Molecules and Cells

Journal Club

Cellular Senescence: The Villain of Metabolic Disease?

Discovery of a distinct senescent cell population in obesity-induced metabolic dysfunction

Gung Lee*

National Leader Research Initiatives Center for Adipocyte Structure and Function, Institute of Molecular Biology and Genetics, School of Biological Sciences, Seoul National University, Seoul 08826, Korea
*Correspondence: pricisor@snu.ac.kr
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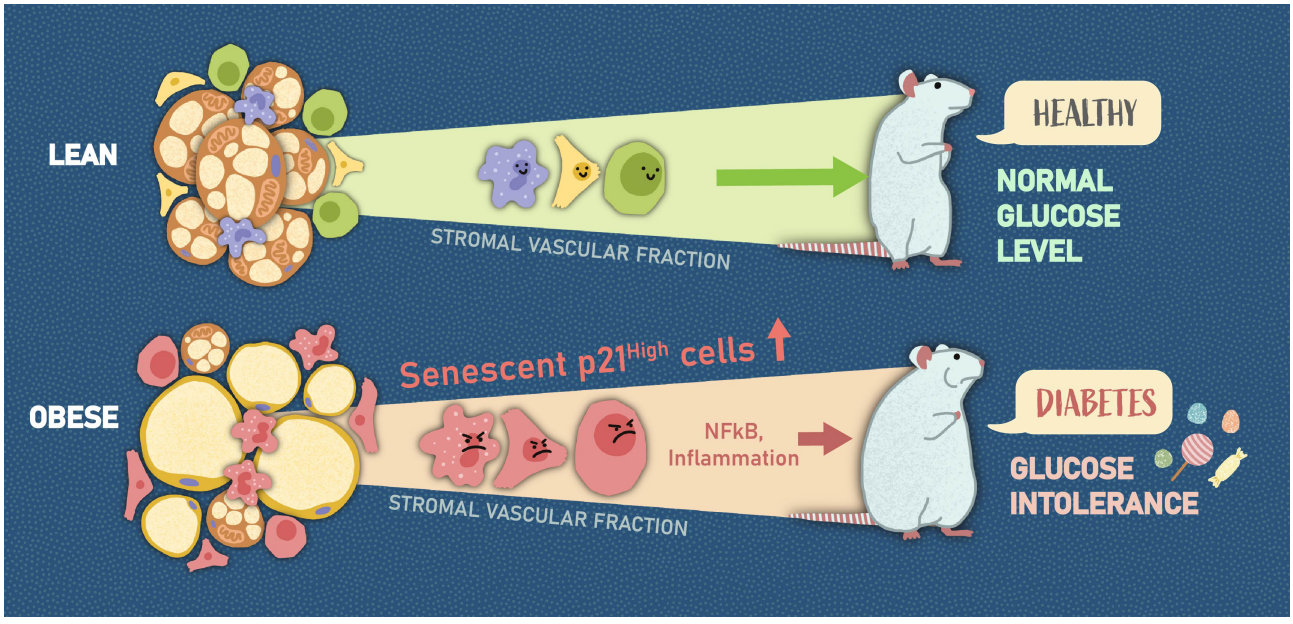

Senescent p21^{high} cells in epididymal white adipose tissue (eWAT) aggravate metabolic dysfunction in obese animals. In obesity, p21^{high} cells are specifically accumulated in stromal vascular fraction of eWAT and they have increased expression of inflammatory genes and NFκB signaling pathway. Transplantation of p21^{high} cells provokes glucose intolerance whereas clearance of p21^{high} cells by senolytic agents relieves insulin resistance in obese animals.

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Cellular senescence is a complex state primarily characterized by permanent growth arrest with high metabolically active (Hernandez-Segura et al., 2018). Cellular senescence occurs in response to various triggers, including DNA damage, telomere shortening, oncogene activation, and metabolic stress (Gorgoulis et al., 2019). Also, it is closely associated with aging, tissue repair, tumor suppression, and metabolic disorders. Senescent cells often secrete a variety of proinflammatory cytokines, extracellular matrix degrading enzymes, and certain metabolites, which is known as the senescence-associated secretory phenotype (SASP) and affect cellular function and microenvironments (Coppe et al., 2010).

Obesity is a crucial risk factor in type 2 diabetes and the acceleration of organismal aging (Kahn et al., 2006; Tchkonia et al., 2010). Senescent cell accumulation is observed in obese animals, and its role in metabolic dysfunction has been reported (Kim and Kim, 2021; Lee et al., 2022). However, due to the heterogeneity of senescent cells and the absence of appropriate animal models, the roles of senescent cells in metabolic dysfunction and the physiological significance of senescent cell removal in metabolic homeostasis have yet to be elucidated.

P21 is known as one of the key regulators and markers of senescent cells, and cells that express high levels of P21 ($p21^{high}$ cells) exhibit distinct senescent features, such as enlarged cell size, higher beta galactosidase activity, inhibited cell proliferation, lower lamin B1 levels, and an increase in the SASP (Wang et al., 2021). However, the roles of $p21^{high}$ cells in various pathological conditions *in vivo* are largely unknown.

Using several mouse models and a fat tissue transplantation approach, Wang et al. (2022) recently reported the physiological roles of $p21^{high}$ cells in epididymal white adipose tissue (eWAT) affecting metabolic dysfunction in obese animals. Specifically, in high-fat diet (HFD)-fed obese mice, $p21^{high}$ cells were found to be dominant in eWAT but were not observed in liver, muscle, pancreas, and brown fat. Furthermore, they showed that $p21^{high}$ cells can provoke metabolic dysfunction in obesity.

To gain a deeper understanding of $p21^{high}$ cells in obese eWAT, Wang et al. (2022) performed single cell transcriptomic analysis of a stromal vascular fraction (SVF) in eWAT of HFD-fed obese mice. Compared with lean mice, obese mice contained more numbers of $p21^{high}$ cells, and these cells were predominantly preadipocytes, endothelial cells, and macrophages. Additionally, $p21^{high}$ cells showed higher expression in the inflammatory response, chemotaxis, and NFκB signaling pathway as well as negative regulation of apoptosis and angiogenesis at the transcriptome level. Since $p21^{high}$ cells exhibited an enhancement of the NFκB signaling pathway, the authors investigated whether inhibition of the NFκB pathway in $p21^{high}$ cells might alleviate obesity-induced metabolic dysfunction. Indeed, inhibition of NFκB signaling reduced the expression of senescence-related genes and improved glucose tolerance of obese mice, suggesting that NFκB signaling in senescent $p21^{high}$ cells would contribute to metabolic dysfunction. Furthermore, they raised the question whether $p21^{high}$ cells play a causal role in the metabolic dysfunction of obese animals by using diphtheria toxin A (DTA)-driven $p21^{high}$ cell elimination mice. Upon DTA administration, $p21^{high}$ cells were reduced in eWAT, consistent with the decreased expression of senescence markers. Removal of $p21^{high}$ cells had no influence on body weight, fat mass, lean mass, or behavioral changes, but it did improve glucose tolerance and insulin sensitivity. In contrast, transplantation of eWAT from obese animals containing senescent cells exacerbated metabolic dysfunction in obese animals. However, DTA-treated eWAT with $p21^{high}$ cell removal prevented these deleterious effects on metabolic dysfunction. In addition, the authors tested the effect of pharmacological elimination of $p21^{high}$ cells in human visceral white adipose tissue (VAT) from individuals with obesity. They used dasatinib and quercetin (D + Q) which have been reported to remove senescent cells (Palmer et al., 2019). D + Q-treated VAT from human individuals with obesity contained fewer $p21^{high}$ cells compared to vehicle treated VAT. D + Q also reduced proinflammatory SASP activation in VAT, implying that D + Q were able to clear senescent $p21^{high}$ cells from human tissue. Next, the authors examined whether senolytic therapy would lessen the detrimental effects of VAT on metabolic dysfunction. To test this, D + Q- or vehicle-treated human VAT was transplanted into immunodeficient mice (SCID-beige [severe combined immunodeficiency-beige] mice). Interestingly, transplantation of VAT from humans with obesity lowered glucose tolerance and insulin sensitivity in the recipient mice, while D + Q treated-VAT largely mitigated the harmful effect on metabolic phenotypes. Taken together, these ndings suggest that $p21^{high}$ cells in human VAT could be a target for senolytic agents and clearance of senescent cells could be a therapeutic strategy for alleviating obesity-induced metabolic dysfunction.

In summary, Wang et al. (2022) have suggested that P21-highly expressing senescent cells in the SVF of eWAT play crucial roles in obesity-induced metabolic dysfunction. Additionally, the NFκB pathway in $p21^{high}$ cells is suggested to be responsible for adipose tissue inflammation and systemic insulin resistance. Further, their study provides important insights that could help researchers understand the relationship between cellular senescence and metabolic disease. Particularly, the authors show that accumulation of senescent cells in eWAT contributes to impaired insulin sensitivity in obese animals. Moreover, $p21^{high}$ cells are increased only in eWAT while they are rarely detected in other metabolic tissues in obese mice. The study highlights senescent cells in eWAT are potential therapeutic targets and implies that senolytic agents could have potential in the treatment of metabolic disease.

Interestingly, there has been a recent report that expands the significance of cellular senescence in eWAT. In this study, obese adipocytes in eWAT exhibited a number of key senescence-related features including P21 expression, and aggravated metabolic dysfunction (Lee et al., 2022). Collectively, these findings demonstrate that eWAT could be a reservoir for senescent cells and suggest that cellular senescence in eWAT is a major cause of obesity-induced metabolic dysfunction. Nonetheless, it remains unclear how and why all the $p21^{high}$ cells are not senescent, and little is known about how P21 expression could affect cellular features, such as the inflammatory pathway. Additionally, the underlying mechanism by which $p21^{high}$ cells in eWAT would affect whole body

energy homeostasis needs to be further explored.

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CONFLICT OF INTEREST

The author has no potential conflicts of interest to disclose.

ORCID

Gung Lee https://orcid.org/0000-0002-0223-7955

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