NUTRIENT SIGNALING: EVOLUTIONARY ORIGINS OF THE IMMUNE-MODULATING EFFECTS OF DIETARY FAT

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ABSTRACT

Many dietary fatty acids (FA) have potent effects on inflammation, which is not only energetically costly, but also contributes to a range of chronic diseases. This presents an evolutionary paradox: Why should the host initiate a costly and damaging response to commonly encountered nutrients? We propose that the immune system has evolved a capacity to modify expenditure on inflammation to compensate for the effects of dietary FA on gut microorganisms. In a comprehensive literature review, we show that the body preferentially upregulates inflammation in response to saturated FA that promote harmful microbes. In contrast, the host often reduces inflammation in response to the many unsaturated FA with antimicrobial properties. Our model is supported by contrasts involving shorter-chain FA and omega-3 FA, but with less consistent evidence for trans *fats, which are a recent addition to the human diet. Our findings support the idea that the vertebrate immune system has evolved a capacity to detect diet-driven shifts in the composition of gut microbiota from the profile of FA consumed, and to calibrate the costs of inflammation in response to these cues. We conclude by extending the nutrient signaling model to other nutrients, and consider implications for drug discovery and public health.*

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INTRODUCTION

CLASSICALLY, fatty acids (FA) have been understood as influencing risk for cardiovascular disease through effects on circulating lipoprotein cholesterol profiles (Remig et al. 2010). Saturated FA tend to elevate low-density lipoprotein cholesterol, while polyunsaturated fatty acids (PUFA) increase high-density lipoprotein cholesterol and reduce trigylcerides (Schaefer 2002). Although these effects on circulating lipids are well established, dietary fats have additional effects on inflammation that are important in the progression of many chronic degenerative diseases (Ridker et al. 2000; Kennedy et al. 2009). In particular, consumption of saturated fats has been associated with the metabolic syndrome and heart disease, while unsaturated fats, particularly the omega-3 PUFA, generally have the opposite effects (Esposito and Giugliano 2006).

Although these inflammatory effects of certain dietary fats are increasingly appreciated, the ubiquity of the body's inflammatory and metabolic response to foods poses a mystery. Because organisms are limited in the pool of energy and substrate available to allocate across the body's various functions, it follows that expenditure on one function necessarily comes at a cost to others (Williams 1966; Stearns 1992). As a result, organisms will tend to evolve strategies that avoid mobilizing costly functions without a reason. Inflammation involves production of toxic oxygen species, acute phase reactants, and chemokines that recruit and activate macrophages, representing a costly mobilization of host resources (Lochmiller and Deerenberg 2000; Zuk and Stoehr 2002; McDade 2003; Hanssen et al. 2004; Sorci and Faivre 2009). The mystery of widespread and costly diet-induced inflammation is further highlighted by the variety of diseases, including obesity, metabolic syndrome, diabetes, and atherosclerosis, which are worsened by chronic inflammation (Ridker et al. 2000; Esposito and Giugliano 2006). Thus, we are faced with an evolutionary paradox: why should the host initiate a costly and injurious response to commonly encountered nutrients?

In this paper, we hypothesize that the inflammatory effects of saturated FA and the anti-inflammatory effects of many unsaturated FA are not accidents, but instead reflect the evolution of host immune responses to dietary signals of impending shifts in gut microbiota and related risks of infection. This hypothesis emerges from the observation that nutrients are not simply energy sources for the host, but also influence the growth and invasiveness of microorganisms in the gastrointestinal tract (Keeney and Finlay 2011; Wu et al. 2011). Dietary FA, in particular, have important effects on gut microbiota, with some FA providing innate defenses against pathogens, while others promote pathogen colonization and growth. As we outline below, these various effects of FA on gut microbiota suggest a novel hypothesis to explain the health effects of dietary fats.

We first review the pathways by which specific FA promote or inhibit the survival and growth of species of bacteria and that influence translocation of bacteria into the host circulation. Based on these effects, we outline a hypothesis for the evolution of inflammatory and anti-inflammatory responses that depend on FA chain length and the nature of double bonds between carbon atoms. We next systematically review the relevant literature to test these hypotheses, finding 67 published studies of FA antimicrobial activity and 56 published studies of direct FA effects on inflammation that meet our inclusion criteria. We conclude by extending our model to carbohydrates and micronutrients, outline testable hypotheses, and consider the broader implications for human nutrition, drug discovery, and public health.

HOW DIETARY FATTY ACIDS AFFECT THE IMMUNE SYSTEM AND GUT MICROBIOTA

MODULATION OF INFLAMMATION BY DIETARY LIPIDS

Dietary fats generally occur as triglycerides, which consist of a glycerol backbone joined to three FA. Lipases in the mouth and gastrointestinal tract hydrolyze triglycerides into mono- and diglycerides and free FA. All of these fat-like compounds are described by the term "lipids," which also

TABLE 1
Nomenclature and dietary sources of fatty acids

Saturation Status	Subtype	Double Bond Position	Double Bond Configuration (*trans* or *cis*)	Common Name	Lipid Number	Representative Dietary Source
Saturated (no double bonds between carbons)	Short-/Medium-Chain ≤12 carbon chain length (SCFA/MCFA)			Butyric acid	C4:0	Butter, Parmesan cheese
				Caproic acid	C6:0	Goat Milk
				Caprylic acid	C8:0	Milk
				Capric acid	C10:0	Coconut
				Lauric acid	C12:0	Coconut, Breast milk
	Long-Chain >12 carbon chain length			Myristic acid	C14:0	Butter, Nutmeg
				Palmitic acid	C16:0	Palm oil
				Stearic acid	C18:0	Animal fat
Unsaturated (at least 1 double bonds between carbons)	Monounsaturated 1 carbon-carbon double bond (MUFA)		*cis*	Myristoleic acid	C14:1	Milk fat (uncommon)
			cis	Palmitoleic acid	C16:1	Animal fat, Macadamia oil
			cis	Oleic acid	C18:1	Olive oil
			cis	Ricinoleic acid	C18:1	Castor oil
			trans	*trans* Vaccenic	C18:1	Dairy products
	Polyunsaturated > 1 carbon-carbon double bond (PUFA)	Omega-6 (final double bond on 6th carbon from methyl end)	all *cis*	Linoleic acid	C18:2	Corn oil
		Omega-6	all *trans*	Linolelaidic	C18:2	Hydrogenated vegetable oil
		Omega-3 (final double bond on 3rd carbon from methyl end)	all *cis*	Linolenic acid	C18:3	Flaxseed oil
		Omega-6	all *cis*	Gamma linolenic acid	C18:3	Evening primrose oil
		Omega-6	all *cis*	Arachidonic acid	C20:4	Eggs
		Omega-3	all *cis*	Eicosapentaenoic acid	C20:5	Salmon, Seaweed
		Omega-3	all *cis*	Docosahexanoic acid	C22:6	Marine fish oils

Note: The numeral following the "C" indicates the number of carbons in the fatty acid. The numeral following the colon indicates the number of double bonds in the fatty acid (degree of unsaturation).

includes phospholipids and cholesterol. A taxonomy of FA and their dietary sources is displayed in Table 1. Diet-derived FA can have markedly different effects on human health and immune activation depending on their structure (Tables 2 and 3). Fatty

TABLE 2
Effects of dietary lipids on human cardiovascular disease and cardiac risk factors

Lipid Class	Effect	References
Long-chain saturated	Increased risk of obesity, metabolic syndrome	(Mozaffarian et al. 2010)
	Increased risk of cardiovascular disease	(Hu et al. 1999)
Short- and medium-chain saturated	No increased risk of cardiovascular disease	(Hu et al. 1999)
	Decreased metabolic syndrome, improved insulin sensitivity	(Nagao and Yanagita 2010)
Polyunsaturated	Reduced cardiovascular risk	(Mozaffarian et al. 2010)
	Reduced obesity and improved insulin sensitivity	(Summers et al. 2002)
Omega-3 polyunsaturated	Reduced cardiovascular risk	(Einvik et al. 2010)
	Improved insulin sensitivity	
Trans unsaturated	Increased risk of cardiovascular disease	(Remig et al. 2010)
	Increased diabetes	(Kummerow 2009)

acids affect inflammatory gene expression in humans by regulating transcription factors such as nuclear factor kappa B (NF-κB) or peroxisome proliferator-activated receptors (PPAR). Gene expression is also modulated by fatty acid-sensing G-protein receptors and signal transduction pathways that depend on membrane lipids and lipid rafts (Jump 2004). Through these pathways, some saturated FA (lipids with carbon chains that are fully saturated with hydrogen atoms) amplify proinflammatory gene expression in innate immune cells (Schwartz et al. 2010). Saturated FA have wide-ranging effects on inflammation, including activation of monocytes, oxygen radical production in vascular endothelial cells, and insulin resistance in muscle and other tissues. By contrast, unsaturated FA, particularly the omega-3 PUFA, have been shown to reduce the activity of NF-κB, PPARs, and membrane-dependent protein kinases, thus decreasing the downstream expression of inflammatory genes (Zhao et al. 2007; Wong et al. 2009; Holzer et al. 2011). As one example, a recently characterized G-protein receptor was shown to act as a sensor for omega-3 PUFA in human and mouse intestinal and adipose cells (Miyauchi et al. 2010); its activation inhibited NF-κB with anti-inflammatory effects in mice (Oh et al. 2010). There are several important exceptions to this general pattern of increased proinflammatory signaling by saturated FA and inhibition of inflammation by unsaturated FA. Some short-chain fatty acids (SCFA), although fully saturated, have the capacity to reduce inflammation in human cells (Hoshimoto et al. 2002; Wanten et al. 2002). Meanwhile, many omega-6 PUFA, although unsaturated, have been reported to generate metabolites and induce gene expression with proinflammatory effects (Teitelbaum and Walker 2001).

How Dietary Fatty Acids Modify Risk of Bacterial Invasion in the Gut

Although the inflammatory effects of FA are well documented, it is less well appreciated that they also influence bacterial survival and proliferation in the gastrointestinal tract. Besides serving as a potential growth substrate and carbon source, a key mechanism by which FA affect bacterial growth and invasiveness is their ability to break down the microbial cell membrane (Chen et al. 2011). FA have a methyl group and a carboxyl group at each terminus and vary in the length of their carbon chains and in the presence of double bonds (Figure 1). Some of these structural features give antibacterial, antifungal, and antiprotozoan activity to FA (Desbois and Smith 2010). Antimicrobial effects of lipids are incompletely understood, but appear to exert their effect, in part, by modifying membrane fluidity and disrupting cell membranes of certain bacteria (Desbois and Smith 2010; Chen et al. 2011).

Some bacteria are sensitive to membrane-destabilizing effects that occur after the incorporation of exogenous FA into membrane phospholipids. Increased membrane fluidity

TABLE 3

Comparing the direct effects of lipids of different classes on inflammation and immune function in human cells and platelets

Lipid Class	Comparison	Lipid Class	Human Cell Type and Pro-inflammatory Effect	References
Saturated	>	Unsaturated	adipocyte inflammatory gene expression	(Yeop Han et al. 2010)
			colonocyte NF-κB and PglyRP3 gene expression	(Zenhom et al. 2011)
			endothelial cell adhesion molecule expression	(De Caterina et al. 1998)
			endothelial cell free radical (superoxide) production	(Richard et al. 2008)
			endothelial cell adhesion molecule expression	(Goua et al. 2008)
			endothelial cell IL-6 inflammatory chemokines	(Krogmann et al. 2011)
			endothelial cell IL-6 mRNA expression	(Staiger et al. 2004)
			endothelial cell ICAM-1 expression	(Harvey et al. 2010b)
			endothelial cell PAI-1 expression	(Nilsson et al. 1998)
			keratinocyte PPAR γ antagonism and COX-2 expression	(Chêne et al. 2007)
			lymphocyte TNFα, IL-1β expression	(Karsten et al. 1994)
			macrophage NF-κB activation	(Laine et al. 2007)
			macrophage TNFα, IL-8, IL-1β expression via JNK	(Håversen et al. 2009)
			monocyte JNK IL-8 and monocyte inflammatory protein	(Choi et al. 2011)
			monocyte tissue factor activity	(Crutchley 1985)
			monocyte inflammatory gene, IL-6 expression	(Schwartz et al. 2010)
			monocyte chemotactic protein-1 and TNFα production	(Kopp et al. 2009)
			monocyte IL-6, IL-1β, TNFα production	(Zhao et al. 2005)
			monocyte MAPK LOX-1 expression	(Ishiyama et al. 2010)
			monocyte IL-1 production	(Baldie et al. 1993)
			myotube PPAR γ coactivator 1α gene inhibition	(Staiger et al. 2005)
Saturated	< =	Unsaturated	endothelial cell PPAR α MCP-1 expression	(Shaw et al. 2007)
			endothelial cell superoxide production	(Horani et al. 2006)
			neutrophil superoxide production	(Hardy et al. 1994)
			neutrophil superoxide production	(Badwey et al. 1984)
			neutrophil superoxide production	(Li et al. 1996)
Long-Chain Saturated	>	Short-/Medium-Chain Saturated	colonocyte production of IL-8	(Hoshimoto et al. 2002)
			epithelial cell inflammatory cytokine production	(Peterson and Schlievert 2006)
			endothelial cell ICAM-1 expression	(Harvey et al. 2010a)
			macrophage TNFα, IL-8, IL-1β expression via JNK	(Håversen et al. 2009)
			monocyte MAPK LOX-1 expression	(Ishiyama et al. 2010)
			neutrophil oxygen radical production	(Wanten et al. 2002)

continued

TABLE 3
Continued

Lipid Class	Comparison	Lipid Class	Human Cell Type and Pro-inflammatory Effect	References
Long-Chain Saturated	<=	Short-/Medium-Chain Saturated	adipocyte inflammatory gene expression	(Yeop Han et al. 2010)
			macrophage NF-κB activation, IL-8, COX-2 expression	(Laine et al. 2007)
			monocyte IL-6 production	(Schwartz et al. 2010)
Monounsaturated	>	Polyunsaturated	adipocyte inflammatory gene expression	(Yeop Han et al. 2010)
			dendritic cell activation by PPAR γ/RXR	(Zapata-Gonzalez et al. 2008)
			endothelial cell VCAM-1 expression	(De Caterina and Libby 1996)
			endothelial cell VCAM-1 expression	(De Caterina et al. 1998)
			endothelial cell free radical (superoxide) production	(Richard et al. 2008)
			endothelial cell IL-6 mRNA expression	(Staiger et al. 2004)
			lymphocyte TNFα, IL-1β expression	(Karsten et al. 1994)
			monocyte IL-1 production	(Baldie et al. 1993)
			monocyte tissue factor production	(Chu and Moore 1991)
			monocyte tissue factor activity	(Crutchley 1985)
			neutrophil free radical (superoxide) production	(Hwang et al. 2009)
Monounsaturated	<=	Polyunsaturated	endothelial cell superoxide production	(Horani et al. 2006)
			endothelial cell PAI-1 expression	(Nilsson et al. 1998)
			endothelial cell IL-8 expression	(Suriyaphol et al. 2002)
			endothelial cell PPAR α, MCP-1, E-selectin expression	(Shaw et al. 2007)
			endothelial cell ICAM-1 expression	(Matesanz et al. 2011)
			monocyte NF-κB activation	(Toborek et al. 2002)
			myocyte IL-8 production	(Leik and Walsh 2005)
			myocyte (intestinal) IL8 production	(Alzoghaibi et al. 2003)
			neutrophil superoxide production	(Badwey et al. 1984)
			neutrophil superoxide production	(Li et al. 1996)

continued

TABLE 3
Continued

Lipid Class	Comparison	Lipid Class	Human Cell Type and Pro-inflammatory Effect	References
Omega-6 polyunsaturated	>	Omega-3 polyunsaturated	colonocyte IL-6 IL-8 production via PPARγ	(Marion-Letellier et al. 2008)
			intestinal cell ICAM-1 expression	(Ramakers et al. 2007)
			endothelial cell free radical (superoxide) production	(Richard et al. 2008)
			endothelial cell production of thromboxane A3	(Mayer et al. 2002)
			endothelial cell adhesion to monocytes	(Schaefer et al. 2008)
			endothelial cell adhesion molecule expression	(De Caterina et al. 1998)
			endothelial cell adhesion molecule expression	(Collie-Duguid and Wahle 1996)
			endothelial cell COX activation	(Massaro et al. 2006)
			endothelial cell PAI-1 expression	(Kariko et al. 1995)
			monocyte IL-1 production	(Baldie et al. 1993)
			monocyte IL-1 production	(Rothman et al. 1997)
			monocyte NF-κB activation	(Toborek et al. 2002)
			monocyte production of platelet activating factor	(Sperling et al. 1987)
			neutrophil superoxide production	(Badwey et al. 1984)
			neutrophil NADPH oxidase activation	(Schneider et al. 2001)
			neutrophil migration	(Tull et al. 2009)
			platelet thromboxane receptor binding	(Swann et al. 1990)
Omega-6 polyunsaturated	< =	Omega-3 polyunsaturated	endothelial cell superoxide production	(Horani et al. 2006)
			endothelial PPAR α, MCP-1, E-selectin expression	(Shaw et al. 2007)
			macrophage NF-κB activation, IL-8, COX-2 expression	(Laine et al. 2007)
			monocyte and macrophage NADPH oxidase activation	(Huang et al. 1997)
			monocyte COX-2 PGE-2 inflammation	(Nauroth et al. 2010)
			monocyte tissue factor production	(Crutchley 1985)
			neutrophil superoxide production	(Li et al. 1996)
			neutrophil superoxide production	(Hardy et al. 1994)

continued

TABLE 3
Continued

Lipid Class	Comparison	Lipid Class	Human Cell Type and Pro-inflammatory Effect	References
Trans unsaturated	>	*Cis* unsaturated	endothelial cell adhesion molecule expression	(Harvey et al. 2008)
			endothelial cell prostacyclin inhibition	(Kummerow et al. 2007)
			endothelial cell adhesion molecule expression	(Siddiqui et al. 2009)
			endothelial cell adhesion molecule expression	(Sanadgol et al. 2010)
Trans unsaturated	< =	*Cis* unsaturated	endothelial cell superoxide production	(Horani et al. 2006)
			endothelial cell VCAM-1 expression	(De Caterina et al. 1998)
			neutrophil superoxide production	(Badwey et al. 1984)
			platelet thromboxane B2 formation	(Stachowska et al. 2004)

Note: These studies—comparing the direct effects of fatty acids on inflammatory processes of human cells—were performed in vitro under sterile conditions. Fatty acids show differences in the immune cell activation and inflammatory gene expression depending on saturation, length, number of double bonds (degree of unsaturation), and position of double bonds (omega-3 versus 6) and the configuration of double bonds (all *cis* versus all *trans*). Abbreviations: COX-2 (cyclooxygenase-2), ICAM-1 (intracellular adhesion molecule-1), IL- (interleukin), JNK (Jun kinase), LOX (oxidized LDL receptor), MAPK (mitogen-activated protein kinase), MCP-1 (monocyte chemotaxis protein-1), NF-κB (nuclear factor kappa B), PAI-1 (plasminogen activator inhibitor-1), PGE (prostaglandin-E), PPAR (peroxisome proliferator-activated receptor), PglyRP3 (PPARgamma-dependent peptidoglycan recognition protein 3), RXR (retinoid X receptor), TNFα (tumor necrosis factor alpha), and VCAM-1 (vascular cellular adhesion molecule-1).

FIGURE 1. SPACE FILL DIAGRAMS OF REPRESENTATIVE FATTY ACIDS

Space fill and structural diagrams are shown for four representative fatty acids. Myristic acid is a 14 carbon saturated FA. Oleic acid is a 18 carbon monounsaturated FA with a single double bond. The double bond introduces a kink in the conformation of the FA. Elaidic acid is a 18 carbon monounsaturated *trans* FA. The *trans* isomerization induces a more linear conformation similar to saturated FA. Linolenic acid, a polyunsaturated omega-3 FA, has three double bonds between carbons.

and permeability caused by free FA have been shown to result in cell lysis, interfere with enzymatic processes and oxidative phosphorylation, and inhibit microbial growth (Desbois and Smith 2010). Inhibition of pathogens by the products of digestion of dietary fat, particularly milk fat, has been demonstrated in mammalian herbivores (Cañas-Rodriguez and Smith 1966; Sun et al. 2007) and in humans (Hamosh et al. 1999; Isaacs 2001). Free FA and monoglycerides with strong antimicrobial activity are generated by the action of gastric lipases on milk fat when infants consume breast milk (Isaacs et al. 1990). Antimicrobial FA derived from breast milk kill viral, bacterial, and protozoan pathogens (Thormar et al. 1987; Hamosh et al. 1999; Isaacs 2001). Shorter-chain FA and monoglycerides in milk and some other foods (Table 1) have surfactant activity that can increase permeability of the cell membranes of gram negative bacteria such as *Escherichia coli*, *Yersinia enterocolitica*, and *Salmonella* sp. (Altieri et al. 2009), the gram positive bacteria *Streptococcus* spp. and *Staphylococcus aureus*, and the yeast *Candida* (Kabara et al. 1972). The observation that

breast milk digestion generates free FA with strong bactericidal effects may explain some of the infant health benefits of breastfeeding and illustrates how the antibacterial activity of FA and monoglycerides could be under selection due to their influence on infectious mortality.

Additional evidence for the evolution of host defenses that harness the natural antimicrobial properties of lipids come from studies that document an abundance of antimicrobial FA in tears, nasal secretions, and on the skin, locations where host cells and microorganisms interact (Do et al. 2008; McCusker and Grant-Kels 2010). Fatty acid defense of the skin is a phenomenon that begins before birth, since vernix caseosa, the substance that covers neonates at birth, contains lipids with antimicrobial activity (Tollin et al. 2005). After birth, antimicrobial FA secreted by sebaceous glands are bactericidal to pathogens and promote the growth of beneficial microorganisms (Ko et al. 1978; Wille and Kydonieus 2003). These various studies of skin and breast milk lipids show that the antibacterial activities of FA and monoglycerides are sufficiently potent to have been harnessed by natural selection to help protect the host from invasive pathogens.

The importance of FA in pathogen survival is illustrated by the fact that many bacteria respond to destabilizing FA, low pH, and other stresses by modifying or replacing cell membrane FA as a defense mechanism (Keweloh and Heipieper 1996). For instance, bacterial enzymes hydrogenate unsaturated membrane lipids and isomerize unsaturated FA from the *cis* to *trans* conformation (Chiou et al. 2004; Yuk and Marshall 2004). The resulting saturated and *trans* FA increase the rigidity of cell membranes and can reduce bacterial susceptibility to lysis. Because many bacterial strains lack the enzymes to interconvert membrane FA, saturated or *trans* fats from food serve as freely available membrane substrates with built-in resistance to host antibacterial defenses, including gastric acid (Sun et al. 2003; Yuk and Marshall 2004) and inhibitory FA liberated by gastric lipases (Isaacs 2001).

Effects of dietary fats on the gut microbiota

Given the powerful effects that various FA have on the growth, inhibition, and killing of bacteria that occur in the gut, it is not surprising that the composition of dietary lipids consumed can affect the colonization and composition of the gut microbiota (Andersen et al. 2011; Jumpertz et al. 2011; Wu et al. 2011). The gut microbiota is a diverse assemblage of microorganisms that number as many as 100 trillion, with the majority resident in the colon (Sekirov et al. 2010). One clue that the gut microbiota may help modulate postprandial inflammation is the finding that consumption of fat causes endotoxin, the cell wall constituent of gram negative bacteria, to translocate from the lumen of the intestine into the bloodstream (Cani and Delzenne 2009). Outside of the intestinal lumen, endotoxin is a powerful proinflammatory stimulus (Cani and Delzenne 2009; Schwartz et al. 2010). However, dietary fats have many additional effects on the gut microbiota besides serving as a conduit for bacterial antigens in chylomicrons to enter the circulation. For example, breast milk lipids, along with milk oligosaccharides and immunoglobulins, are thought to prevent intestinal colonization of dangerous microbes and help establish the neonatal microbiota (Goldman 2002; Andersen et al. 2011).

Along similar lines, Finch proposed that because bacteria often contaminate meat, inflammation from dietary fat could have provided protection from foodborne illness (Finch 2007). Foodborne illness is a ubiquitous threat to human survival, and has shaped dietary practices of many cultures (Billing and Sherman 1998). Bacterial colonization of the gut is only half the story, however, because diet also shapes the composition of indigenous gut microbiota (Jumpertz et al. 2011). Alteration of gut microbiota, known as dysbiosis, can also create opportunities for pathobionts, organisms that are generally benign coinhabitants of the gut, but that have pathogenic potential (Lee and Mazmanian 2010). Dietary FA and lipid metabolites of commensal bacteria have been shown to promote growth and virulence of some potential

pathogens (Keeney and Finlay 2011) and may also induce disease from pathobionts. In addition, altered gut flora have been shown to be an important cause of gut-derived sepsis that can lead to death (Shimizu et al. 2011). Thus, two related dietary risk factors—inoculation of new pathogens and changes in the composition of resident gut bacteria—may provide ongoing selective pressure for an immune modulating function of fat.

Inflammation generated by certain bacteria, and by the nutrients that feed them, has the effect of eliciting host functions that reduce the likelihood of overgrowth at the intestinal epithelium, and may help prevent bacteria from invading epithelial cells and sterile tissues. An increased abundance of pathogens and pathobionts stimulate a host immune response via activation of pattern recognition receptors of the innate immune system (Schwartz et al. 2010). One host response to dysbiosis is the production of antimicrobial peptides, including α defensin and β defensin and phospholipase A2. These antimicrobial peptides have innate immune activity that prevents luminal bacteria from attaching to the epithelium (Mukherjee et al. 2008; Ciccia et al. 2010). Defensins are produced constitutively by intestinal epithelial cells, generating an antimicrobial environment that helps maintain homeostasis at the intestinal mucosa. Inducible defensin expression, with direct antibiotic-like effects, occurs during overgrowth by pathogens and commensal bacteria (O'Neil et al. 1999). Inflammation also increases the production of secretory mucin by specialized intestinal cells. During infection, the host increases the production of mucin, thus causing shedding of the mucus layer and associated bacteria (Bergstrom et al. 2010). In addition to inflammation caused by bacterial antigens, nutrients also induce the proinflammatory pathways that result in production of defensins and expression of mucin genes (Figure 2; O'Neil et al. 1999; Ahn et al. 2005). The pathways involved in intestinal inflammation also induce the production of monocyte chemokine protein-1, which recruits phagocytic cells that engulf and neutralize pathogens. Through this mechanism, consumption of proinflammatory fats results in increased phagocytosis of microbes by activated monocytes and macrophages (Schaeffler et al. 2009). Exposure to pathogenic microorganisms and FA causes increased oxygen uptake and production of oxygen radicals (e.g., superoxide), which increase the bactericidal capacity of activated neutrophils and macrophages (Wanten et al. 2002; Sorci and Faivre 2009). Increased oxidative load during inflammation generates strongly antimicrobial oxidized lipids, which are important in innate immune defense of the host (Khovidhunkit et al. 2004; Schwartz et al. 2010).

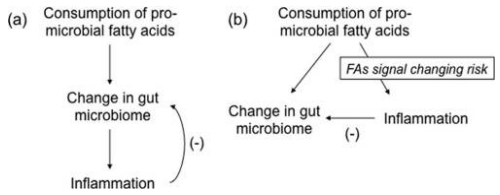

FIGURE 2. TWO POSSIBLE CAUSES FOR INFLAMMATORY EFFECTS OF DIETARY NUTRIENTS

(a) A dietary nutrient can result in inflammation when it changes the composition of gut microbiota and increases the flow of bacterial lipopolysaccharide into the blood, resulting in immune activation. A second inflammatory pathway, the focus of the present model (b), occurs when cell membrane receptors interact with fatty acids, resulting in an immune response that does not require microorganism intermediaries. The direct immune effects of fatty acids occur in parallel with diet-induced changes in gut microbiota and provide an early signal of changing risk from the gut.

THE NUTRIENT SIGNALING MODEL OF DIETARY INFLAMMATION

In light of the broad effects of specific nutrients on microbes and innate immunity, we propose that the vertebrate immune system has evolved the ability to use nutrients, and the bacterial metabolites of nutrients, as an "early warning system" that signal impending changes in infectious risk at the microbial-epithelial interface. Nutrients that provide growth substrates and competitive opportunities for potential pathogens require a compensatory mobilization of immune resources. The host thus responds to

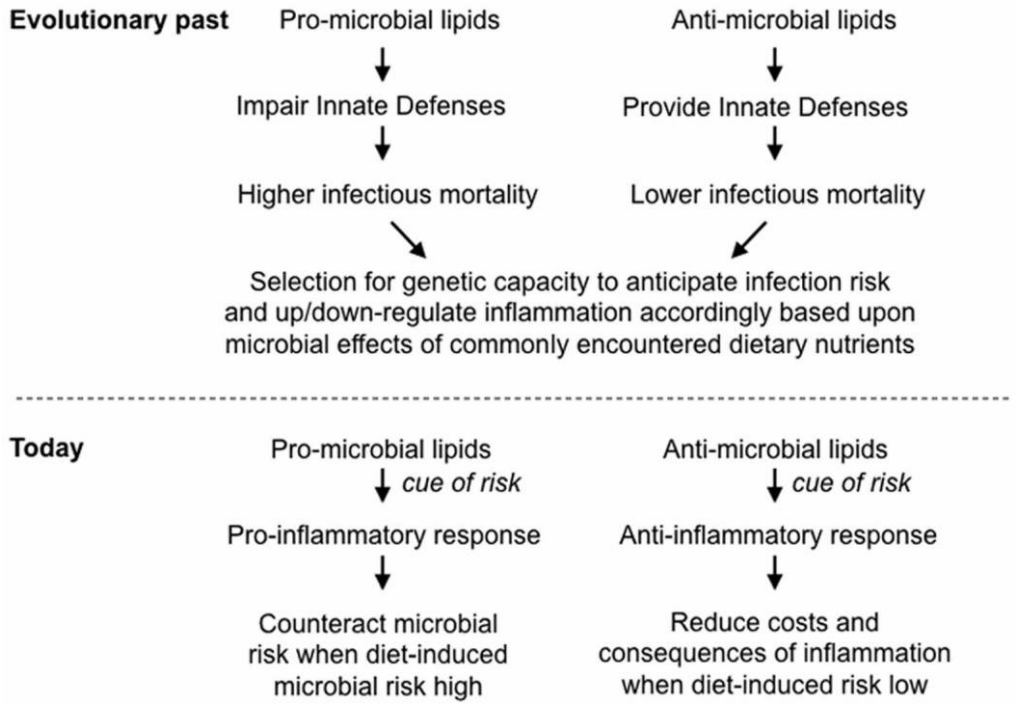

Figure 3. How Direct Nutrient-Based Immune Signaling is Hypothesized to have Evolved

Nutrients that are commonly encountered in the diet consistently increase or decrease risk of microbial overgrowth and infection (top pane). Through time, the vertebrate immune system obtained the ability to use these nutrients as cues of impending changes in microbial risk, allowing anticipatory up- or down-regulation of inflammation in anticipation of impending diet-induced microbial changes.

these nutrients by upregulating inflammation. Because inflammation is costly and damaging, the vertebrate immune system has also evolved a capacity to suppress inflammation in response to nutrients that inhibit harmful gut microbes (Figure 3). This model leads to the prediction that there will be a correspondence between the effects of a commonly encountered FA on harmful gut microbes and its direct signaling effect on host inflammation. The model is formalized in the following testable hypotheses:

1) Commonly consumed fatty acids that enhance the colonization and growth of pathogens and pathobionts will have direct proinflammatory effects in the host.

2) Commonly consumed fatty acids that suppress the colonization and growth of pathogens and pathobionts will have direct anti-inflammatory effects in the host.

Testing the Hypothesis

Here we compile findings from the published literature to test this model and its predictions. All dietary FA can be separated into two categories, saturated or unsaturated, depending on the presence or absence of double bonds. Because saturated and unsaturated FA both occur in meat, as well as breast milk and many vegetable foods, they are thought to have been commonly consumed throughout human evolution (Eaton et al. 1988). Because of their ubiquity, and because saturation status is a key determinant of biologic activity, these nutrients provide a critical test of Hypotheses 1 and 2. For each comparison of saturated versus unsaturated FA documented in the literature, we first review what is known about the effect of each lipid on pathogenic gut microorganisms, which sets up the expectations from our model for differences in inflammation (caused

directly by FA, independent of microbes) between saturated and unsaturated FA and other lipid classes. We then review the literature to evaluate whether the direct inflammatory and anti-inflammatory effects of each lipid are consistent with our model of nutrient signaling.

Search Methodology for Literature Reporting Microbial and Direct Inflammatory Effects of Dietary Lipids

We conducted a comprehensive literature review using PubMed and ISI Web of Knowledge. We searched for the terms "fatty acid," specific names of lipids and lipid categories with the terms "antimicrobial," "antibacterial," "inhibit," or "growth" with "bacteria," "pathogen," "parasite," "fungi," or specific names of enteric pathogens and potential pathogens. Literature cited in review articles of these topics was also included. Of these studies, we included in our analyses that subset of studies that: reported comparisons of the in vitro effects of purified lipids in different classes (below) on the survival of potential pathogens; included species that are potential gastrointestinal pathogens of humans, identified as such in a major gastroenterology textbook (Feldman et al. 2010); and included even-numbered carbon chain length FA and monoglycerides, which constitute greater than 95% of the FA typically consumed in the human diet. Because methods and protocols vary across studies, comparisons were limited to within-study contrasts of the effects of different lipid classes. In each study that met the inclusion criteria, the "more antimicrobial" and "less antimicrobial" lipid class was determined by tallying the direction of the differences between individual lipids. Studies that reported equal effects of different FA were also noted; these were divided into "equal NI" (noninhibitory) and "equal" (both lipids show pathogen inhibition). Lipid comparisons performed under comparable conditions (e.g., same dosage, organism, pH) within a study were aggregated to display relative numbers of differences in each direction and the number of equal comparisons.

To maximize the number of potential comparisons, we employed the total evidence approach (Kluge 2004; Sherman et al. 2008), in which all information is considered and data are not weighed by quality of evidence. Although the total evidence approach is subject to the biases and errors of individual studies, we deemed it preferable to the alternative "quality analysis" method (Sherman et al. 2008) in part because of the difficulty of objectively evaluating the relative validity and quality of the widely heterogeneous data sets that we reviewed.

A similar search protocol was followed to compare the direct effects of FA on inflammation. This search used the PubMed and ISI Web of Knowledge terms: "fatty acids" and "inflammation." Additional searches were performed with individual names of FA. Again, we limited comparisons to within-study comparisons of the direct inflammatory effects of different lipids. Studies were included if they reported differences in the in vitro direct inflammatory effects (i.e., not mediated by bacteria or lipopolysaccharide) between lipid classes on human cells and platelets. Outcomes included activation of innate immune pathways involving nuclear receptors NF-κB and PPARγ, mitogen-activated protein kinases (MAPK) and Jun kinases (JNK), and downstream expression of pro- and anti-inflammatory cytokines, tumor necrosis factor (TNF), monocyte chemoattractant protein-1 (MCP-1), white blood cell and endothelial cell expression of adhesion molecule (E-selectin, VCAM, and ICAM), platelet activation, and oxygen radical production. All searches were limited to studies published in English.

We used these data to test Hypotheses 1 and 2. Specifically, when microbial properties of multiple lipid classes were reported in the same study, we hypothesized that the more antimicrobial lipid class would have a more prominent, direct anti-inflammatory effect than its counterpart. Published studies allowed us to test our hypotheses using the main comparison of unsaturated versus saturated FA. These data also allowed us to pursue additional more nuanced contrasts within subgroups of saturated FA: short- and medium-chain length versus long-chain saturated FA (see Table 1 for definitions) and for subgroups of unsaturated FA. The additional contrasts of unsaturated FA were omega-3 versus omega-6 PUFA, polyunsaturated ver-

sus monounsaturated FA, and unsaturated FA with all *cis* versus all *trans* double bonds.

All comparisons were made between FA of the same chain length, unless otherwise noted. When available, monoglycerides and diglycerides were also compared. For studies that met our criteria and showed a difference in pathogen inhibition or inflammation, the direction of the difference was recorded and tabulated in a contingency table. With individual studies as the unit of comparison, a Fisher's exact test (Stata 11.0) was used to test for an association between antimicrobial activity and inflammatory effect of lipids.

Findings

findings: do antimicrobial fats have direct anti-inflammatory effects on the host?

Comparison 1. Unsaturated versus Saturated Fatty Acids

In data pooled from all studies meeting our criteria, the antimicrobial activity of unsaturated FA exceeded that of saturated FA in a majority of observations (Figure 4a). Unsaturated FA had stronger antibacterial effects than saturated FA in 27 studies; six studies showed stronger bacterial inhibition by saturated FA; equivalent inhibition was reported in one study (Table 4). Overall, gram positive bacteria were more sensitive to antimicrobial effects of unsaturated FA (Marounek et al. 2003). For instance, Kabara et al. (1972) showed that three of five unsaturated 18 carbon FA were potent inhibitors of Group A *Streptococcus*, with linoleic acid (C18:2) showing activity at the lowest concentration (0.089 μmoles/ml). The saturated 18 carbon FA failed to inhibit pathogen growth, as did the two 18 carbon unsaturated *trans* fats at much higher concentrations ($\geq$3.5 μmoles/ml) (Kabara et al. 1972). Under certain growth conditions, some FA were found to promote the growth of bacteria by providing a source of carbon. Saturated FA tended to be more effective growth promoters than unsaturated FA, resulting in exponential replication of *Staphylococcus aureus* that had been exposed to a growth inhibitor (Altenbern 1977a). Some unsaturated FA affect innate immunity by affecting the ability of pathogens to adhere to intestinal epithelial binding sites. Monounsaturated oleic acid and the polyunsaturated linoleic acid and linolenic acid have been shown to prevent pathogen binding to human intestinal cells in culture. These unsaturated FA have been reported to enhance the competitive exclusion of *Salmonella* by the commensal *Lactobacillus* bacteria (Muller et al. 2011).

Saturated FA tend to induce inflammation by activating nuclear transcription factors such as nuclear factor kappa B (NF-κB) and peroxisome proliferator-activated receptors (PPAR) (Schwartz et al. 2010). Saturated FA are also ligands for mitogen-activated protein kinase (MAPK) (Ishiyama et al. 2010) and Jun kinases (JNK) (Håversen et al. 2009) and other protein kinases that regulate nuclear factor transcription activity. Saturated FA tend to generate the expression of proinflammatory cytokines and chemokines such as TNF-α, IL-8, IL-1β, IL-6, and MCP-1 (Håversen et al. 2009; Kopp et al. 2009). Saturated FA have also been reported to induce inflammation and insulin resistance by increasing the activity of pattern recognition receptors, such as toll-like receptors (TLR) (Shi et al. 2006). Inflammatory gene expression is also modulated by fatty acid-sensing G-protein receptors and signal transduction pathways that depend on membrane lipids and lipid rafts (Holzer et al. 2011) and by the action of fatty acid metabolites such as ceramide (Håversen et al. 2009). Using a mouse model, Holzer et al. demonstrated that inflammatory signaling depends on membrane incorporation of saturated versus unsaturated lipids (Holzer et al. 2011). Because of their effects on membrane fluidity, saturated fatty acid-enriched membranes cause c-SRC tyrosine kinases to cluster in the cell membrane, where they activate JNK, eliciting the proinflammatory signaling that is associated with obesity, atherosclerosis, and metabolic syndrome. Increased membrane fluidity caused by unsaturated FA prevents c-SRC clustering, thus inhibiting JNK inflammation (Holzer et al. 2011).

Comparisons of the direct effects of these FA on human cell inflammation were generally in agreement with the expectations of the nutrient signaling model. In most pub-

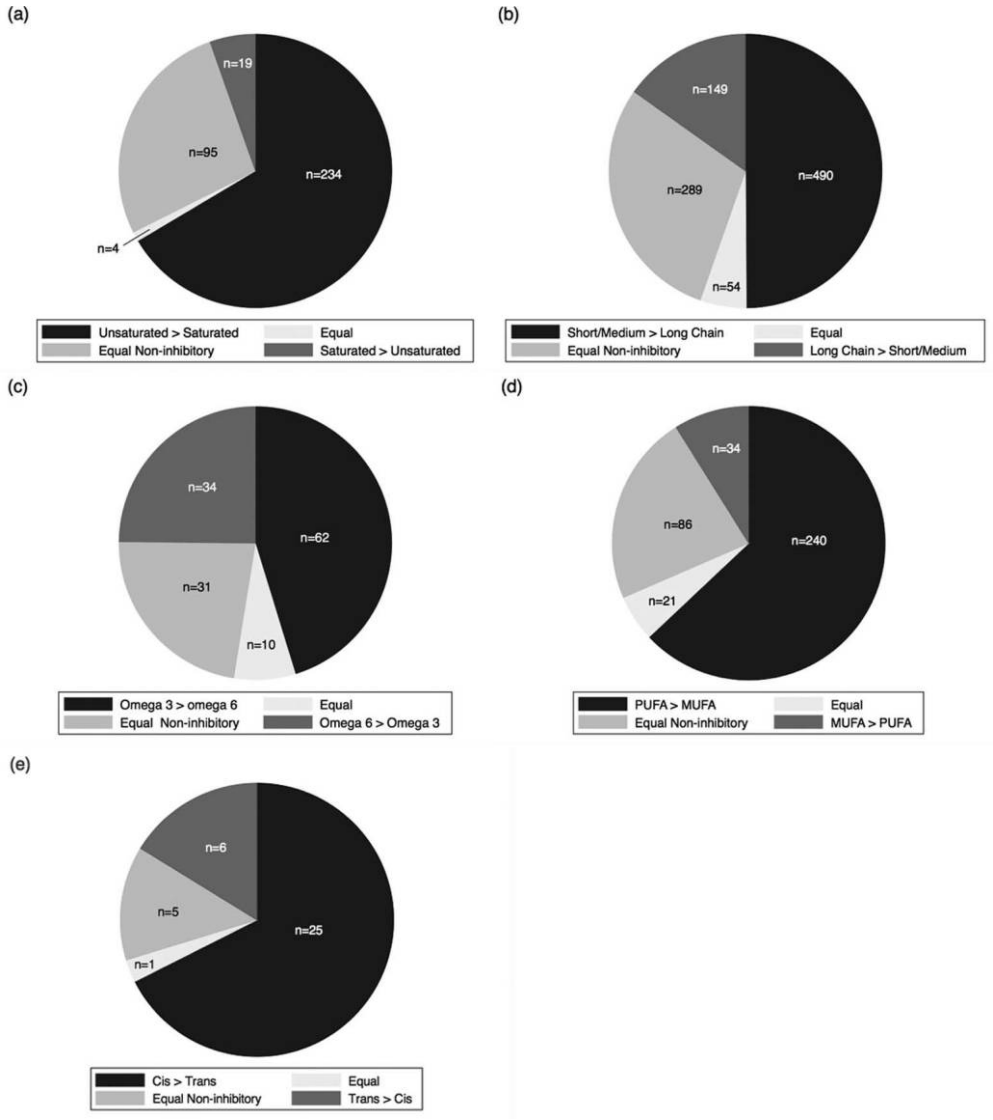

FIGURE 4. AGGREGATED LIPID-LIPID COMPARISONS OF ANTIMICROBIAL ACTIVITY

Comparing the relative antimicrobial effects in vitro of different lipid classes evaluated under identical conditions (see methods for details). Lipid contrasts include: (a) unsaturated versus saturated; (b) short- and medium-chain versus long-chain saturated; (c) polyunsaturated versus monounsaturated; (d) omega-3 versus omega-6 polyunsaturated; and (e) *cis* versus *trans* unsaturated.

lished studies, saturated FA usually caused proinflammatory signaling, while unsaturated lipids often had the opposite effect. Saturated FA caused more inflammation than unsaturated FA in 21 studies; four studies showed the opposite relationship; and one study had mixed results (Shaw et al. 2007; Table 3). In this comparison, the tendency for FAs with promicrobial effects to trigger direct proinflammatory on host cells was strongly statistically significant ($p<0.001$, Fisher's exact test, Table 5).

TABLE 4
Antimicrobial activity of unsaturated and saturated fatty acids of the same chain length

Unsaturated fatty acids studied	Antimicrobial comparison	Saturated fatty acids studied	Pathogens inhibited by FA*	Are unsaturated lipids more antimicrobial?	References
even C14:1–C22:1 C18:1 elaidic C18:1 petroselinic C18:1 cis vaccenic C18:2, C18:3 C20:2, C20:3,C20:4 C20:5, C22:6	>	even C14:0–C22:0	*Bacillus cereus* *Candida albicans* *Clostridium perfringens* *Clostridium botulinum* *Cryptosporidium parvum* *Giardia lamblia* *Enterococcus* *Helicobacter pylori* *Listeria monocytogenes* *Mycoplasma bovis* *Mycoplasma tuberculosis* *Salmonella typhimurium* *Staphylococcus aureus* *Streptococcus faecalis* *Streptococcus* Group A *Streptococcus* Group B	yes (27)	(Kodicek 1945; Hassinen et al. 1951; Willett and Morse 1966; Fuller and Moore 1967; Galbraith et al. 1971; Kabara et al. 1972; Kondo and Kanai 1972; Altenbern 1977b; Kabara et al. 1977; Kondo and Kanai 1977; Greenway and Dyke 1979; Carson and Daneo-Moore 1980; Dye and Kapral 1981; Knapp and Melly 1986; Reiner et al. 1986; Rohrer et al. 1986; Hogan et al. 1988; Ababouch et al. 1992; Wang and Johnson 1992; Petrone et al. 1998; Sprong et al. 1999; Sun et al. 2003; Skrivanova et al. 2005; Zheng et al. 2005; Kelsey et al. 2006; Sun et al. 2007; Schmidt and Kuhlenschmidt 2008)
even C6:1–C10:1 C16:1, C18:1 C18:2 MG C12:1 C18:1 elaidic C18:1 cis vaccenic	<	even C6:0–C10:0 C16:0, C18:0 MG C12:0	*Candida albicans* *Clostridium perfringens* *Aeromonas hydrophila* *Helicobacter pylori* *Listeria monocytogenes* *Staphylococcus aureus*	no (6)	(Cañas-Rodriguez and Smith 1966; Butcher et al. 1976; Lacey and Lord 1981; van der Kooij and Hijnen 1988; Petschow et al. 1996; Mbandi et al. 2004)
MG C18:1 MG C18:2	=	MG C18:0	*Listeria monocytogenes*	no (1)	(Wang et al. 1993)

Note: C preceded by MG indicates a monoglyceride. C preceded by DG indicates diglyceride. Mono- and diglycerides were only compared to other mono- and diglycerides. No prefix indicates a free fatty acid. C18:1 is oleic acid unless otherwise specified. Pathogen names have been updated.
*Pathogens listed showed sensitivity to at least one fatty acid in the comparison.

TABLE 5
Contingency table analysis of lipid effects on pathogens and inflammation

Fatty acid	More antimicrobial lipid*	More inflammatory lipid**	p value***
Saturated	7	21	$p < 0.001$
Unsaturated	27	5	
Long-Chain Saturated	7	6	$p = 0.005$
Short-/Medium-Chain Saturated	35	3	
Omega-6	7	17	$p = 0.02$
Omega-3	15	8	
Monounsaturated	12	11	$p = 0.094$
Polyunsaturated	27	9	
trans fatty acid	1	4	$p = 0.28$
cis fatty acid	7	4	

*Data points are publications comparing the antimicrobial activity of lipids (references are listed in Tables 4, 6–8). Publications showing equal and mixed antimicrobial activity between lipid categories were included with first FA in each comparison: saturated, long-chain saturated, monounsaturated, and omega-6 FA, respectively.
**Data points are publications comparing the direct inflammatory effects of lipids (references are listed in Table 3).
***Fisher's exact test.

Comparison 2. Short- and Medium-Chain Saturated Fatty Acids versus Long-Chain Saturated Fatty Acids

Many studies reported differences in the antimicrobial activity of saturated FA depending on chain length. In pooled data, the bactericidal activity of shorter-chain saturated FA tended to exceed that of longer-chain saturated FA (Figure 4b). Although the potency of individual FA is highly variable, shorter-chain FA (four to 12 carbons in length) were shown to inhibit a wide variety of gastrointestinal pathogens. The FA in this group with the most potent inhibitory effect were 8-to-12 carbon FA and monoglycerides (Batovska et al. 2009). For example, lauric acid (C12) inhibits *Listeria monocytogenes* with a minimum inhibitory concentration of 31–40 μg/ml (Mbandi et al. 2004; Batovska et al. 2009), and the C12 monoglyceride kills *Staphylococcus aureus* at 8–25 μg/ml (Kelsey et al. 2006; Batovska et al. 2009). *Escherichia coli*, like some other gram negative bacteria, are resistant to many FA, but showed inhibition by caprylic acid (C8) at a minimum concentration of 300–850 μg/ml (Marounek et al. 2003). Meanwhile, long-chain saturated FA (more than 12 carbons) were often inactive against these pathogens. Inhibition of potential pathogens by shorter-chain FA is not limited to direct antimicrobial effects. Short-chain fatty acids (SCFA) produced by commensal bacteria have been shown to displace pathogens such as *Salmonella typhimurium* from intestinal cell binding sites along the gut epithelium (Cox et al. 2008). SCFA also prevented the growth of pathogenic organisms by decreasing intestinal pH (Lin et al. 2008) and interfering with the capacity of enteric pathogens to invade intestinal cells (Van Deun et al. 2008). Overall, short- and medium-chain FA and monoglycerides had stronger antimicrobial activity than long-chain saturated FA in 35 studies; longer-chain saturated FA were more antimicrobial in five studies, and two studies showed equivalent inhibition (Table 6).

The tendency of saturated FA to directly induce host inflammation appears to be influenced by the carbon chain length, with one study finding evidence for proinflammatory effects on JNK limited to long-chain saturated fat (with more than 16 carbons) (Holzer et al. 2011). Shorter-chain saturated FA failed to elicit proinflammatory signaling in this cell-based model. Additional anti-inflammatory effects of shorter-chain FA occur because these FA are ligands for G-protein receptors that tend to elicit anti-inflammatory signaling functions (Cavaglieri et al. 2003; Hamer et al. 2008).

TABLE 6
Antimicrobial activity of SCFA/MCFA and long-chain saturated fatty acids

Short/medium fatty acid studied	Antimicrobial comparison	Long-chain saturated fatty acids studied	Pathogens inhibited by FA*	Are short and medium chain lipids more antimicrobial?	References
even C4:0–C12:0 even MG C8:0–MG C12:0	>	even C14:0–C20:0 even MG C14:0–MG C18:0	*Aerobacter* *Aeromonas hydrophila* *Campylbacter jejuni* *Candida albicans* *Bacillus cereus* *Clostridium botulinum* *Clostridium perfringens* *Escherichia coli* *Helicobacter pylori* *Listeria monocytogenes* *Proteus vulgarus* *Salmonella enteriditis* *Salmonella typhimurium* *Staphylococcus aureus* *Streptococcus* Group A *Streptococcus* Group B *Vibrio cholerae*	yes (35)	(Hassinen et al. 1951; Cañas-Rodriguez and Smith 1966; Fuller and Moore 1967; Galbraith et al. 1971; Salanitro and Wegener 1971; Kabara et al. 1972; Fay and Farias 1975; Altenbern 1977a; Miller et al. 1977; Beuchat 1980; Lacey and Lord 1981; Hogan et al. 1988; van der Kooij and Hijnen 1988; Ababouch et al. 1992; Wang and Johnson 1992; Wang et al. 1993; Petschow et al. 1996; Petrone et al. 1998; Sprong et al. 1999; Bergsson et al. 2001; Sprong et al. 2001; Bergsson et al. 2002; Lee et al. 2002; Marounek et al. 2003; Sun et al. 2003; Kitahara et al. 2004; Mbandi et al. 2004; Skrivanova et al. 2004; Skrivanova et al. 2005; Kelsey et al. 2006; Thormar et al. 2006; Skrivanova and Marounek 2007; Sun et al. 2007; Batovska et al. 2009; Huang et al. 2011)
even C4:0–C12:0 MG C12:0–MG C16:0 DG C12:0–DG C16:0	<	even C14:0–C18:0 MG C14:0 MG C16:0 DG C14:0 DG C16:0	*Giardia lamblia* *Mycoplasma bovis* *Mycoplasma tuberculosis* *Staphylococcus aureus* *Streptococcus* Group B	no (5)	(Willett and Morse 1966; Kondo and Kanai 1972; Kondo and Kanai 1977; Naidoo 1981; Reiner et al. 1986)
C4:0–C12:0	=	C14:0	*Enterococcus faecalis* *Listeria monocytogenes*	no (2)	(Sun et al. 2002)** (Kinderlerer et al. 1996)

Note: C preceded by MG indicates a monoglyceride. C preceded by DG indicates diglyceride. Mono- and diglycerides were only compared to other mono- and diglycerides. No prefix indicates a free fatty acid.

*Pathogens listed showed sensitivity to at least one fatty acid in the comparison. Pathogens that failed to show inhibition by either category of FA included *Salmonella typhimurium*, *Salmonella enteritidis*, and *E. coli* 0157:H7 (Lee et al. 2002) and *Klebsiella pneumoniae* and *Escherichia coli* (Hogan et al. 1988).

**Mixed results by pathogen, grouped with "no." *Enterococcus faecalis* (*Streptococcus faecalis*) was more sensitive to short-chain fatty acids.

As predicted by our model, long-chain saturated FA were more directly inflammatory than shorter-chain saturated FA in six studies while only three studies reported the opposite findings (Table 3). The inverse relationship between inflammation and antimicrobial activity was statistically significant ($p=0.005$, Fisher's exact test, Table 5).

Comparison 3. Omega-3 versus Omega-6 PUFA

The position of the C-C double bond from the methyl end of PUFA (the third or sixth position) determines whether a FA is an omega-3 FA or omega-6 FA. Omega-3 FA have been shown to kill and inhibit bacteria more readily than omega-6 FA in 15 studies; five studies had the opposite findings; and two studies reported mixed or equal inhibition of bacteria (Table 7). In pooled data from 20 of 22 studies, most comparisons showed greater pathogen inhibition by omega-3 FA than by omega-6 FA (Figure 4c). Two studies, excluded from Figure 4c because they did not provide the exact identification of pathogen strains, also showed stronger bacterial inhibition by omega-3 FA (Heczko et al. 1979; Lacey and Lord 1981). Heczko et al. showed that of 242 strains of *Staphylococcus aureus*, most strains were sensitive to the omega-3 linolenic acid (C18:3) at a minimum concentration of 0.19 mmol/L while most strains were inhibited by the omega-6 linoleic acid at a minimum concentration of 6.25 mmol/L (Heczko et al. 1979). Some studies reported the opposite findings (Kabara et al. 1972), but most publications that met inclusion criteria favored pathogen killing by omega-3 FA (Table 7).

In addition to changes in chemokine, cytokine, and adhesion molecule expression caused by PUFA, the omega-3 and omega-6 FA also undergo metabolism to pro- and anti-inflammatory eicosanoids that are involved in the progression of atherosclerosis and insulin resistance (Das 2010). Fatty acid synthesis pathways begin with so-called essential 18 carbon FA linoleic acid (omega-6) and linolenic acid (omega-3) that cannot be synthesized in humans *de novo* and thus must be obtained in the diet. These FA undergo conversion by elongases and desaturases to 20 carbon PUFA arachidonic acid and eicosapentaenoic acid, respectively. The omega-3 FA eicosapentaenoic acid undergoes preferential metabolism to anti-inflammatory eicosanoids, including leukotrienes, prostacyclins, lipoxins, protectins, and maresins. The metabolic pathway utilizing omega-6 arachidonic acid, meanwhile, often generates proinflammatory eicosanoids (Teitelbaum et al. 2001). The eicosanoid products of omega-6 metabolism are responsible for symptoms of inflammation—e.g., fever—and modulate the intensity and duration of inflammation (Calder 2002). Omega-3 FA metabolites—e.g., resolvins and protectins—are important in resolving inflammatory processes (Calder 2002). Decreased inflammation from eicosanoids derived from omega-3 FA compared to omega-3 FA is in line with the antimicrobial activity of its FA precursors.

As predicted by our model, in 17 studies, omega-6 were more directly inflammatory than omega-3 FA (Table 3), while six studies had the opposite results and two studies had mixed findings (Shaw et al. 2007; Nauroth et al. 2010). When omega-6 and omega-3 FA were compared, there was a statistically significant inverse relationship between antimicrobial activity and inflammation ($p=0.02$, Fisher's exact test, Table 5).

Comparison 4. Polyunsaturated versus Monounsaturated Fatty Acids

Monounsaturated fatty acids (MUFA) occupy an intermediate position between the saturated FA and FA with multiple double bonds (PUFA). In general, PUFA usually killed or inhibited sensitive gastrointestinal pathogens at lower concentrations than MUFA of the same chain length (Kabara et al. 1972). Growth of *Listeria monocytogenes* is inhibited by PUFA in milk fat, including linolenic acid (C18:3), an omega-3 FA that was antibacterial at 2 μg/ml (Petrone et al. 1998). This difference is repeated in most of the pooled lipid-lipid comparisons (Figure 4d). By comparison, the MUFA oleic acid (C18:1) inhibited *Listeria* at a much higher concentration, 200 μg/ml (Petrone et al. 1998). PUFA were more antimicrobial than MUFA in 27 of 39 studies (Table 8). Of the remainder, eight studies re-

TABLE 7
Antimicrobial activity of polyunsaturated and monounsaturated fatty acids of same chain length

Polyunsaturated fatty acids studied	Antimicrobial comparison	Monounaturated fatty acids studied	Pathogens inhibited by FA*	Are PUFA more antimicrobial?	References
C18:2, C18:3 C18:3 gamma linolenic C20:2, C20:3, C20:4, C20:5 C22:5	>	C18:1 C20:1 C22:1	*Bacteroides fragilis* *Bacillus cereus* *Campylobacter jejuni* *Clostridium botulinum* *Clostridium perfringens* *Cryptosporidium parvum* *Giardia lamblia* *Helicobacter pylori* *Enterococcus* *Listeria monocytogenes* *Mycoplasma bovis* *Mycoplasma tuberculosis* *Staphylococcus aureus* *Streptococcus* Group A *Streptococcus* Group B	yes (27)	(Fuller and Moore 1967; Kabara et al. 1972; Kondo and Kanai 1972; Kabara et al. 1973; Gutteridge et al. 1974; Butcher et al. 1976; Altenbern 1977b; Kondo and Kanai 1977; Naidoo 1981; Campbell et al. 1983; Knapp and Melly 1986; Rohrer et al. 1986; Hogan et al. 1988; Thompson et al. 1990; Crouch et al. 1991; Ababouch et al. 1992; Wang and Johnson 1992; Thompson et al. 1994; Khulusi et al. 1995; Petrone et al. 1998; Dilika et al. 2000; Sprong et al. 2001; Sun et al. 2003; Zheng et al. 2005; Kelsey et al. 2006; Schmidt and Kuhlenschmidt 2008)
C16:3 C18:2, C18:3	<	C16:1 C18:1 oleic C18:1 ricinoleic	*Aeromonas hydrophila* *Bacillus cereus* *Candida* sp. *Clostridium perfringens* *Escherichia coli* *Listeria monocytogenes* *Salmonella enteriditis* *Staphylococcus aureus*	no (8)	(Willett and Morse 1966; Dye and Kapral 1981; van der Kooij and Hijnen 1988; Sprong et al. 1999; Mbandi et al. 2004; Skrivanova et al. 2005; Desbois et al. 2008; Chen et al. 2011)
MG C18:2 C18:2, C18:3	=	MG C18:1 C18:1	*Candida albicans* *Giardia lamblia* *Staphylococcus aureus*	no (4)	(Lacey and Lord 1981; Reiner et al. 1986; Wang et al. 1993; Huang et al. 2010)

Note: Pathogen names have been updated.
*Pathogens listed showed sensitivity to at least one fatty acid in the comparison. Pathogens that failed to show inhibition by either category of FA included *Pseudomonas aeruginosa* and *Escherichia coli* (Zheng et al. 2005) and *Listeria monocytogenes* (Reiner et al. 1986).

TABLE 8
Antimicrobial activity of omega-3 and omega-6 polyunsaturated fatty acids

Omega-3 PUFA studied	Antimicrobial comparison	Omega-6 PUFA studied	Pathogens inhibited by FA*	Are omega-3 PUFA more antimicrobial?	References
C18:3 linolenic	>	C18:2	*Bacillus cereus*	yes (15)	(Gutteridge et al. 1974; Butcher et al. 1976; Altenbern 1977b; Kondo and Kanai 1977; Heczko et al. 1979; Lacey and Lord 1981; Knapp and Melly 1986; Rohrer et al. 1986; Hogan et al. 1988; Thompson et al. 1990; Ababouch et al. 1992; Wang and Johnson 1992; Thompson et al. 1994; Petrone et al. 1998; Sun et al. 2003)
C20:5		C20:4	*Bacteroides fragilis*		
C22:6		C18:3 gamma linolenic	*Bacteroides* spp.		
			Clostridium botulinum		
			Clostridium perfringens		
			Escherichia coli		
			Enterococcus faecalis		
			Helicobacter pylori		
			Giardia lamblia		
			Listeria monocytogenes		
			Mycoplasma bovis		
			Mycoplasma tuberculosis		
			Salmonella typhimurium		
			Staphylococcus aureus		
			Streptococcus spp.		
C18:3	<	C18:2	*Candida albicans*	no (7)	(Willett and Morse 1966; Fuller and Moore 1967; Kabara et al. 1972; Raychowdhury et al. 1985; Reiner et al. 1986; Mbandi et al. 2004; Zheng et al. 2005)**
		C20:4	*Giardia lamblia*		
			Listeria monocytogenes		
			Staphylococcus aureus		
			Streptococcus Group A		
			Streptococcus Group B		

Note: When the lipid number fails to distinguish between similar FA, common names of fatty acids are given in parentheses.
Pathogens listed showed sensitivity to at least one fatty acid in the comparison.
*Pathogens listed showed sensitivity to at least one fatty acid in the comparison. Pathogens that failed to show inhibition by either category of FA included *Escherichia coli* and *Klebsiella pneumoniae* (Hogan et al. 1988).
**Mixed results depending on pathogen, grouped with "no."

ported increased bacterial inhibition by MUFA, and four had mixed results (Table 8).

Although antimicrobial activity generally increased with rising numbers of double bonds (Knapp and Melly 1986), studies report less consistent relationships between the number of double bonds and inflammatory activity of unsaturated FA. MUFA had stronger proinflammatory effects compared to PUFA in 11 studies that we found; nine studies showed the opposite pattern; and one study showed equivalent inflammation (Tables 3 and 5). The outcome of these comparisons often depended on whether the MUFA oleic acid was compared to the (generally proinflammatory) omega-6 PUFA (Suriyaphol et al. 2002; Matesanz et al. 2011) or the (generally anti-inflammatory) omega-3 PUFA (Carluccio et al. 1999; Shaw et al. 2007).

Independence testing of effects on microbial growth and human cell inflammation showed a borderline-significant statistical trend for MUFA versus PUFA of the same chain length ($p=0.094$, Fisher's exact test, Table 5).

Comparison 5. *Trans* versus *Cis* Unsaturated Fatty Acids

Kabara and colleagues found that for gram positive organisms, *trans* isomers of C16 and C18 were inactive as antimicrobial agents, whereas replacement of a *trans* with a *cis* double bond increased their antimicrobial activity (Kabara et al. 1972, 1977). These results have since been replicated (Table 9). *Trans* fats have a similar structure to saturated fats and likewise are often ineffective in killing gut microbes (Desbois and Smith 2010). Increased antimicrobial activity of *cis* FA compared to *trans* FA was the most frequent observation in pooled lipid-lipid comparisons (Figure 4e). Replacement of all *trans* double bonds with *cis* double bonds made the FA more antimicrobial in seven of eight studies (Table 9). In contrast to the predictions of our model, and contrary to supplementation trials and observational studies (Mozaffarian 2006), *trans* FA were equally likely to be less or more inflammatory than their *cis* isomers in our review of in vitro studies. Although *trans* FA can show

TABLE 9

Antimicrobial activity of cis *versus* trans *unsaturated fatty acids*

***cis* unsaturated fatty acids studied**	**Antimicrobial comparison**	***trans* unsaturated fatty acids studied**	**Pathogens inhibited by FA***	**Are *cis* unsaturated FA more antimicrobial?**	**References**
C16:1 (*cis*)	>	C16:1 (*trans*)	*Giardia lamblia*	yes (7)	(Kabara et al. 1972; Butcher et al. 1976; Altenbern 1977a; Kondo and Kanai 1977; Reiner et al. 1986; Rohrer et al. 1986; Kelsey et al. 2006)
C18:1 (oleic)		C18:1 elaidic	*Mycoplasma bovis*		
C18:1 linoleic		C18:2 (linolelaidic)	*Mycoplasma tuberculosis*		
C18:1 (petroselinic)		C18:1 (vaccenic, *trans*-11)	*Staphylococcus aureus*		
			Streptococcus Group A		
			Streptococcus sp.		
C18:1 (oleic)	<	C18:1 (elaidic)	*Staphylococcus aureus*	no (1)	(Lacey and Lord 1981)

Note: For this contrast, fatty acids with the same chain length and number of double bonds were compared. Common names of fatty acids are given in parentheses and, when indicated in a publication, the location of double bonds is also given.

*Pathogens listed showed sensitivity to at least one fatty acid in the comparison.

proinflammatory effects much like long-chain saturated FA (Turpeinen et al. 1998), in the comparison of *trans* versus *cis* FA, the relationship between inflammatory effects and antimicrobial activity was not significant ($p=0.28$, Fisher's exact test, Table 5).

Discussion

The inflammatory effects of foods have generated much scientific interest, but have lacked a conceptual framework to explain the myriad immune modulatory effects of specific dietary nutrients. Our model builds from the observation that many of the same nutrients that modulate inflammation have powerful effects on the survival of harmful gut microorganisms and the ability of pathogens to adhere to epithelial cells. Because of these effects, some nutrients are better suited than others to participate in a coordinated defense with antimicrobial effector molecules of the host immune system (Nakatsuji et al. 2010). Inflammation caused by nutrients requires mobilization of scarce host resources (McDade 2003), while also potentially contributing to tissue damage (Margioris 2009). The nutrient signaling hypothesis proposes that the direct postprandial inflammatory effects of FA are an evolved response that help the host balance these costs of immune activation with the potential benefit of mobilizing these costly resources. When commonly encountered nutrients consistently alter patterns of gut bacterial growth and increase the ability of pathogens or pathobionts to adhere to the intestinal epithelium, our model predicts that natural selection will have favored inflammatory signaling that corresponds to the change in risk. We find substantial support for this hypothesis in previously published research on the antimicrobial effects of saturated and unsaturated FA. With some notable exceptions, contrasts of FA that differed in other structural features were also generally in line with the expectations of this model (Table 5).

In our primary comparison between saturated versus unsaturated FA, lipids that met the nutrient needs of pathogens (by providing a source of carbon) tended to have direct proinflammatory effects on the host; in contrast, lipids that impaired the growth of harmful pathogens tended to attenuate inflammation in human cells (Table 5). Similar associations between antimicrobial and anti-inflammatory effects were found for the contrasts involving omega-3 FA and for the effects of increasing chain length in saturated FA (Table 5). We found less consistent support for our hypothesis in several comparisons that examined other structural differences between unsaturated FA. For example, monounsaturated fats were not found to clearly serve a proinflammatory signaling role compared to PUFA (Table 5). These equivocal results are in line with uncertainty about whether increased consumption of MUFA decreases or increases cardiovascular risk and diabetes (Micha and Mozaffarian 2010). On the other hand, consumption of *trans* fats from industrial sources has been shown to increase the risk of heart disease (Mozaffarian 2006; Kummerow 2009). Despite strong epidemiologic evidence linking *trans* fats to diseases, we did not find consistent evidence for a direct proinflammatory signaling role of *trans* fats on human cells (Table 5). One possible explanation for our inability to demonstrate a significant association of the effects of *trans* versus *cis* FA on microbes and inflammation is simply the small sample of studies available to test it. Alternatively, our findings may reflect the fact that *trans* fats are often manufactured as hydrogenated vegetable oils and comprised a trivial fraction of the preindustrial diet (Cordain et al. 2005), and thus would not have exerted strong selection pressure on the human immune system until the past few generations.

An important limitation of our approach is that the studies we reviewed evaluated FA effects on a narrow spectrum of gut microbes, mostly pathogens such as *Staphylococcus aureus* and *Listeria monocytogenes* (Batovska et al. 2009). These pathogenic microorganisms comprise a small minority of the gut microbiota (Wu et al. 2011). Compared to specialized pathogens, the potentially harmful commensals known as pathobionts are quantitatively more numerous and persistent in the microbiome (Lee and Mazmanian 2010). Because of these features, Lee and Mazmanian (2010) have suggested that pathobionts are more important than pathogens in shaping the evolution of immune responses. If this proposal is

true, then FA inhibition of pathobionts, such as *Bacteroides fragilis* (Gutteridge et al. 1974; Thompson et al. 1990), may have a disproportionate selective impact on nutrient-related inflammation. However, FA have similar effects on bacteria from both groups (e.g., Table 7) and nutrient-induced immune responses may compensate for the adverse effects of increased numbers of either pathogens or pathobionts on the host's resistance to infection.

Because the studies that we review document microbial effects of FA in vitro, it is not certain how these in vitro effects manifest in vivo, and whether the concentrations of FA available in the diet can affect the growth of bacteria in the gut. However, some studies suggest that concentrations of lipids present in the gastrointestinal tract are sufficient to influence bacterial growth (Shin et al. 2002; Sun et al. 2007). For example, hydrolysis of milk fat by lipases yields FA and monoglycerides in millimolar (mM) concentrations in the stomach (3.35 mM and 12 mM) that are effective in killing bacteria such as *Helicobacter pylori* (Sun et al. 2007). In the small intestine, the site of absorption of most dietary FA, triglycerides and free FA also have been measured in millimolar concentrations in the postprandial state (Di Maio and Carrier 2011); similar concentrations are bactericidal to a variety of gut pathogens (Sprong et al. 2001). In the human colon, the concentration of shorter-chain FA have been measured in the millimolar range (e.g., 124 mM; Bergman 1990) and that has been shown to inhibit the growth of bacteria such as *E. coli* O157:H7 (Shin et al. 2002). Although the effects of inhibitory FA and monoglycerides on bacterial growth are additive (Sun et al. 2003), many FA have synergistic effects against pathogens with other elements of the innate immune system, including antimicrobial peptides (Nakatsuji et al. 2010), lactoferrin and lysozyme (Ellison and Giehl 1991; Martinez et al. 2009), and gastric acid (Bergsson et al. 2002; Thormar et al. 2006). The amplification of antipathogen activity by host factors suggests that some FA, even at concentrations in which they are inactive in isolation, may have the ability to modify the gut microbiota in vivo and thus alter infectious risk.

Despite the limitations described above, our model holds promise to help explain why the host immune system has evolved a capacity to modulate inflammation in response to dietary fats. The parallels between the effects of many lipids on pathogens and on host immunity (Table 5) are consistent with our hypothesis that the lipid effects on gut microorganisms have shaped the vertebrate immune system to modify expenditure on costly host defenses in ways that are appropriate in light of impending changes in gut biota predicted by the pattern of ingested nutrients. Anti-inflammatory signaling from antimicrobial nutrients reduces the energetic costs and tissue damage associated with inflammation, while potentially also sparing protective commensal gut organisms. Meanwhile, our model argues that inflammation from promicrobial nutrients, while costly, provides a benefit to host defense by improving resistance to infection at the intestinal epithelial barrier.

Evolutionary Symbiosis in Immune Defense

Several recent papers have presented models of immune defense that share similarities with the nutrient signaling model outlined here. These studies point to the plausibility of the general framework that we review, and also highlight differences in the predictions of the various models that have been presented. In several elegant experiments, Nakatsuji et al. (2010) and Chen et al. (2011) have shown how innate immune defense of the skin relies on FA, symbiotic bacteria, and host antimicrobial peptides to prevent infection by pathogens. These researchers have shown that FA on the skin work in concert with antimicrobial peptides to maintain a protective antimicrobial environment. Various FA stimulate the production of skin defensins that function together to prevent overgrowth by the skin commensal *Propionibacterium acnes* (Nakatsuji et al. 2010). These findings highlight the ability of FA to provide an important adjunct to the antimicrobial molecules of the innate immune system. Coordinated innate defense involving nutrient FA and antimicrobial products of the immune system occurs throughout the gastrointestinal tract (Figure 5). However, the nutrient signaling model differs in one critical way from the viewpoint offered by these authors.

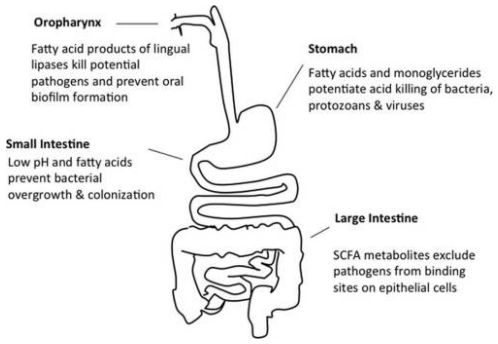

FIGURE 5. FATTY ACIDS PARTICIPATION IN INNATE IMMUNE DEFENSES ALONG THE GASTROINTESTINAL TRACT

Nutrients vary in their capacity to participate in innate immune defense of the gastrointestinal (GI) tract. Although some FA impair the intestinal barrier function, other FA kill microbes and coordinate with antimicrobial defenses of the host throughout the GI tract.

Nakatsuji et al. (2010) suggest that the benefit of antimicrobial FA relies on the ability of these FA to stimulate the host to *increase* the production of immune products (e.g., antimicrobial peptides) that participate in a coordinated antimicrobial defense. The nutrient signaling model predicts the opposite: that exogenous FA with intrinsic antimicrobial properties allows the host to *decrease* its investment in antimicrobial defenses. In fact, findings of Nakatsuji and colleagues suggest that skin FA with the least intrinsic antimicrobial activity against *P. acnes* (oleic acid and palmitic acid) are the FA that stimulate the greatest production of antimicrobial peptides by the host. The FA with the greatest antimicrobial activity against *P. acnes* (lauric acid) showed the least ability to upregulate defensin production by epithelial cells. These results are in line with expectations of the nutrient signaling model.

NUTRIENT SIGNALING VERSUS THE PALEOLITHIC DIET

It has been suggested previously that human metabolism was adapted to the diet and lifestyle of nomadic foragers during several million years of hominin evolution (Neel 1962; Eaton et al. 1988). According to this framework, rapid changes in diet in recent generations have led to a "discordance" or "mismatch" between a modern diet and the ancestral diet that our metabolisms have evolved to expect. Many nutrients that are commonly consumed today were rare or absent in past environments. Processed foods and refined sugars that dominate the typical Western diet represent a radical transformation from the diet of humans and hominins during the Paleolithic era (2.6 million to 10,000 years ago) (Cordain et al. 2005). *Trans* fats have been introduced in great quantities into the food supply by the industrial hydrogenation of vegetable oils (Cordain et al. 2005). Modern agricultural practices have also allowed the harvesting of meat with a much higher concentration of saturated FA than wild game, in which much edible carcass fat consists of monounsaturated fat or PUFA (Cordain et al. 2005). In addition, the omega-3 FA content is higher in wild fish and game than in farmed meat. As a result, ancestral human populations likely consumed omega-3 FA in much higher proportion to omega-6 FA compared to today (Teitelbaum and Walker 2001). It has been suggested that the decreased ratio of omega-3 to omega-6 FA in the diet, compared to the ancestral human state, is a source of increased proinflammatory eicosanoid synthesis contributing to the epidemic of diabetes and cardiovascular disease (Teitelbaum and Walker 2001).

Our hypothesis differs fundamentally from the Paleolithic diet concept in proposing that nutrients themselves will only have a direct proinflammatory or anti-inflammatory signaling role if human ancestors commonly encountered them in the past, or if they chemically mimic nutrients that were commonly encountered. The immune system would have evolved a capacity to mobilize nonspecific immune defenses, notably inflammation, in response to commonly encountered nutrients (those ingested or transformed by bacteria) that had adverse effects on the gut microbiota. Today, exposure to these lipids should initiate inflammation, while the immune system would not be expected to have evolved a response to a compound that was not consumed by human ancestors, or only rarely. In this sense, our model is distinct in

its predictions from most evolutionary models linking disease to gene-diet mismatch secondary to rapid changes in the quantities or types of nutrients consumed. That said, we emphasize that the two models are fundamentally complementary, and lead to distinct predictions: the Paleolithic diet model predicts that rapid change in the nutrient composition of the diet can lead to metabolic dysregulation and disease. The nutrient signaling model predicts that high consumption of nutrients that were common in ancestral diets and had pro-microbial effects will contribute to diet-induced inflammation.

Generalizing the Model to Other Nutrient Classes

The nutrient signaling model proposed here inspires novel hypotheses that are testable both within and across species, and across different nutrient classes. At a broad level, the model makes three general predictions: A dietary compound will exert direct effects on inflammatory gene expression if it has been a feature of an organism's environment and influences the gut microbiota; the direction of the effect of a compound, either proinflammatory or anti-inflammatory, will depend on whether it promotes or inhibits the growth or invasiveness of pathogens and pathobionts at the mucosal interface, either by direct toxic effects or by promotion of competitor organisms; and the intensity of the inflammatory effect of a nutrient is predicted to depend on the degree to which it influences the abundance of gut pathogens and pathobionts or impairs the host's ability to contain microorganisms to the gastrointestinal tract. These hypotheses apply broadly across different classes of micro- and macronutrients that have been commonly ingested by animals, and provide a rich framework for devising testable hypotheses. Here we consider a few examples of these extensions of the model and its predictions.

Our model not only potentially helps explain the inflammatory effects of dietary fat, but also may be expanded to account for the production and modification of lipids by intestinal bacteria, which may have similar effects on pathogen colonization and thus are well suited to serve as signals of changes in microbial risk. Indeed, most SCFA are produced by commensal gut bacteria, primarily as a result of the fermentation of carbohydrates (Newburg et al. 2005). The importance of this source of SCFA is highlighted by recent studies that document high rates of sepsis and death when fecal SCFA disappear (Shimizu et al. 2011), a mortality risk that can be ameliorated by feeding patients SCFA precursors (galactooligosaccharides; Shimizu et al. 2009). Some saturated, *trans,* and hydrogenated FA are the products of bacterial metabolism and many of these FA also have antimicrobial properties (O'Shea et al. 2012). Thus, the FA milieu of the gut sends signals to innate immune cells not simply of impending risk due to ingestion of dietary FA, but also of the current makeup of the gut microbiota (Tazoe et al. 2008; Lee et al. 2010). Note that the predictions of our model are not changed by the source of FA: regardless of whether they originate in the diet or as a byproduct of in situ microbial metabolism, FA may alter gut microbiota and the invasiveness of bacteria at the intestinal mucosa and thus serve as signals of risk of bacterial infection and colonization.

If the nutrient signaling model is correct, similar predictions should apply to other nutrient classes encountered during vertebrate or human evolution and that reliably influence the gut microbiota. In this regard, it is notable that many secondary plant compounds generally follow the expected pattern of antimicrobial and anti-inflammatory effects. For example, phenolics from raspberries and blueberries inhibit the growth of pathogens such as *Salmonella typhimurium* and exert anti-inflammatory effects in humans (Puupponen-Pimia et al. 2005). Plant-derived phenolics also exert strong antimicrobial effects against oral pathogens, including *Porphyromonas gingivalis*; these compounds also inhibit the enzyme cyclooxygenase with strong anti-inflammatory effects (Sreenivasan and Gaffar 2008). The same pattern applies to resveratrol in red wine (Boban et al. 2010) and to antimicrobial spices used in many cuisines (Choi et al. 2011). Commonly used spices have broad-spectrum antimicrobial effects, and

their use by humans coincides with increased risk of bacterial contamination of food (Billing and Sherman 1998). Many spices and phenolics, particularly curcumin, directly inhibit NF-κB proinflammatory signaling in adipocytes, macrophages, and muscle cells (Aggarwal 2010).

In addition, carbohydrates are good candidates for nutrient signaling. Simple sugars, such as glucose and sucrose, increase the survival of pathogens in an acidic environment such as that represented by the gut (Goepfert and Hicks 1969). Overconsumption of simple sugars results in proliferation of gut bacteria and the appearance of bacterial products in blood (Bergheim et al. 2008). Like long-chain saturated fats, simple sugars can directly stimulate an inflammatory response (Brown et al. 2008). Other carbohydrates, particularly oligosaccharides (dietary fiber) and glycans, interfere with pathogen binding to intestinal epithelial cells. Human milk oligosaccharides have been shown to interfere with the adherence of *E. coli, Vibrio cholerae*, and *Salmonella* to human colonocytes (Coppa et al. 2006) and can reduce bacterial toxin production (Newburg 2009). Pectin oligosaccharides can have similar beneficial effects in preventing colonization of *Campylobacter* (Ganan et al. 2010) and galactooligosaccharides reduce the epithelial adherence of *E. coli* and other pathogens (Shoaf et al. 2006; Quintero et al. 2011). Other oligosaccharides exert direct bactericidal effects on *Staphylococcus aureus* and *E. coli* (Fernandes et al. 2008). Oligosaccharides are also the precursors of SCFA production in the human colon by bacterial fermentation. These fermentation products lower intestinal pH, inhibiting the growth of pathogenic species (Newburg et al. 2005). Oligosaccharides also stimulate the growth of beneficial commensals such as *Bifidobacterium* and competitively displace pathogens (Kapiki et al. 2007). Human milk oligosaccharides are the primary nutrient substrate for beneficial *Lactobacillus* and *Bifidobacterium* species that have a proctective function by producing antibacterial peptides (Fakhry et al. 2009). The antibiotic-like substances (bacteriocins) produced by commensal *Lactobacillus* in the small intestine have activity against a wide variety of enteric pathogens, including *E. coli*, *Shigella sonnei*, and *Salmonella typhimurium* (Fakhry et al. 2009; O'Shea et al. 2012). In light of the antipathogen effects of oligosaccharides and their ability to promote the growth of beneficial commensals, our model suggests that it is no coincidence that oligosaccharides have direct anti-inflammatory effects similar to those initiated by "healthy" fats (Bode et al. 2004). The nutrient signaling model is eminently testable, and may be applied to any class of nutrient that has been common in the human diet and that influences gut microbiota.

Although the hypothesis can be generalized to other nutrients, cross-species differences provide important test cases of the model and its predictions. In species with long evolutionary histories of reliance upon narrow diets, the absence of nutrient variability should be associated with little or no diet-induced variation in gut flora. Such species are thus predicted to exhibit reduced immune sensitivity to nutrients. Parasitic species, whose diet is limited to nutrients derived from its host, provide an example of an organism with a constrained diet. For example, lampreys and vampire bats that consume blood exclusively are expected to show little direct nutrient-induced inflammation compared to taxonomically related nonparasitic species that rely upon a more diverse and variable diet. We imagine that ecologists and nutritionists will be able to devise a wide range of innovative tests of the model that we propose here.

Public Health and Clinical Implications

The nutrient signaling model has important implications for the treatment and prevention of diseases that involve chronic, low-grade inflammation. Although we have focused narrowly on testing a hypothesis for the evolutionary function of diet-based inflammatory modulation, it is important to note that inflammation is itself also a trigger of metabolic disturbances (such as insulin resistance) that are independent risk factors for many common diseases such as diabetes and cardiovascular disease

(Fernández-Real and Ricart 2003). Thus, our model could help explain not only the body's inflammatory responses to specific nutrients, but could also shed light on downstream physiologic and health impacts of diet-induced inflammation. The model proposed here leads to a testable framework to refine our understanding of the health impacts of specific nutrients and food types. Screening of foods for effects on the gut microbiota and on intestinal barrier function may reveal new roles for gut microorganisms in the pathogenesis of chronic degenerative diseases and could also point to new antimicrobial treatment strategies. Improved understanding of the mechanisms by which specific nutrients are recognized and used to induce changes in inflammation could provide rich targets for pharmaceutical development and drug discovery. Ultimately, if validated, this model holds promise to bring order to a large and important domain of nutrition research aimed at identifying helpful nutrients and related pharmaceuticals.

Although the literature that we review provides preliminary support for the model that we outline, diet can influence health via many pathways. A direct inflammatory effect of nutrients is only one such effect, and only part of the inflammatory burden is attributable to diet. Proinflammatory risk factors for chronic inflammatory diseases also include factors such as excess accumulation of abdominal fat (McDade et al. 2009), cigarette smoking (Ridker and Silvertown 2008), and exposure to bacterial endotoxin (Cani and Delzenne 2009). Our model potentially complements current understanding of diseases that involve chronic low-level inflammation by helping explain inflammation that is directly induced by dietary fats and other immune-modulating nutrients.

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