Stem cells that generate fat tissue have circadian clock

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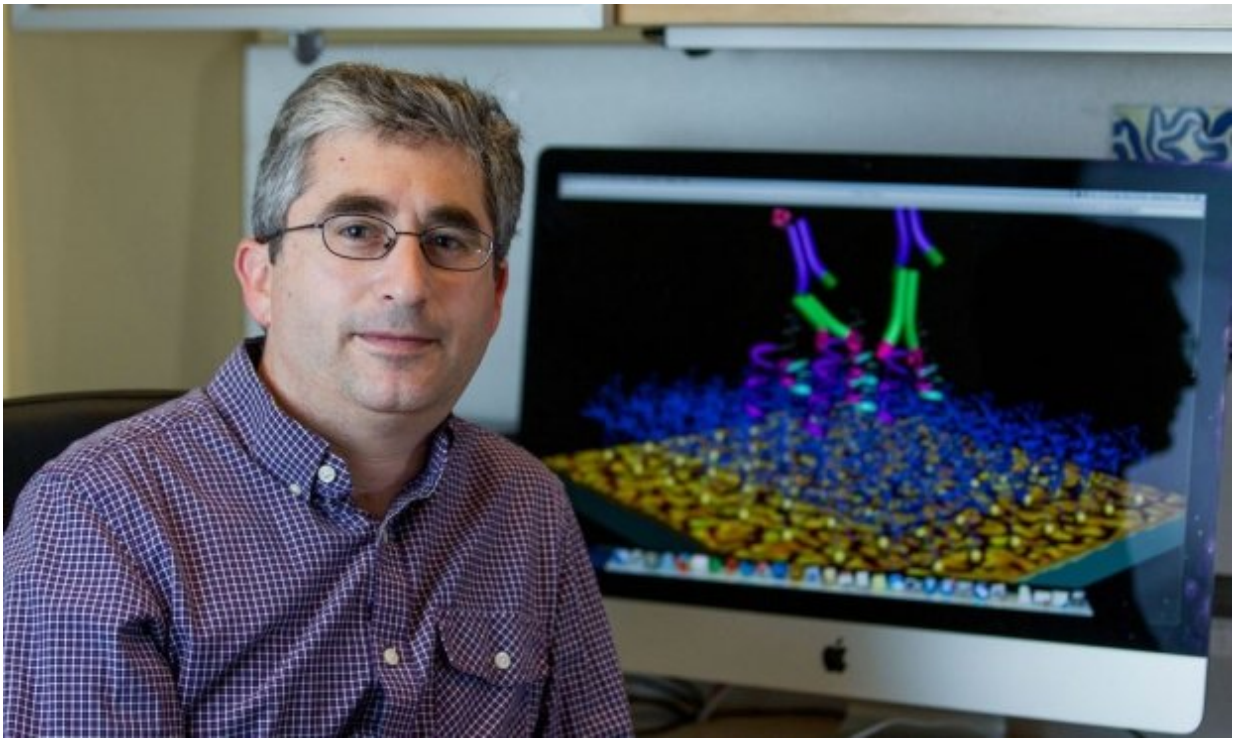

Brian Feldman and his colleagues found that stem cells that give rise to fat cells have a circadian clock. Credit: Norbert von der Groeben

New discoveries about the circadian-clock machinery in the precursors to fat cells may explain why shift workers are prone to metabolic diseases, such as diabetes, a Stanford study finds.

A circadian clock is embedded in the stem cells that give rise to fat and plays a decisive role in determining when the cells mature, according to a new study by researchers at the Stanford University School of Medicine.

The study, which was published online Nov. 28 in *Cell Reports*, shows that adipocyte precursor cells, as these stem cells are called, have a circadian clock that functions differently than the kind found in most of the body's other cells. Perturbing the clock changes the pace at which the cells turn into mature adipocytes, or fat cells. The discoveries could help explain why night-shift workers are at risk for metabolic diseases, such as diabetes.

"Before this study, we knew we could disturb someone's circadian clock and change their metabolism, but how that happened at a cellular and molecular level was very mysterious," said Brian Feldman, MD, PhD, senior author of the study and assistant professor of pediatrics at Stanford. Postdoctoral scholar Abhishek Aggarwal, PhD, and research assistant Maria José Costa PhD, share lead authorship.

Prior research had shown that mature fat cells have a circadian clock, but it was not known if a clock existed in their stem cells. The role of the clock in helping the cells decide when to mature was a surprise to the researchers.

A specific protein, a cog in the workings of the clock, drives the cells' differentiation process, Feldman's team found. "We think this mechanism prevents you from making adipocytes when you don't need to," he said.

Integrating hormone signals

Several hormonal signals that influence fat maturation are known to rise and fall in patterns throughout the day. Glucocorticoids, such as the

stress hormone cortisol, are typically highest just before waking. Insulin rises in response to meals. In a lab dish, adipocyte precursor cells can be induced to mature by adding large doses of glucocorticoids or insulin, but the cells do not mature every time the body experiences surges of these hormones in real life.

"The cells do not just take any one signal as 'go or no go' to differentiate," Feldman said. "Embedding a clock in the differentiation pathway integrates all the signals. They all have to be in alignment before the cells push forward."

In most cell types, the core circadian clock machinery consists of a family of proteins, whose levels oscillate over the course of the day, encoded by three genes: Per1, Per2 and Per3.

To look for a circadian clock in adipocyte precursor cells, Feldman's team needed to track the cells in living mice. They developed several strains of genetically modified mice for their experiments.

First, they used mice whose cells express luciferase, a fluorescent protein, whenever the Per2 gene is expressed, which they used to show that the adipocyte precursor cells do have a circadian clock; the cells exhibit daily oscillations in Per2 expression.

The team then studied what happened over a full day to expression of the three PER genes in mice that were kept in constant darkness. Keeping the animals in darkness enables researchers to separate intrinsic functions of the circadian clock from those that occur in response to external dark-light cycles.

To their surprise, the researchers saw that Per1, a core component of the circadian clock in most cell types, does not oscillate in adipocyte precursor cells. However, expression of both the Per2 and Per3 genes

oscillates in a daily rhythm. The oscillations of Per3 were intriguing because the gene previously had been considered unimportant, as mice lacking Per3 show no major changes in their sleep-wake patterns.

But follow-up experiments by Feldman's team demonstrated that Per3 plays a big role in adipocyte precursor cells. Mice lacking the Per3 gene had higher levels of fat-cell maturation than those with a functioning Per3 gene, and mice that overexpressed Per3 blocked fat cell maturation. The Per3 protein acts directly with another protein to regulate a gene known to begin the cells' maturation process, the researchers found.

Effects of shift work

Extensive research has shown that late-shift workers, who are awake at night and asleep during the day, are at increased risk for diabetes and obesity. But scientists have not known why.

"This work is connecting the dots of how altered biological rhythms can lead to metabolic derangement," Feldman said. In those who sleep at night, the adipocyte precursor cells' circadian clock guards against maturing too many fat cells. "But what happens in shift workers is that this ends up working against you," he said. "If the rhythm of making mature adipocytes is thrown off and you're not making adipocytes when you should, that may place you at greater risk for diabetes in the future."

Future research may address how the discovery could help prevent metabolic disease, Feldman said, though he cautioned that using the new discovery to prevent fat cells from maturing would not necessarily be desirable. Extra fat from the diet will go to other tissues if it cannot be stored in fat cells, and excess fat in locations such as the liver or muscle can be damaging.

The new research also illuminates a long-debated question: Should we

avoid snacking at night?

"I have to say, I think there's some truth to that," Feldman said. "I do think the timing of our meals is an overlooked factor; our bodies work best if we eat in defined periods during the day, and not during periods when we are not supposed to be active."

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