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ADIPOSE TISSUE

Reversing age-related decline in beiging

> "...cold-induced beige adipocyte formation fails with age..."

Inducing the formation of metabolically active brown adipocytes in white adipose tissue, a process known as beiging, is a potential therapeutic strategy to treat obesity; however, the capacity of cells to undergo beiging declines with age. In new research, investigators have identified a mechanism that underpins this decline and have sought to reverse this decline using a pharmacological agent.

"We aimed to examine how beiging fails in an age-dependent manner and if we could rejuvenate beiging and thereby restore metabolic function," explains researcher Dan Berry. "Our study identifies that beige adipocyte progenitors undergo a cellular ageing/senescence-like phenotype that blocks their ability to form beige adipocytes in response to cold exposure."

The team found that the cold-induced beiging potential in mice begins to decline at 6 months of age and is completely absent by 1 year. As ageing induces cellular senescence, Berry and his colleagues investigated if this process underpinned the reduction in beiging potential. They found that stromal vascular cells from old mice expressed markers of cellular senescence (such as senescence-associated β-galactosidase, $p16^{Ink4a}$, $p19^{Arf}$ and p21). These findings were also replicated in stromal vascular cells from young and old BMI-matched humans.

The investigators then developed a mouse line in which they could selectively induce p21 in beige adipocyte precursors to induce senescence, which prevented the formation of beige adipocytes in young mice. Conversely, blocking the induction of senescence in beige adipocyte progenitors by deleting *Ink4a/Arf* reactivated cold-induced beiging of adipocytes in 12-month-old mice.

Finally, using an pharmacological inhibitor (SB202190) of the p38 MAPK pathway, which is an upstream regulator of the Ink4a/Arf pathway, the team reduced expression of senescence markers and re-enabled the beiging of adipose tissue in aged mice. SB202190 had a similar effect on human cells. "We identified that targeting the p38 MAPK–Ink4a/Arf pathway could rejuvenate aged beige progenitors to induce beiging," clarifies Berry.

The team hope that their findings will lead to the development of agents that enhance beiging in humans. "We are interested [in determining] if senolytic agents, which selectively induce senescent cell death, could restore beige progenitor cell health and function, and reignite cold-induced beiging potential," clarifies Berry.

Tim Geach

ORIGINAL ARTICLE Berry, D. C. *et al.* Cellular aging contributes to failure of cold-induced beige adipocyte formation in old mice and humans. *Cell Metab.* http://dx.doi.org/10.1016/j.cmet.2016.10.023 (2016)