See corresponding articles on pages 1278 and 1287.

Is the fatty acid composition of immune cells the key to normal variations in human immune response?[1,2]

Susanna Cunningham-Rundles

Current interest in the effect of fats on human immune response is centered on the possibility that altering dietary intake could have a beneficial effect on a wide range of inflammatory and autoimmune disorders and lead to the prevention of these conditions (1). Atherosclerosis is now being considered an inflammatory disease that is mediated by immune cell activation and recruitment (2), and the interactions between lipids and cytokines such as tumor necrosis factor α, interleukin 1β (IL-1β), IL-6, and IL-8 are under investigation (3). Studies in humans with inflammatory conditions such as Crohn disease or rheumatoid arthritis suggest that both the amount and the type of fat are critical regulators of immune response (4). In contrast, few studies have examined the possible association between fat intake and variability in the normal immune response or to determine whether a modest change in dietary fat intake might affect immune response. Findings from the investigations of Kew et al (5, 6) published in this issue of the Journal address these questions and provide some interesting answers.

In the first of these articles, Kew et al (5) report that measures of both innate and adaptive functional immunity were directly associated with immune cell phospholipids and were independent of body mass index, age, or sex, which have otherwise been linked to observed variation in immune response among apparently healthy persons. Many correlations with specific fatty acids were found in the course of analysis and are likely to engender further study. Some other general observations are of particular interest. Phagocytic activity and neutrophil oxidative burst response were negatively related to the ratio of saturated fatty acids (SFAs) to polyunsaturated fatty acids (PUFAs) and to the ratio of n−6 to n−3 PUFAs, but they were positively affected by increases in total dietary n−3 and n−6 PUFAs. These innate immune functions are critically important for bacteria clearance, and they require both membrane functionality and signal transduction to activate the NADPH oxidase enzyme system. The proliferative response to stimulated mitogen and cytokine production was similarly affected, and there was some indication of activator-specific effects that might reflect different activation pathways. Intriguingly, dietary intake was unrelated to the proportions of SFAs and PUFAs in membrane composition, which showed higher concentrations of linoleic acid in women and no sex differences in n−6 PUFAs, despite significantly higher intakes of both in men. Thus, membrane composition but not current dietary intake was directly linked to variations in normal immune response.

In the second of their articles, Kew et al (6) found no correlation between modestly increased dietary PUFA intake and the immune response. This placebo-controlled study was designed to assess the longer-term effects of diets enriched in α-linolenic acid (ALA) or in both eicosapentaenoic acid (EPA) and decosahexaenoic acid (DHA), which were equalized for vitamin E according to double bonds. Although dietary ALA was increased by 3- to 6-fold, the proportion of this PUFA was not increased in peripheral blood mononuclear cells (PBMCs), whereas the derived product, EPA, was increased and DHA was decreased over the 6-mo period of study. Increases in PBMC concentrations of EPA accompanied by some increase in DHA and followed by decreased concentrations of arachidonic acid (AA) were observed in the EPA+DHA groups. This study found that increasing ALA intake well above usual levels but still well below levels reported to be suppressive did not alter measures of immune response. The significance of altered n−6:n−3 PUFAs in this diet is unclear. Similarly, the increased intake of EPA+ DHA altered the n−6:n−3 PUFAs, whereas the ratio of linoleic acid to ALA remained constant. This diet also did not affect the immune response in healthy subjects. Taken together, these 2 studies strongly suggest that membrane phospholipid composition has a major regulatory effect on immune response, which develops over time and is closely controlled by host factors rather than being a simple reflection of dietary intake.

The immunosuppressive effects of a high-fat diet in healthy humans can be inferred from studies showing that reduction of fat from a baseline level of ≈35%–40% to ≈25% of total energy intake enhanced the proliferative response of PBMCs to a standard mitogen in vitro (7). One inference from that study may be that fats can act as negative regulators of immune response. That function may have a protective effect in a healthy host, but negative effects may predominate in situations of enhanced risk. Recent studies have shown that the type of fat—whether saturated or unsaturated and, if unsaturated, whether hydrogenated and high in *trans* fatty acids—has a major effect on cytokine production. Thus, short-term dietary consumption of hydrogenated fats high in *trans* fatty acids by human volunteers who had moderately elevated cholesterol at baseline led to increased production of the proinflammatory cytokines tumor necrosis factor α and IL-6 when immune response was studied in vitro (8).

Ideas about how fats work have undergone vast changes over the past 2 decades. Human studies showed that fatty acid metabolism is linked to the immune system through effects on eicosanoids

[1] From the Immunology Research Laboratory, Department of Pediatrics, The New York Presbyterian Hospital–Cornell University Weill Medical College, New York.

[2] Address reprint requests to S Cunningham-Rundles, Cornell University Weill Medical College, 1300 York Avenue, New York, NY 10021. E-mail: scrundle@mail.med.cornell.edu.

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(prostaglandins, leukotrienes, and thromboxanes). Prostaglandin E_2 and other prostaglandins in particular are major regulators of immune response and are modulated by dietary fatty acids through the metabolism of AA. These complex interactions affect inflammation and the immune response (9, 10). Although the general effects of fats on immune response occur at the level of cellular function and include apparently nonspecific physical effects, such as plasma membrane fluidity, immune cell types might be expected to respond in a differential fashion according to function and activation state, and this would determine receptor signaling and transduction pathways. The effects of PUFAs are increasingly being differentiated according to their source and type as well as by specific cellular immune functions such as antigen presentation and the initiation of immune response (11). Fish oil–derived long-chain n−3 PUFAs act to decrease both helper T (Th)-1 and Th-2 cytokine responses as shown at the mucosal level, whereas plant-derived borage oil rich in PUFAs increases Th-1 cytokine response and decreases Th-2 cytokine response (12). Further studies investigating the interactions between fatty acids and the immune response in healthy humans under physiologic conditions such as those presented here are critical for the future development of this emerging field.

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