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Diet and leukocytes[1,2]

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In this issue of the Journal, Erridge et al (1) cited work from several laboratories on postprandial activation of blood leukocytes. The evidence of leukocyte activation in these studies includes increases in circulating leukocytes (neutrophils, lymphocytes, and platelets), activation of the transcription factor nuclear transcription factor κB (NF-κB) in peripheral blood mononuclear cells, increased expression of tumor necrosis factor-α (TNF-α) in monocytes, and alterations in some surface adhesion molecules in neutrophils and monocytes (eg, increased surface levels of CD11B, the α-subunit of one member of the β_2 integrin family). The test diets that apparently induced these changes were high in fat (eg, butter or cream), glucose, or mixed carbohydrates and fats. The mechanisms for this acute postprandial activation of inflammation are unclear. Ting et al (2) recently reported that triacylglycerol-rich lipoproteins isolated from 3.5 h postprandial blood significantly augmented TNF-α–dependent activation of endothelial cells, which resulted in the expression of adhesion molecules capable of capturing monocytes under conditions of fluid shear. Erridge et al provide evidence of postprandial elevations in venous blood samples of endotoxin (lipopolysaccharide), a cell wall component derived primarily from Gram-negative bacteria. Published evidence (cited by Erridge et al) from animal models and human investigations is consistent with endotoxin release from the gut. Given the fact that leukocytes, particularly monocytes, and endothelial cells express the Toll-like receptor 4 (TLR4) complex, a key cell surface–signaling receptor for endotoxin, postprandial elevations in blood endotoxin may contribute to leukocyte and endothelial activation. Shi et al (3) raise additional considerations. They showed that the saturated free fatty acids (FFAs) lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0) stimulate macrophage activation of NF-κB and expression of proinflammatory cytokines. These responses were largely dependent on the TLR4 receptor complex. Thus, postprandial activation of inflammation appears multifactorial, possibly involving several potential agonists for the TLR4 receptor complex as well as other mechanisms.

Heightened interest in the TLR4 receptor complex comes from observations that mice deficient in TLR4 are substantially protected against high-fat diet–induced vascular inflammation (4), insulin resistance, and expression of proinflammatory cytokines in adipose tissue and liver (3, 5). If high-fat meals provoke repeated surges in TLR4 agonists such as endotoxin, saturated FFAs, and other factors that induce endothelial capture of leukocytes and if tissue cells expressing the TLR4 receptor complex are activated to release proinflammatory cytokines and chemokines, the emigration of leukocytes (eg, monocytes) into tissues is not unexpected. Lumeng et al (6) and Weisberg et al (7) published evidence of the emigration of proinflammatory macrophages in adipose tissue in an animal model, and other investigators have observed macrophages in human adipose tissue, especially omental adipose tissue (8). Suganami et al (5) analyzed the potential interplay between adipocytes and macrophages by using a coculture setting in vitro. They found that coculture induced significant release of FFAs by adipocytes and significant increases in proinflammatory cytokines from macrophages. The FFAs from adipocytes were capable of activating macrophage NF-κB in a TLR4-dependent manner, and mice deficient in TLR4 had significantly reduced proinflammatory cytokine production from adipose tissue. Thus, mounting evidence from animal models positions TLR4 as a critical link in the proinflammatory aspects of obesity. That this apparent link could be simply triggered by the availability of TLR4 ligands such as endotoxin was recently questioned by Tang et al (9). They proposed that, under normal conditions, many cells expressing TLR4 do not respond readily to TLR4 agonists but must be released from "constitutive suppression." They provided evidence that neutrophil elastase potentiates TLR4 responsiveness and that endogenous ligands for TLR4, such as heparan sulfate, a ubiquitous component of tissue matrix, will induce TLR4-dependent activation in the absence of exogenous agonists. They found that treatment of mice with amounts of elastase insufficient to directly activate responses greatly augmented inflammatory responses to exogenous TLR4 agonists. There may be, therefore, reason to consider diet-induced activation of neutrophils (a source of elastase) as a step in the inflammatory cascade where TLR4 is a link.

Investigation of blood leukocytes and soluble inflammatory markers in humans will certainly yield insights into diet-activated inflammatory pathways, but an important complexity that must be addressed is the diversity of leukocyte subsets. The functional significance of changes in activation signals detected

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in mixed populations of leukocytes is obscured by the diversity of cell types. To date, no studies have dealt with this issue in sufficient detail. Neutrophils, lymphocytes, and platelets show postprandial increases in number, and neutrophils express activation markers. Platelets have received little attention, although they have been shown to play critical roles in many inflammatory responses (10). Several investigations have studied peripheral blood mononuclear cells, a substantial fraction of blood leukocytes that contains numerous subsets of lymphocytes and monocytes with both pro- and antiinflammatory activities. T lymphocyte subsets have been observed in adipose tissue in obese humans (11). Even studies focusing on isolated monocytes are confounded by the fact that subpopulations exist with different response capabilities and functions (12). For example, one population expresses a receptor (CCR5) that is capable of recognizing the chemokine CCL5, produced by adipose tissue in response to a high-fat diet (11). Another subpopulation of monocytes lacks this receptor. Edwards et al (13) defined 3 activation pathways for macrophages in response to different combinations of cytokines with and without TLR4-dependent signaling. Two pathways result in macrophages that produce antiinflammatory factors, and one pathway results in macrophages that produce predominately proinflammatory factors. A subset referred to as "alternatively activated" macrophages can produce high concentrations of interleukin 10, a cytokine that protects adipocytes from TNF-α–induced insulin resistance (6). Studies in an animal model indicate that this population assists in counterbalancing the proinflammatory effects of a high-fat diet (14). Sorting out the effects of dietary stimuli on these various subsets of leukocytes in humans will be a substantial effort, but future studies of defined leukocyte populations can be facilitated by the ready availability of marker antibodies and isolation techniques.

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