Killing 'angry' immune cells in fat could fight diabetes

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By killing off "angry" immune cells that take up residence in obese fat and muscle tissue, researchers have shown that they can rapidly reverse insulin resistance in obese mice. The findings reported in the October *Cell Metabolism*, a publication of Cell Press, suggest that treatments aimed at specific subsets of the so-called macrophage cells might offer a very effective new antidiabetic therapy, according to the researchers.

" We used a genetic 'trick' that allowed us to rapidly kill these macrophages," said Jerrold Olefsky of the University of California, San Diego. "The treatment killed these cells within hours, and insulin resistance simply reversed itself. It argues strongly that macrophages are causative for the inflammation that leads to diabetes [in those who are obese]."

" The most interesting thing is that this reversal occurs very rapidly," added Jaap Neels of INSERM in France, who led the work while in Olefsky's lab. "Twenty-four hours later the animals' insulin response had completely normalized. They were still obese, but no longer insulin resistant."

Of course, Neels said, the strategy used in the obese mice wouldn't translate to the clinic directly. It's also unclear whether or not it is the same subtype of macrophage cells that invade fat tissue in people who are obese. Nevertheless, the findings suggest that you would not necessarily need to target all macrophages to have a beneficial effect on the diseases associated with obesity. That's critical because "you don't

want to knock out the whole immune system."

Over the past decade, it has become quite clear that obesity gives rise to a state of chronic, low-grade inflammation that contributes to insulin resistance and type 2 diabetes, the researchers explained.

Olefsky and Neels' team along with others recently found that a specific subset of macrophages invades obese fat and muscle tissue. Although little was known about them, those macrophages are defined by a CD11c marker expressed on their surfaces. They also produce high levels of proinflammatory chemicals that are linked to the development of obesity-associated insulin resistance.

In the new study, the researchers tested the idea that killing those cells would reverse the inflammatory symptoms that come with obesity using a mouse model developed earlier in which the CD11c-expressing macrophages were artificially made susceptible to diphtheria toxin.

They found that treatment with the toxin not only reversed the animals' resistance to insulin, but also led to a marked decline in inflammatory signs through the body. The treated animals showed a decline in the CD11c macrophages in both fat and muscle, they confirmed.

" It shows that high triglycerides in muscle don't necessarily have to lead to insulin resistance as it has been thought—as long as the high lipid levels aren't accompanied by inflammation," Neels said.

The obese mice also had less fat in their livers, an important find given the epidemic of obesity-associated fatty liver disease.

If a unique marker can be identified on the macrophages found in human fat tissue, a drug could be designed to take advantage of those features to bind and kill them, Neels said. Alternatively, it may be

possible to convert the macrophage cells into another, less inflammatory type.

Source: Cell Press