Clinical Summary

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Palmer AK, Xu M, Zhu Y, et al. Targeting senescent cells alleviates obesity-induced metabolic dysfunction. Aging Cell 2019;18:e12950.

Quercetin Helps Target Pathways of Cell Aging and Survival

This preclinical study demonstrates that diet-related acceleration of cellular aging contributes to immune and metabolic changes seen in those with obesity. It further shows that strategic targeting of molecular networks associated with senescence may present a way of aiding immune balance and carbohydrate metabolism.

In weight gain, increased adiposity is accompanied by accelerated aging of fat tissue. This change is most marked in visceral adipose, where it cultivates a specific array of inflammatory changes that enable these fat cells to survive under the disadvantageous conditions. With the expansion of fat tissue, this pattern of altered cytokine production is known as a "senescence-associated secretory phenotype," or SASP. In adipose, having a SASP affects immune homeostasis and energy metabolism, with long-term health consequences.

A number of plant nutrients have long been studied for their effects on biological aging, and an emerging priority is the identification of natural and synthetic senolytic agents, which aid the elimination of overly-aged and damaged cells. The dietary flavonoid quercetin, for example, is known to target senescent cells within the endothelium of blood vessels. By aiding clearance of poorly functioning cells, senolytics have the potential to allow organs, in turn, to regain healthier function.

In previous studies, the researchers discovered that senescent cells depend on survival-oriented metabolic networks to avoid normal programmed cell death. In this experiment, mice with either high-fat diet-induced obesity or genetic predisposition to obesity were given a combination of two senolytic substances: quercetin and the drug dasatinib. During multiple courses of administration of these senolytics, animals were examined for functional and structural changes in vital organs, the abundance of senescent cells within adipose tissue, and alterations in animals' senescence-associated secretory phenotype (SASP).

The study's authors, led by pioneering senescence researcher Dr. James Kirkland, state that:

"Our results implicate cellular senescence as a causal factor in obesity-related inflammation and metabolic derangements, and show that emerging senolytic agents show promise."

Study Results

Researchers first confirmed that the abundance of senescent cells was increased in obese animals compared to controls, and they found that senescent cell burden was most concentrated in visceral adipose tissue. They then used the senolytic combination of quercetin and dasatinib to reduce senescent cell burden, employing them in an intermittent fashion that mimics the opportunistic occurrence of autophagy during periods of low food intake or heightened physical activity.

After repeated intermittent provision of the senolytic combination, the following was found:

- In obese animals, reducing senescent cell burden improved their metabolic phenotype
- Separately as well as together, quercetin and dasatinib induced programmed cell death in senescent cells without having significant effect on normal cells
- Clearing senescent cells improved glucose tolerance and reduced hemoglobin A1c (HbA1c) levels in affected animals
- The overall metabolic benefits were found to result mainly from increased insulin sensitivity after reduction of senescent cell burden
- Levels of numerous inflammatory mediators that contribute to the SASP, from acquired as well as innate immune cell lines, were ameliorated by reducing adipose senescent cell burden
- Some groups of treated animals also showed lower fat contents in muscle and liver tissue
- Immune cell migration into visceral adipose was decreased
- In some animals, improved cardiac and renal function was observed
- Senolytic substances improve elimination of senescent cells by each influencing a different set of molecular targets involved in cell aging and survival

CONCLUSION

In fat tissue, increased senescent cell burden appears to drive insulin resistance by cultivating a senescence-associated secretory phenotype (SASP) and encouraging immune infiltration of tissues, especially in metabolically sensitive visceral adipose. This innovative study highlights quercetin as a nutritional means of improving normal elimination of aged or damaged cells—an action that may also benefit healthy organ function.