Pathological Role of Adipose Tissue Dysfunction in Cardio-Metabolic Disorders

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Summary
Obesity has dramatically increased throughout the world, and has become one of the chief healthcare problems in many societies. Evidence has emerged that adipose tissue dysfunction associated with obesity is critically involved in the development of cardiovascular and metabolic disorders. In this review, we delineate the link between adipose tissue abnormalities and systemic metabolic dysfunction in patients with cardio-metabolic diseases and discuss the underlying mechanisms.

Key words: Aging, Diabetes, Insulin, Heart failure, White adipose tissue, Brown adipose tissue

Aging can be characterized as an age-dependent decline of physiological function that leads to an increased risk of death. Chronological aging has been linked to genomic instability, loss of telomeres, epigenetic modifications, alterations of intercellular communication, and cellular senescence, all of which contribute to the pathology of aging and age-related disorders. The exact mechanism of aging is yet to be defined, but several factors have been reported to be involved. Calorie restriction and inhibition of insulin signaling are well known to delay the aging process and extend longevity in various species, including monkeys.

Obesity and diabetes have dramatically increased throughout the world and have become major healthcare problems in many societies. Obesity has a central role in the development of diabetes and atherosclerotic disease, and being obese increases the risk of death, particularly from cardiovascular disease. Systemic insulin resistance (hyperinsulinemia) is one of the crucial molecular mechanisms involved in the pathology of obesity and diabetes. Chronic low-grade sterile inflammation affecting visceral fat leads to systemic insulin resistance. Excessive uptake of free fatty acids by visceral fat in obese persons drives the production of reactive oxygen species (ROS) and initiates cellular senescence. Several lines of evidence have clearly shown a pathological role of cellular senescence in the progression of age-related diseases, such as atherosclerosis, obesity, and diabetes. Recently, occurrence of cellular senescence in cardiac tissue and adipose tissue was reported to have a causal role in accelerating heart failure and diabetes, respectively. Occurrence of cellular senescence in white adipose tissue (WAT) induces inflammation and systemic insulin resistance in a murine heart failure model, thus accelerating cardiac remodeling. Conversely, suppression of cellular senescence in adipose tissue ameliorates inflammation and systemic metabolic dysfunction, inhibiting the progression of heart failure and the development of diabetes via modulation of insulin signaling. In addition to WAT, other types of fat are known to be involved in regulating metabolic homeostasis. Brown adipose tissue (BAT) is highly vascular and abundant in mitochondria that are rich in uncoupling protein-1 (UCP-1), which produce heat by uncoupling the respiratory chain involved in ATP synthesis. BAT is abundant in newborn infants and small rodents, and was once thought to disappear with aging. However, recent studies have shown that adult humans also possess active BAT. Besides being involved in thermogenesis, BAT has been suggested to contribute significantly to systemic metabolism because of its high energy expenditure ratio. Although BAT is now recognized as a potential regulator of systemic metabolism in persons with obesity and diabetes, the molecular mechanism underlying the decline of BAT activity in obesity and its physiological implications are largely unknown. Over-nutrition was recently shown to promote hypoxia in BAT, causing it to “whiten” through dysfunction and loss of mitochondria, thus contributing to impairment of systemic glucose metabolism. Suppression of the dysfunction of BAT and maintenance of BAT homeostasis may be new therapeutic targets for preventing diseases associated with age-related systemic metabolic dysfunction such as obesity, diabetes, and heart failure. In this review, we delineate the link between adipose tissue abnormalities and systemic metabolic dysfunction in patients with cardio-metabolic diseases.

References:

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Abnormalities of WAT and Systemic Metabolic Dysfunction in Obesity

The aging process is closely connected with accumulation of genomic instability and telomere shortening. In addition, genotoxic stimuli like oxidative stress can induce irreversible cell growth arrest and alter the genetic profile of cells to a state that has been described as “cellular senescence”. While it was initially discovered in vitro, several studies have suggested that cellular senescence also occurs in vivo and that its prevalence increases with chronological aging.\(^1,30,32\) Cellular senescence is an effective anticancer mechanism, but its overactivation was recently shown to promote the progression of age-related disorders in mice.\(^33,34\) Signaling via p53/p21 or p16/Rb has a central role in cellular senescence, with the influence of p53 having been most extensively studied. The protein p53 is a transcriptional factor involved in coordination of DNA repair, cell cycle regulation, apoptosis, and senescence, so that it is active in preserving genomic stability and inhibiting tumorigenesis. There is also accumulating evidence that p53 is involved in regulating metabolic homeostasis through the modulation of glycolysis, mitochondrial function, and autophagic responses.\(^35\)

Recently, p53 was reported to have some undesirable effects in relation to age-related disorders.\(^36\) An increase of p53-mediated transcriptional activity is associated with chronological aging, while a low level of constitutive p53 activation is mediated transcriptional activity is associated with chronological aging.\(^1,30,32\) Cellular senescence is an effective anticancer mechanism, but its overactivation was recently shown to promote the progression of age-related disorders in mice.\(^33,34\) Signaling via p53/p21 or p16/Rb has a central role in cellular senescence, with the influence of p53 having been most extensively studied. The protein p53 is a transcriptional factor involved in coordination of DNA repair, cell cycle regulation, apoptosis, and senescence, so that it is active in preserving genomic stability and inhibiting tumorigenesis. There is also accumulating evidence that p53 is involved in regulating metabolic homeostasis through the modulation of glycolysis, mitochondrial function, and autophagic responses.\(^35\)

Chronic low-grade inflammation associated with age-related disorders such as diabetes, atherosclerosis, and heart failure is postulated to have a central role in accelerating the progression of these diseases. WAT was initially thought to be mainly involved in energy storage, but is now well known to be an endocrine organ that secretes various chemokines known as adipokines. There is evidence that inflammation of WAT, which is characterized by infiltration of inflammatory cells and increased production of pro-inflammatory cytokines by these immune cells or resident senescent cells, induces systemic insulin resistance and accelerates the development of diabetes.\(^3,34,42,43\) Excessive energy intake results in the hypertrophy of adipocytes by increasing the influx of fatty acids into these cells and promotes a pro-inflammatory phenotype in adipose tissue. These changes up-regulate the production of various chemotactic agents, including chemokine (C-C motif) ligand 2 (CCL2), which is also known as monocyte chemotactic protein-1 (MCP-1). Subsequent recruitment of inflammatory cells results in a vicious cycle of increasing adipose tissue inflammation that leads to systemic metabolic dysfunction.\(^11,44,46\) Circulating pro-inflammatory cytokines, largely originating from inflamed adipose tissue, inhibit insulin signaling in key organs and this leads to systemic insulin resistance (hyperinsulinemia) and accelerates progression toward diabetes.\(^11,44,45\)

Chronic low-grade inflammation is also known to sustain the production of pro-inflammatory cytokines by resident senescent cells in adipose tissue.\(^12,13\) Metabolic stress increases ROS and induces cellular senescence, mainly via p53/p21 signaling. Altered gene expression profiles in senescent cells promote the production of several pro-inflammatory chemokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and CCL2 (MCP-1). In mice, forced expression of p53 by adipose tissue provokes adipose tissue inflammation and systemic metabolic dysfunction. Semaphorins and their receptors (plexins) are the axon-guiding molecules that are known to regulate the development of vascular networks during embryogenesis. Semaphorin3E (Sema3E) is one of the secreted class 3 semaphorins, while plexinD1 is its receptor. It was recently shown that sema3E is regulated by p53 and secreted by visceral fat in obesity, after which it acts as a chemotactic agent for inflammatory macrophages, thus contributing to the initiation and maintenance of inflammatory responses in adipose tissue that lead to systemic insulin resistance.\(^7,9\) These findings suggest that inhibition of cellular senescence in adipose tissue, especially by targeting the p53-sema3E-plexinD1 axis, could be a potential new target for the prevention/treatment of diabetes.

BAT Dysfunction is Linked to Systemic Insulin Resistance in Obesity

Evidence has been obtained that human adults possess abundant brown BAT. It is thought that there is 50-80 g of active BAT in the average adult. In humans, it has been demonstrated that cold exposure to cold (18°C for 3 hours) increases the uptake of glucose and fatty acids by BAT and also increases energy expenditure,\(^48\) while chronic exposure to cold results in a 37% increase of estimated BAT volume and increases nonshivering thermogenesis.\(^49\) In addition to its thermogenic function, BAT may have a role in suppressing metabolic diseases because of its high oxidative capacity. In mice with type 1 diabetes, housing in a cold environment has been shown to ameliorate systemic metabolic dysfunction,\(^50\) and activation of BAT by acute cold stress contributes to the clearance of circulating lipids in mice.\(^51\) Importantly, even in persons whose BAT has been depleted, chronic exposure to cold (17oC for 2 hours daily for 6 weeks) recruits BAT and decreases body fat mass despite no change of body weight.\(^52\) Several studies have demonstrated that the vascularity of WAT has a crucial role in maintaining systemic metabolic homeostasis,\(^12,50\) but whether the vascularity of BAT is also important remains unclear. A decline of BAT function is associated with obesity and aging, but the reasons are unknown.\(^53,54\) Recently, obesity was shown to cause much more prominent capillary rarefaction and hypoxia in BAT than in WAT. This leads to “whitening” of BAT that is associated with diminished β-adrenergic signaling, accumulation of large lipid droplets, and mitochondrial dysfunction. These changes of BAT impair its thermogenic response and contribute to dysfunction of glucose metabolism. In a model of dietary obesity maintained on a high-fat, high-sucrose diet, BAT displays reduced expression of adrenergic receptors and VEGF-A, capillary rarefaction, and evidence of hypoxic damage. Whitening of BAT was also observed following the targeted ablation of Vegfa in adipose tissue of non-obese mice, which then demonstrated impairment of systemic glucose metabolism and a reduced thermogenic response. Furthermore, specific introduction of Vegfa into the BAT of obese mice restored its vascularity and ameliorated adipocyte dysfunction,
has recently been shown to regulate metabolic dysfunction in the development of heart failure. Systemic insulin resistance was reported to be a risk factor for the prevalence among patients with cardiac dysfunction, and systemic metabolism in obesity, but its role in heart failure is unknown.

**Pathological Effect of Excessive Insulin Signaling on the Heart**

Pathological effect leads to increased ROS production and activation of p53 signaling, resulting in adipose tissue senescence. Interestingly, inhibition of adipose tissue senescence ameliorates metabolic abnormalities and improves cardiac function in the chronic phase of heart failure. These findings suggest that inhibition of WAT inflammation and systemic insulin resistance via modulation of cellular senescence has the potential to become a new treatment option for metabolic abnormalities and systolic dysfunction in patients with heart failure. Although BAT has recently been shown to regulate metabolic dysfunction in obese rodents, its pathological role in heart failure is still largely unknown and further studies are therefore needed.

**Link Between Cardiac Aging and Adipose Tissue Dysfunction**

Systolic heart failure develops as a result of various factors that reduce cardiac pump function. It has been reported that DNA damage accumulates in cardiomyocytes and contributes to negative cardiac remodeling. ROS and p53 both increase in the failing heart and these changes inhibit cardiac function. It is also well known that heart failure is associated with cardiac and systemic metabolic dysfunction. Several studies have shown that systemic insulin resistance is prevalent among patients with cardiac dysfunction, and systemic insulin resistance was reported to be a risk factor for the development of heart failure. Thus, there is evidence of a link between heart failure and systemic metabolic dysfunction, but the underlying molecular mechanisms and the clinical implications have not been clarified. Recently, systemic insulin resistance (hyperinsulinemia), including hepatic insulin resistance, was shown to develop in murine models of chronic heart failure. In contrast, cardiac insulin signaling was markedly upregulated to induce cardiac hypertrophy and hypoxia via insulin/Akt signaling, which was detrimental for the maintenance of cardiac homeostasis. It has also been found that cellular senescence in visceral fat provokes adipose tissue inflammation and systemic insulin resistance in response to pressure overload. Excessive lipolysis associated with high sympathetic activity leads to increased ROS production and activation of p53 signaling, resulting in adipose tissue senescence. Interestingly, inhibition of adipose tissue senescence ameliorates metabolic abnormalities and improves cardiac function in the chronic phase of heart failure. These findings suggest that inhibition of WAT inflammation and systemic insulin resistance via modulation of cellular senescence has the potential to become a new treatment option for metabolic abnormalities and systolic dysfunction in patients with heart failure. Although BAT has recently been shown to regulate metabolic dysfunction in obese rodents, its pathological role in heart failure is still largely unknown and further studies are therefore needed.
ess of cellular senescence, and provokes inflammation through production of pro-inflammatory cytokines, further accelerating the process of tissue remodeling. Sterile inflammation in visceral fat is well accepted as a cause of systemic insulin resistance in obesity and diabetes. Inhibition of cellular senescence ameliorates adipose tissue inflammation, improves metabolic disorders, and inhibits aging phenotypes in models of obesity, demonstrating that modulation of this signaling pathway could become a treatment for systemic metabolic dysfunction in persons with age-related disorders. Dysfunction of BAT is associated with aging and obesity. Recently, vascular rarefaction was shown to lead to the “whitening” and dysfunction of BAT, which induces systemic metabolic disorders. There is a growing body of evidence, including human studies, that suggests a potential role of BAT in regulating systemic metabolic homeostasis. However, the process of senescence in BAT is largely unknown and further studies are needed to elucidate its pathological role in age-related diseases.

There is also accumulating evidence of a link between insulin signaling and aging. Inhibition of the insulin signaling pathway extends the lifespan of various animals, including monkeys. Systemic insulin resistance (hyperinsulinemia) is well accepted to have a central role in accelerating the pathologies of obesity and diabetes. In addition, the pathological role of adipose tissue inflammation and systemic insulin resistance in heart failure was demonstrated recently. Inhibition of senescence-induced adipose tissue inflammation ameliorates systemic metabolic dysfunction and improves cardiac function in the setting of pressure overload. Excessive lipolysis due to sympathetic overactivity results in elevation of ROS production and p53 expression, leading to senescence-induced adipose tissue inflammation. Importantly, inhibition of adipose tissue inflammation and systemic metabolic dysfunction improved cardiac dysfunction in a murine heart failure model, while excessive cardiac insulin signaling had a detrimental effect on systolic function. Although it is well accepted that basal insulin signaling is essential for maintaining homeostasis, excessive activation of the insulin-signaling pathway may promote aging and pathological changes. Cellular senescence in adipose tissue leads to systemic insulin resistance in the chronic phase of heart failure. Hepatic insulin resistance also develops in this setting, while in contrast cardiac insulin signaling is maintained at a high level. BAT has been shown to regulate systemic metabolism in obesity, but its role in heart failure is unknown and further investigations are needed to assess its potential pathological role.

In conclusion, we described the central role of WAT and BAT dysfunction in dysregulation of metabolic homeostasis. Inhibition of adipose tissue dysfunction and systemic insulin resistance may have the potential to become new treatments for age-related disorders such as heart failure and diabetes.

References


