Scientists closer to finding what causes the birth of a fat cell

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Just what causes the birth of a human fat cell is a mystery, but scientists using mathematics to tackle the question have come up with a few predictions about the proteins that influence this process.

The research is intended to increase understanding of how and why preadipocytes, or pre-fat cells, either lie dormant, copy themselves or turn into fat. But the findings eventually could lead to a way to freeze these early cells in their current state before they can ever become the basis of fat tissue, according to Ohio State University researchers.

Every human body needs fat to store and produce energy, but in excess, the tissue made up of fat cells begins to secrete molecules that send out complicated signals. This process can lead to inflammation and, in turn, to insulin resistance or diabetes, and contributes to the development of other diseases.

The scientists focused on three proteins that are known to have an impact on the fate of preadipocytes - one protein that influences inflammation; another that drives the creation of fat cells; and a third that is involved in the proliferation, or copying, of almost all cells in the body.

A series of differential equations determined how the complex interactions among these three proteins would likely affect what happens to pre-fat cells, including conditions most associated with quiescence, or keeping those preadipocytes from turning into fat.

A better appreciation of this process could help researchers more fully understand the causes of disorders associated with excess fat, including obesity and insulin resistance.

"A potential benefit of figuring out this process is to see how we could manipulate certain parameters to arrest cells in this quiescent region, and that could have an effect on obesity," said Huseyin Coskun, a visiting assistant professor in the Department of Mathematics at Ohio State and lead author of the study.

"Obesity is certainly related to the types and amounts of foods people consume. But how the body responds to this can differ from one person to another, and could be related to some abnormalities in these protein interactions. The amount consumed may not be the only reason behind obesity. With this study, we started to understand how protein levels and complex molecular interactions in the body may influence the development of fat cells."

The research is published in a recent issue of the *Journal of Theoretical Biology*.

Coskun, a mathematician, began this project by reading hundreds of journal articles about the biology behind the transition of preadipocytes into adipocytes, or fat cells. He identified 16 proteins that appeared to be the most active in the process.

He and the research group, a team of math and biology experts, narrowed that number to three high-impact proteins as a starting point. Coskun then designed differential equations based on the biological model that would show how the pre-fat cells behaved under a variety of conditions, depending on the proteins' activity.

The three proteins are NF-kB, PPAR-gamma and cyclin D. NF-kB

initiates inflammation in tissue. PPAR-gamma must be present for adipogenesis, or the creation of fat cells, to occur. And cyclin D is responsible for cell proliferation, or copying and growth, in almost all cells, including pre-fat cells and fat cells.

"The three target proteins of this initial model are the most commonly studied, but their mutual relationships in relation to the creation of fat cells are still not well-known, so we are putting their roles together to see how they contribute to fat cell determination for the first time, as far as we know, in the literature," Coskun said.

The mathematical equations in which these three protein levels were manipulated resulted in a model that helped define the conditions under which pre-fat cells would remain dormant, start copying themselves or turn into fat cells. Two-parameter bifurcation curves are used for interpretation of model outcomes, which itself is a novel approach in terms of mathematical terminology.

The main parameters driving this model were two substances that affect the target proteins: a protein called IkB, which inhibits the inflammatory NF-kB protein, and the concentration of a chemical stimulant, called a mitogen, that stimulates production of cyclin D.

According to the model, if the level of IkB is high and the level of the cyclin D stimulant is low, the pre-fat cells remain dormant. The model then shows what is called a "curve of uncertainty," which predicts the circumstances that are required for preadipocytes to either remain dormant or proliferate in their current state. The region of uncertainty then determines the conditions for coexistence of a pair of these three states: differentiation and quiescence, or proliferation and differentiation.

The researchers also conducted preliminary experiments to test the

model's outcomes by exposing mouse cells to TNF-alpha, a mitogen that stimulates cyclin D. They found that the concentrations of the proteins in those cells generally behaved as the model suggested they would. In addition, previous research reports of similar experiments also support the model's outcomes, Coskun said.

He noted that more experiments are needed to further test the model, which also could be expanded to add more proteins to the equations.

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