medulloblastoma, however, because activation of the Hedgehog signaling pathway downstream of the receptor may occur in some tumors[9,10]. In tumor tissue samples, Han *et al.*[2] found that ciliated tumor cells had either active Hedgehog or Wnt signaling pathways, which is a suggestive correlation but one that needs confirmation in larger studies.

Activation of the Hedgehog pathway downstream of the receptor may select against the presence of cilia in a tumor, and recent observations show that the relative level of Gli3 repressor can be lowered independently of cilia[11]. In light of these observations, the diagnostic value of cilia as a biomarker for targeted therapy with SMO antagonists will require assessment of Hedgehog pathway activity in addition to cellular morphology.

Perhaps hints about the potential for therapeutics can be found in pancreatic cancer, where Hedgehog signaling is also frequently activated. Most pancreatic tumor cells are unciliated[12], potentially as a result of prevalent KRAS oncoprotein mutations. Tumor cells express and secrete Hedgehog ligand, but an autocrine response is absent. Instead the cells of the tumor stroma, which frequently have cilia, respond to the Hedgehog signal in a paracrine manner. Recently, a study found that SMO antagonists could deplete tumor stroma[13], implying the importance of cilia for the Hedgehog pathway for these cells.

Despite these advances, deeper understanding of how primary cilia operate in Hedgehog signaling and other pathways is urgently needed before the introduction of diagnostic tests or therapies targeting ciliary function for treatment of BCC or medulloblastoma.

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Connecting obesity, aging and diabetes

Rexford S Ahima

Obesity accelerates the aging of adipose tissue, a process only now beginning to come to light at the molecular level. Experiments in mice suggest that obesity increases the formation of reactive oxygen species in fat cells, shortens telomeres—and ultimately results in activation of the p53 tumor suppressor, inflammation and the promotion of insulin resistance.

As technology has improved hygiene, the food supply and living standards overall, there has been a rise in such age-related illnesses as cardiovascular disease, cancer, degenerative diseases of the brain and other organs, and metabolic disorders such as diabetes. Age-related disorders have become widespread throughout the world, replacing infectious diseases as the leading cause of death in developed countries. As we age, many people develop the metabolic syndrome, characterized by central (visceral) obesity, insulin resistance, impaired glucose tolerance or overt diabetes, hypertension, dyslipidemia and cardiovascular complications.

Diabetes is also a recognized cause of accelerated aging, but the mechanisms linking diabetes and aging are not well understood. Work from Minamino *et al.*[1] in this issue of *Nature Medicine* offers insights into how obesity affects the aging of adipose tissue, influencing inflammation and glucose homeostasis.

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Obesity is a major cause of insulin resistance, which progresses to type 2 diabetes when the pancreas is unable to produce sufficient amounts of insulin. In recent years, evidence has emerged that inflammation has a crucial role in the development of insulin resistance, diabetes and cardiovascular diseases associated with obesity[2,3]. Macrophages infiltrate adipose tissue in obese states, and cytokines levels are elevated and cause insulin resistance and diabetes[2,3].

The deterioration of the structure and function of organs during aging is associated with oxidative stress, genetic instability and disruption of homeostatic pathways[4]. Much aging research has studied telomeres, which are composed of tandem repeats of the TTAGGG sequence and associated proteins and are located at the ends of chromosomes[5]. Stem cells and cancer cells are able to continue dividing because the telomeres are maintained by an enzyme called telomerase. In contrast, in normal somatic cells, the telomeric repeats are lost with each cell cycle until a 'critical length' is attained. The shortening of telomeres leads to activation of tumor suppressors, in particular p53, which induces cell cycle arrest and aging.

Genomic damage can also accrue over time from reactive oxygen species (ROS). Diabetes, among other age-related illnesses, is associated with an inability to detoxify ROS[6]. Similarly, telomere shortening has been linked to obesity, insulin resistance, diabetes and coronary artery disease[7].

Because there are similarities in metabolic dysregulation in aging and obesity, it is likely these conditions share similar cellular pathways. To test this hypothesis, Minamino *et al.*[1] analyzed the adipose tissue of obese mice for evidence of oxidative stress, aging and inflammation. Adipose tissue from agouti mice, which are genetically obese, had higher levels of ROS and DNA damage than lean mice when both groups were on a normal diet for 20 weeks[1]. Adipose tissue from agouti mice showed features of premature aging, such as a higher expression of senescence-associated β-galactosidase, p53 and cyclin-dependent kinase inhibitor 1A (*Cdkn1a*).

The researchers then determined whether age-related changes in adipose tissue were responsible for insulin resistance[1]. Adipose tissue from agouti mice also expressed proinflammatory cytokines that attract macrophages to adipose tissue, tumor necrosis factor and monocyte chemoattractant protein-1, which are associated with insulin resistance. Adiponectin, which enhances insulin action, was suppressed in adipose tissue from agouti mice.

Minamino *et al.*[1] proposed that the link between obesity and aging and abnormal metabolism was p53. They found that p53 deficiency lowered inflammation and improved insulin sensitivity in obese agouti mice on a regular diet or obese wild-type mice on a high-sugar–high-fat diet compared with wild-type lean mice[1]. Glucose tolerance improved when mice without p53 in their adipose tissue received a bone marrow transplant from normal mice, indicating a key role for macrophages in glucose metabolism. What's more, transgenic overexpression of p53 and *Cdkn1a* in adipose tissue induced inflammation and insulin resistance. These results suggest that p53 is derived from adipocytes and macrophages and contributes to the aging of adipose tissue in obese animals.

Because p53 is activated in response to shortened telomeres in aging cells, Minamino *et al.*[1] investigated whether telomere length affected obesity-induced inflammation and insulin resistance. Mice that lack telomerase (*Tert*) develop shorter telomeres with successive generations and eventually become infertile by the fourth to sixth generation (G4–G6). As expected, Minamino *et al.*[1] found that G4 *Tert*-deficient mice had increased DNA damage and high expression of senescence markers (for example, senescence-associated β-galactosidase, p53 and *Cdkn1a*) in adipose tissue. The authors also detected large amounts of senescence and inflammatory markers in adipose tissue biopsies from individuals with diabetes compared to individuals without diabetes, suggesting that adipose tissue is associated with an aging phenotype.

The G4 *Tert*-deficient mice showed signs of abnormal metabolism: they were more prone to developing glucose intolerance and insulin resistance on a high-fat–high-sugar diet compared to age-matched wild-type mice on a similar diet[1]. Macrophages infiltrated the adipose tissue of G4 *Tert*-deficient mice, and they developed insulin resistance in the liver and, to a lesser extent, in muscle. These effects were independent of body weight.

Surgical removal of adipose tissue led to improvement in glucose metabolism in G4 *Tert*-deficient mice, whereas transplantation of G4 *Tert*-deficient adipose tissue into normal mice induced insulin resistance, indicating that the aging of adipose tissue has a profound influence on insulin action in adipose tissue and other organs. This response was attenuated when adipose tissue deficient in both telomerase and p53 was transplanted into normal mice, thus establishing a functional connection between telomere dysfunction and p53 activation.

Minamino *et al.*[1] then searched for a link between oxidative stress and aging and inflammation in human adipose tissue. Primary human adipocytes treated with hydrogen peroxide (H_2O_2), a source of ROS, expressed high levels of p53 and the proinflammatory cytokines tumor necrosis factor and monocyte chemoattractant protein-1, uncovering a molecular mechanism for metabolic damage from oxidative stress.

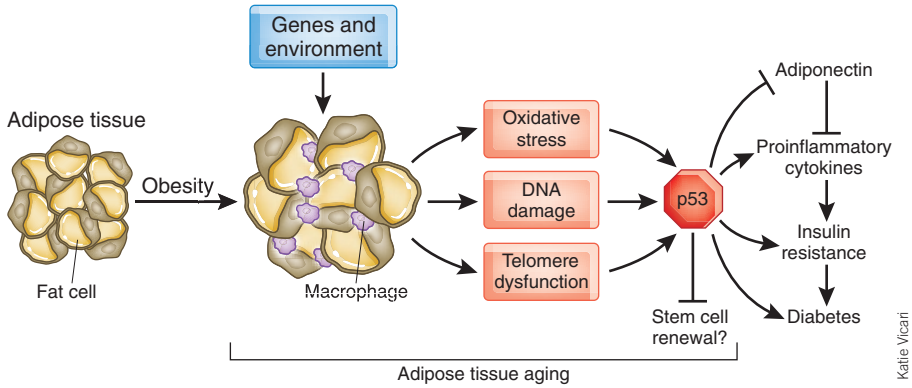

Figure 1 The connection between obesity-mediated aging of adipose tissue and diabetes. In obese states, adipose tissue is subjected to oxidative stress, resulting in aging, accumulation of macrophages, production of proinflammatory cytokines and suppression of adiponectin. Activation of p53 tumor suppressor is pivotal in the aging process, stimulates inflammation and possibly attenuates the capacity of stem cell renewal. The aging of adipose tissue induces insulin resistance in adipose tissue, liver and muscle and mediates the progression to diabetes.

These data offer new insights into how obesity promotes the aging of adipose tissue and insulin resistance (**Fig. 1**). Obesity resulting from genetic and environmental factors, for example, overnutrition, stimulates the generation of ROS. These molecules probably overwhelm the antioxidant protection in adipose tissue, thus accelerating DNA damage and aging. The obesity-mediated aging of adipose tissue is also associated with telomere shortening, which leads to activation of p53. These alterations trigger inflammatory responses in adipose tissue and stimulate cytokine production, which then lead to insulin resistance locally and systemically (**Fig. 1**).

Minamino *et al.*[1] propose a model in which aging and inflammation is initiated in adipose tissue and subsequently induces insulin resistance in adipose tissue, liver and muscle (**Fig. 1**). However, they did not elucidate the timing of these changes in obesity. Adipose tissue communicates via fatty acids and a myriad of circulating factors with the brain and other organs[8], yet the study focused exclusively on proinflammatory cytokines and adiponectin. Contrary to the focus on adipose tissue, a more likely scenario is that aging occurs at differing rates in various organs and has local and distant effects on inflammation and insulin sensitivity. Insulin resistance of the liver is prominent in type 2 diabetes and increases glucose production[9]. Skeletal muscle is the major organ responsible for insulin-mediated glucose uptake, and this is blunted in aging and obesity as a result of a relative decrease in muscle mass[9]. Aging and obesity may disrupt insulin production by the pancreas[10]. Furthermore, aging is associated with oxidative injury to the brain and could potentially impair insulin secretion and sensitivity[11].

Another open question is whether the obesity-mediated aging of adipose tissue is reversible by dieting and other treatments. Caloric restriction reduces aging and improves glucose homeostasis[12]. Perhaps adiponectin treatment could reduce oxidative damage and inflammation in adipose tissue, as has been shown in liver and blood vessels[8]. Decreasing the activity of p53 is a logical strategy for slowing aging and inflammation, and improving insulin action, but can adipose tissue and other organs be targeted specifically? Can antioxidants ameliorate cellular aging, thus reducing inflammation and enhancing insulin sensitivity? Finally, it would be interesting to study whether the p53 tumor suppressor mediates the lipid abnormalities and cardiovascular morbidity associated with obesity. The work of Minamino *et al.*[1] is a major step toward answering these questions.

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