Scientists identify molecular process in fat cells that influences stress and longevity

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C. Ronald Kahn, M.D., is Chief Academic Officer at Joslin Diabetes Center and the Mary K. Iacocca Professor of Medicine at Harvard Medical School. Credit: John Soares

As part of their ongoing research investigating the biology of aging, the greatest risk factor for type 2 diabetes and other serious diseases, scientists at Joslin Diabetes Center have identified a new factor—microRNA processing in fat tissue—which plays a major role in aging and stress resistance. This finding may lead to the development of treatments that increase stress resistance and longevity and improve metabolism. The findings appear in the September 5 online edition of

Cell Metabolism.

Over the past several years, it has become clear that fat cells (adipocytes) are more than just repositories to store fat. Indeed, fat cells secrete a number of substances that actively influence metabolism and systemic inflammation. Previous studies have found that reducing fat mass by caloric restriction (CR) or surgical or genetic means can promote longevity and stress resistance in species from yeast to primates. However, little is known about how CR and fat reduction produce these beneficial effects. This study investigated one type of molecular mediator – change in microRNAs (miRNAs) and the processing enzymes required to make them – that is influenced by aging and reversed by caloric restriction. miRNAs are involved in the formation of mature RNA.

Based on studies conducted using human cells, mice and C. elegans (a microscopic worm used as a model organism for aging studies), the researchers demonstrated that levels of multiple miRNAs, decrease in fat tissue (adipose) with age in all three species. This is due to a decrease in the critical enzyme required from converted pre-miRNAs to mature miRNAs, Dicer. In the human study, which compared the miRNA levels in preadipocytes (fat cell precusors) of young, middle-aged and older people, people aged 70 and older had the lowest miRNA levels. "The fact that this change occurs in humans, mice and worms points to its significance as a general and important process," says lead author C. Ronald Kahn, MD, Chief Academic Officer at Joslin Diabetes Center and the Mary K. Iacocca Professor of Medicine at Harvard Medical School.

Caloric restriction, which has been shown to prolong lifespan and improve stress resistance in both mice and worms, prevents this decline of Dicer, and in the case of the mice, restore miRNAs to levels observed in young mice. Conversely, exposure of adipocytes to major stressors

associated with aging and metabolic diseases, including toxic agents, Dicer levels decreased. Mice and worms engineered to have decreased Dicer expression in fat showed increased sensitivity to stress, a sign of premature aging. By contrast, worms engineered to "overexpress" Dicer in the intestine (the adipose tissue equivalent in worms) had greater stress resistance and lived longer.

Overall, these studies showed that regulation of miRNA processing in adipose-related tissues plays an important role in longevity and an organism's ability to respond to age-related and environmental stress. "This study points to a completely new mechanism by which fat might affect lifespan and is the first time that anyone has looked at fat and miRNAs as factors in longevity," according to co-author T. Keith Blackwell, MD, PhD, co-head of Joslin's Section on Islet Cell and Regenerative Biology and Professor of Pathology at Harvard Medical School.

Based on this study, Blackwell suggests that "finding ways to improve miRNA processing to keep miRNA levels up during aging might have a role in protecting against the stresses of everyday life and the development of age- and stress-related disease."

Dr. Kahn and the study investigators are currently working on ways to genetically control Dicer levels in the fat tissues of mice, to create mouse models that are more or less resistant to stress. "We would love to find drugs that would mimic this genetic manipulation to produce a beneficial effect," says Dr. Kahn. "If we can better understand the biology of aging, we might also understand how age impacts diabetes," says Kahn.

Provided by Joslin Diabetes Center

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