Saturated Fatty Acids and Inflammation: Who Pays the Toll?

Alan Chait, Francis Kim

Since the discovery that obesity is associated with macrophage accumulation in adipose tissue, mechanisms by which adipose tissue becomes inflamed, resulting in insulin resistance, have remained elusive. Several studies have demonstrated that saturated fatty acids (SFAs) stimulate adipose tissue inflammation by a process that involves Toll-like receptor 4 (TLR4), a receptor that binds bacterial lipopolysaccharide (LPS). TLR4 is a pattern recognition receptor that plays a key role in the innate immune response. The observation that TLR4 deficiency protected against insulin resistance suggested that TLR4 was the link between diet excess and insulin resistance. Attenuation of diet-induced insulin resistance suggested that TLR4 deficiency protected against insulin resistance. 

In vitro studies have shed light on how SFAs lead to adipose tissue inflammation. TLR4 activation by SFAs increases the expression of a number of inflammatory genes in adipocytes by a nuclear factor κB–dependent mechanism, similar to TLR4 activation by LPS. SFAs also stimulate inflammatory molecules in macrophages. TLR4’s critical role has been demonstrated by silencing TLR4 expression in macrophages. On the basis of coculture experiments, macrophages recruited into adipose tissue by SFAs have also been observed in C3H/HeJ mice with a loss of function mutation in TLR4.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Schwartz et al provide a new light on how SFAs cause adipose tissue inflammation. In this study THP-1 monocytes and human monocytes and macrophages exposed to SFAs demonstrated enhanced interleukin-8 and interleukin-6 expression in response to low dose LPS. Amplification of the LPS response required metabolism of the SFAs to ceramide, and it involved activation of C-κB mitogen-activated protein kinase. It demonstrates a novel way by which fatty acids might modulate the innate immune response, ie, by their metabolites cooperatively enhancing TLR/nuclear factor κB–mediated inflammation. LPS frequently circulates at low concentrations in the bloodstream because of absorption from the bacterial flora of the gut, subclinical infections, or food contamination. The simultaneous ingestion of foods rich in SFAs might amplify stimulation of inflammatory gene expression in macrophages. Minimal contamination of reagents with LPS might also explain some of the in vitro findings with SFAs. However, they do not explain why some fatty acids have no effect whereas others inhibit inflammatory gene expression because they all are complexed with albumin, the most likely source of LPS contamination.

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Deficiency of TLR4, confined to macrophages, was not associated with a reduction of macrophage accumulation in adipose tissue or insulin resistance in response to a SFA-rich diet in mice. However, total body TLR4 deficiency or a nonfunctional mutation of the TLR4 gene was associated with reduced insulin resistance and macrophage accumulation in response to a high-fat diet. If the findings with deficiency of TLR4 in macrophages are confirmed, this suggests that TLR4 on adipocytes rather than macrophages might play an important role in macrophage accrual and insulin resistance in response to a diet rich in SFAs. One way that this might work is by adipocytes generating monocyte chemotactic factors, which play an important role in macrophage accumulation and insulin resistance in adipose tissue. Activation of TLR4 by SFAs on endothelial cells may also lead to insulin resistance at sites such as the artery wall, perhaps suggesting a common mechanism for fatty acid-induced insulin resistance in several cells, such as adipocytes, B cells, and myocytes. The current study thus adds a new level of complexity to an evolving story concerning the role of dietary SFAs in the pathogenesis of insulin resistance. Future studies concerning the interplay of fatty acids, LPS, and TLRs are likely to further unravel the intricate web that leads to adipose tissue inflammation.

Disclosures

None.

References

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