Scientists identify process that affects fat distribution and metabolic syndrome

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C. Ronald Kahn, M.D., is Chief Academic Officer at Joslin Diabetes Center. Dr. Kahn is co-head of the section on Integrative Physiology & Metabolism and the Mary K. Iacocca Professor of Medicine at Harvard Medical School. Credit: Joslin Diabetes Center

Building upon their earlier research on the biology of fat metabolism, Joslin scientists discovered that microRNAs –small RNA molecules that play important roles in regulation in many types of tissue – play a major role in the distribution and determination of fat cells and whole body metabolism. Also, the study is the first to reveal that microRNAs (miRNAs) influence the development of lipodystrophy (abnormal fat accumulation) which affects many people with HIV receiving anti-retroviral therapy. The findings appear in the August issue of the *Journal of Clinical Investigation*.

Previous Joslin studies have demonstrated that fat cells (adipocytes) have functions far beyond fat storage: they secrete substances that actively influence metabolism and are also a site of systemic inflammation leading to insulin resistance. The body has two types of fat – the more common white adipose fat (WAT), which stores fat; and brown adipose fat (BAT), which burns fat to produce heat. BAT plays a beneficial role in regulating body weight and metabolism, which has generated considerable interest among scientists and pharmaceutical companies looking for treatments for obesity. Excess WAT, on the other hand, especially in the intra-abdominal area, is associated with metabolic diseases, such as type 2 diabetes.

In the current study, Joslin scientists were interested in learning more about miRNAs and their role in the creation of fat cells and the function of brown and white fat. Earlier Joslin research revealed that with aging, miRNA processing in fat tissue decreases due to a decrease in Dicer, a critical enzyme that converts pre-miRNAs to mature miRNAs. Using a mouse model in which expression of Dicer was specifically knocked out in fat tissue, the researchers found that mice that lacked Dicer in fat developed abnormal fat distribution resembling HIV-related lipodystrophy (which is associated with antiviral treatment). In mice, this form of lipodystrophy was also characterized by "whitening" of brown fat cells, a loss of white fat, and signs of metabolic syndrome, including insulin resistance, fat tissue inflammation, dyslipidemia (elevated cholesterol and fat), increased resting energy use, and increased markers of cardiovascular disease.

The researchers also found lower Dicer levels in

the fat tissue of patients with HIV and HIV-related lipodystrophy, suggesting that low levels of Dicer expression in fat in HIV patients may contribute to the development of this syndrome, a complication which limits therapy in some people with HIV.

Together, these findings indicate an essential role for Dicer and miRNA processing in white and brown cell differentiation and whole body metabolism that may contribute to the development of HIV-related lipodystrophy. "It's good to build on our previous research on miRNA processing and Dicer in aging and find that a decline in Dicer may also play an important role in HIV lipodystrophy by dramatically changing the biology of fat and the tendency towards diabetes and metabolic syndrome," 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. "This research is a good example of how we go from the "bench" to the bedside and how discoveries in one area or research can lead to insights into other clinical disorders."

This research suggests that therapy with an agent that increases levels of Dicer or specific miRNA expression could be beneficial to people with metabolic syndrome. "If we could increase Dicer activity, fat tissue would have a healthier metabolism which would improve the metabolism of people being treated. It may also reduce the effects of changes in fat that cause insulin resistance and other symptoms of metabolic diseases, such as diabetes," Dr. Kahn says.

Dicer-related therapy might also help patients with HIV-related lipodystrophy. "In some people with HIV, lipodystrophy is so disfiguring that they alter or stop HIV therapy. If we could address the abnormal fat accumulation, people could continue their HIV therapies and get maximal benefit," Dr. Kahn says.

One possible agent that might increase Dicer levels is Rapamycin, an immunosuppressant used to prevent rejection in organ transplantation. Dr. Kahn and Joslin researchers are planning to investigate whether Rapamycin increases Dicer in cellular models.

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