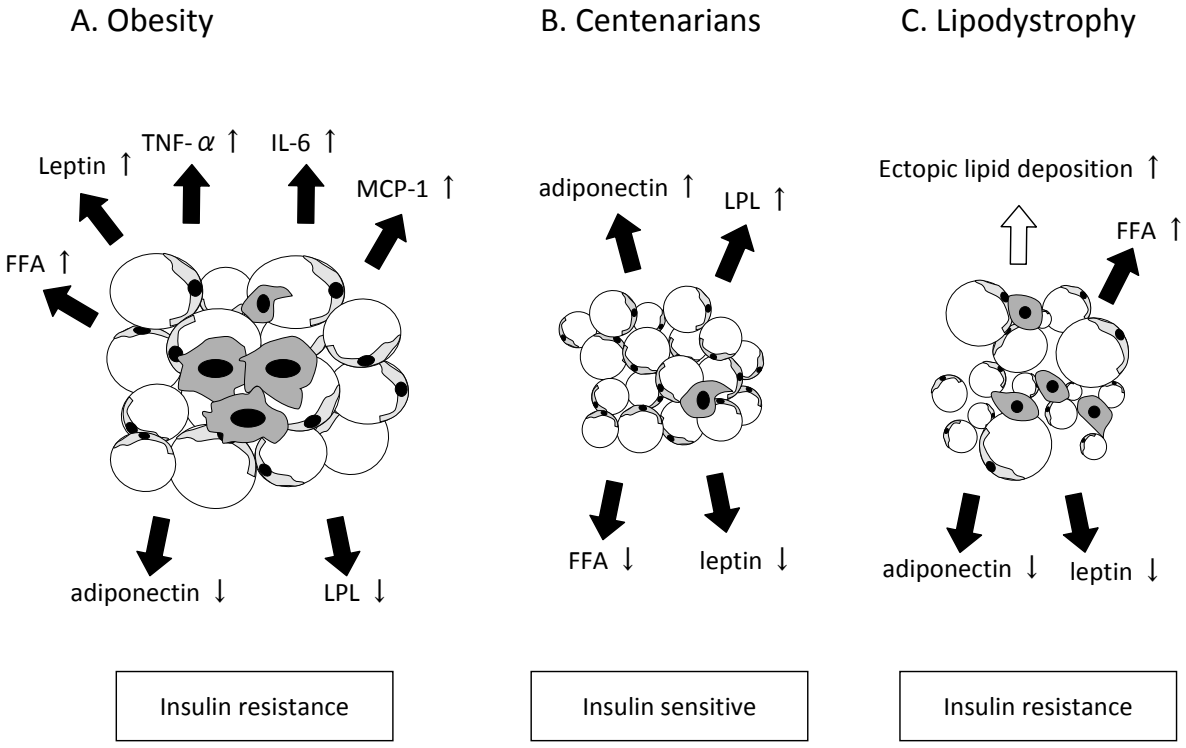

Fig. 1

Hypothetical link between adipokines, insulin sensitivity, and longevity. In the context of obesity (A), hypertrophic adipocytes upregulate the expression of inflammatory cytokines such as TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1), and downregulate adiponectin and lipoprotein lipase (LPL) expression, followed by an increase in angiogenesis, immune cell infiltration, and further adipose tissue inflammation, leading to insulin resistance. In patients with lipodystrophies (C), adipose tissue phenotypes are heterogeneous. In general, there is an absolute or relative lack of lipid storage capacity; this enhances ectopic lipid accumulation, resulting insulin resistance in liver (hepatic steatosis) and skeletal muscles. It is not known the extent to which low levels of leptin and adiponectin are relevant to insulin resistance in lipodistrophies. Centenarians (B) may have healthy functioning adipose tissue that contains few macrophages, and secretes high levels of adionection, and low levels of leptin, maintaining glucose homeostasis and insulin sensitivity.

such as low serum albumin, IL-6, and HDL-C concentrations[44]. In contrast to obesity-related conditions, adipokine dysregulation in centenarians was uniquely associated with very low levels of leptin (less than 2.6 ng/mL) and low BMI, suggesting that age-related fat loss or lipoatrophy is major factor for adipose tissue dysfunction in centenarians. These findings are concordant with studies showing the protective functions of fat mass against morbidity and mortality in geriatric patients[45] and patients undergoing hemodialysis[46]. Although further studies focusing on the distribution of fat pads, adipocyte size and adipocyte metabolism in association with aging and age-related pathology are required, maintaining adipose tissue mass and function, particularly leptin signaling, seems to be indispensable for normal physiological functions under energy-deprived conditions, such as cachexia, or wasting syndrome, and chronic inflammation, which are associated with advanced aging.

Conclusion

The endocrine function of adipose tissue, as indicated by adipokine profiles, is altered in obesity, and less frequently in lipoatrophy with aging. Centenarians maintain adipose endocrine function and insulin sensitivity under both conditions, thereby achieving healthy aging and longevity (**Fig. 1**). The literature suggests that adipokines are involved in a highly integrated metabolic network, which is composed of the hypothalamus as a central nervous system (CNS) integrator, adipokines as afferent signals to the CNS, and sympathetic nerves as a wiring link between key tissues to maintain whole-body energy homeostasis[47]. Focus areas for future studies may include elucidation of the mechanisms underlying adipose tissue aging and the metabolic network, as well as identification of genetic and lifestyle factors that promote healthy adipose aging.

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