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Bacteria and fat: A 'perfect storm' for inflammation, may promote diabetes

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Making fat cells immortal might seem like a bad idea to most people, but for a team of University of Iowa scientists it was the ideal way to study how the interaction between bacteria and fat cells might contribute to diabetes.

The connection between fat, bacteria, and diabetes is inflammation, which is the body's normal reaction to infection or injury. Inflammation is beneficial in small, controlled doses but can be extremely harmful when it persists and becomes chronic.

"The idea is that when fat cells (adipocytes) interact with environmental agents—in this case, bacterial toxins—they then trigger a chronic inflammatory process," says Patrick Schlievert, Ph.D., UI professor and head of microbiology and co-senior author of a new study published Oct. 30 in the journal *PLOS ONE*. "We know that chronic inflammation leads to insulin resistance, which can then lead to diabetes. So people are very interested in the underlying causes of chronic inflammation."

The UI researchers used immortalized fat cells to show that bacterial toxins stimulate fat cells to release molecules called cytokines, which promote inflammation. By immortalizing fat cells the UI team created a stockpile of continuously dividing, identical cells that are necessary for repeat experiments to validate results, explains Al Klingelhutz, Ph.D., UI microbiologist and co-senior author of the study.

Previous studies have shown that a toxin called lipopolysaccharide (LPS)

produced by *E. coli* bacteria that reside in the human gut, triggers fat cells to produce pro-inflammatory cytokines, and this interaction has been proposed to contribute to the development of diabetes.

The UI team focused on a different bacterium, *Staphylococcus aureus* (staph), which appears to be important in the context of diabetes for two reasons. First, as people become obese and then progress into diabetes they become very heavily colonized with staph bacteria. Secondly, staph is the most common microbe isolated from diabetic foot ulcers, one of the most common and health-threatening complications of diabetes.

All staph bacteria make toxins called superantigens—molecules that disrupt the immune system. Schlievert's research has previously shown that superantigens cause the deadly effects of various staph infections, such as toxic shock syndrome, sepsis, and endocarditis.

The new UI study shows that superantigens from staph bacteria trigger fat cells to produce pro-inflammatory molecules. Moreover, the study found that superantigens synergized with LPS from *E. coli* to magnify fat cells' cytokine responses, amplifying the inflammation, which could potentially boost the likelihood of developing diabetes.

"The *E. coli* that resides in our gut produces LPS and every day a small amount of this toxin gets into our circulation, but it is generally cleared from the circulation by the liver. However, people colonized by staph bacteria are also chronically exposed to superantigens, which shut down the LPS detoxification pathway," Schlievert explains. "That creates a synergy between the 'uncleared' LPS and the superantigen. All these two molecules do is cause inflammation and cytokine production. So in essence, their presence together creates a perfect storm for inflammation."

The findings suggest that by promoting chronic inflammation through

their effect on fat cells, staph superantigens may play a role in the development of diabetes. In addition, the chronic inflammation caused by the superantigens may also hinder wound healing in diabetic foot ulcers. The ulcers, which affect 15 to 25 percent of people with diabetes, are notoriously difficult to heal and can often lead to amputation.

Why immortalize fat cells?

The UI team created immortalized fat cells for their research because primary fat cells (taken directly from fat tissue) are not very useful for lab experiments. Once the primary cells are grown in a dish, they quickly stop dividing and can't be used for repeated experiments. In contrast, the immortalized fat cells allow experiments to be repeated multiple times on identical cells ensuring consistent, reproducible results.

Klingelhutz and his team immortalized immature precursor fat cells by adding in two genes from HPV (the virus that causes cervical cancer) along with a gene for part of an enzyme that controls the length of cells' telomeres—the pieces of DNA that protect chromosome tips from deterioration. These immortal precursor cells could then be "grown up" in petri dishes and differentiated into normal fat cells.

"The immortal fat cells are a great experimental tool that will allow us to investigate the mechanisms of the inflammation and allow us to test ways to potentially inhibit the response," says Klingelhutz. "That would be a goal in the future."

More information: dx.plos.org/10.1371/journal.pone.0077988

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