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DIABETES

Plasma membrane key to diet-induced insulin resistance

Although a high-fat diet (HFD) is known to promote insulin resistance via chronic inflammation, the precise mechanisms leading to this pathological state have remained unclear. Now, in a new study published in *Nature*, Clay Semenkovich and colleagues show that endogenous fatty acid synthesis (*de novo* lipogenesis) in macrophages is required for the development of diet-induced insulin resistance as this process creates an environment at the plasma membrane conducive to cholesterol retention and the propagation of inflammatory signals.

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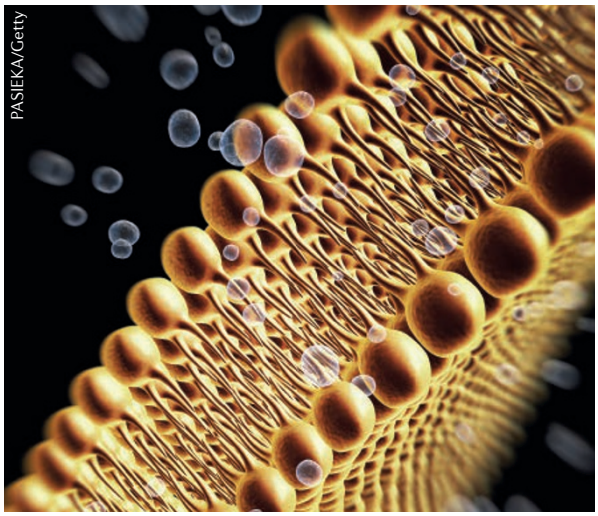
"For the past few years, we have pursued the idea that fatty acid synthase (FAS), which mediates *de novo* lipogenesis, channels lipids to specific intracellular sites to alter cell function relevant to complications of diabetes mellitus," explains Semenkovich. "In this study, we set out to determine if this process in macrophages impacts the chronic inflammation of obesity-related diabetes mellitus, as inflammation underlies many complications of this condition, such as limb amputations, heart attacks and strokes."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Using a combination of genetic manipulation of mice, metabolic phenotyping similar to that used in humans with diabetes mellitus, and cell biology techniques directed at how the plasma membrane is organized into domains that propagate inflammatory signals, the researchers uncovered a specific mechanism underlying diet-induced inflammation.

Mice with macrophages deficient in FAS (LysM–Cre-induced myeloid cell FAS-deficient mice) had better glucose tolerance on a HFD and lower blood glucose levels in response to insulin than wild-type control mice, despite all mice having a similar body weight and composition. FAS deficiency also prevented recruitment of macrophages to adipose tissue and chronic inflammation; steatosis and inflammatory gene expression were also decreased in the livers of HFD-fed FAS-deficient mice compared with control mice. In a second Cre-induced FAS-deficient mouse model (Tie2–Cre-induced endothelial and haematopoietic cell FAS-deficient mice), FAS deficiency also protected against diet-induced insulin resistance and inflammation, consistent with FAS promoting macrophage activation and diet-induced insulin resistance.

Next, Semenkovich and his team showed that FAS deficiency altered the order and composition of specific domains within the plasma membrane, whilst preserving whole-membrane integrity. In FAS-deficient macrophages, levels of 534 of 794 proteins were reduced by >40% in detergent-resistant microdomains (DRMs), while only 17 of 681 proteins were reduced by >40% in whole membranes. Levels of glycerophospholipids were also lower in detergent-resistant microdomains than in whole membranes. Moreover, FAS deficiency impaired the retention of cholesterol in the plasma membrane and disrupted Rho GTPase trafficking and JNK activation, which are mediators of the inflammatory response. Importantly, loading of FAS-deficient macrophages with exogenous cholesterol rescued inflammatory signalling and restored FAS-induced perturbations in membrane structure.

"It turns out that when macrophages are exposed to extracellular fatty acids, they must synthesize intracellular fatty acids to generate an inflammatory response," comments Semenkovich on the significance of their findings. "The newly synthesized fat is channelled to the plasma membrane, where it creates an environment that retains cholesterol, which is required for assembling signalling complexes that mediate the inflammatory response and lead to insulin resistance."

Although the findings support the potential of FAS inhibition to treat diabetes mellitus, global inhibition of this enzyme could have unintended adverse effects owing to the pleiotropic effects of FAS. "Defining how lipids are channelled inside the cell could reveal better targets and lead to new therapies for diabetes mellitus and its complications," speculates Semenkovich.

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ORIGINAL ARTICLE Wei, X. *et al.* Fatty acid synthesis configures the plasma membrane for inflammation in diabetes. *Nature* http://dx.doi.org/10.1038/nature20117 (2016)