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# Fatty acid metabolism: Implications for diet, genetic variation, and disease

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ABSTRACT

Cultures across the globe, especially Western societies, are burdened by chronic diseases such as obesity, metabolic syndrome, cardiovascular disease, and cancer. Several factors, including diet, genetics, and sedentary lifestyle, are suspected culprits to the development and progression of these health maladies. Fatty acids are primary constituents of cellular physiology. Humans can acquire fatty acids by *de novo* synthesis from carbohydrate or protein sources or by dietary consumption. Importantly, regulation of their metabolism is critical to sustain balanced homeostasis, and perturbations of such can lead to the development of disease. Here, we review *de novo* and dietary fatty acid metabolism and highlight recent advances in our understanding of the relationship between dietary influences and genetic variation in fatty acid metabolism and their role in chronic diseases.



## Contents



Abbreviations: SNP, single nucleotide polymorphism; SAFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; ACLY, ATP citrate lyase; ACACA, acetyl-CoA carboxylase 1; ACACB, acetyl-CoA carboxylase 2; FASN, fatty acid synthase; ELOVL, elongation of fatty acid; LPL, lipoprotein lipase; SCD, stearoyl-CoA desaturase; FADS, fatty acid desaturase; ALA, alpha-linolenic acid; SREBF, sterol response element binding factor; SREBP, sterol response element binding protein; ChREBP, Carbohydrate response element binding protein; BRCA1, breast cancer susceptibility gene 1; EPA, eicosapentaenoic acid; ETA, eicosatetraenoic acid; AA, arachidonic acid; DGLA, dihomo-gamma-linoleic acid; LC-PUFA, long chain polyunsaturated fatty acid; DHA, docosahexaenoic acid; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; DOHaD, Developmental Origins of Health and Disease; GWAS, genome wide association study

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## 1. Introduction

The epidemic spread of obesity and metabolic syndrome is raising public health concerns across the globe. The factors that distinguish these diseases are also known contributors to cardiovascular disease and cancer, the two most common causes of death in the United States (Hoyert & Xu, 2012). Epidemiologic studies have shown an increased prevalence of these diseases in immigrating populations to Western societies (Nasseri & Moulton, 2011; Seeff & McKenna, 2003). One of the major hypotheses to explain this observation is the abrupt and dramatic change in diet upon emigration, particularly changes in dietary fatty acid consumption. A prevailing body of literature suggests not only the quantity, but more importantly, the quality, of dietary fat consumption modulates disease (Berquin, Edwards, Kridel, & Chen, 2011; Berquin et al., 2007; Suburu & Chen, 2012). Specifically, dietary omega-6 polyunsaturated fatty acid (PUFA) can be pro-inflammatory mediators, while omega-3 PUFA acts as anti-inflammatory mediators (Serhan & Petasis, 2011). As such, tipping the balance of an immigrant's dietary consumption can lead to a chronic state of inflammation and promote the development and progression of cardiovascular disease and cancer.

New evidence suggests various populations may differentially metabolize dietary fatty acids (Teslovich et al., 2010), implying that the risk for chronic inflammation, metabolic syndrome, and cardiovascular disease may be inheritable. Even the progression of cancer, which is well known to be a disease of genetic alterations, can be exacerbated by pro-inflammatory lipid metabolism (Wang & Dubois, 2010). Discrepancies observed in the incidence of cardiovascular disease and cancer in various ethnic populations have been attributed to socioeconomic variance (Marmot, Allen, Bell, Bloomer, & Goldblatt, 2012). However, more recent data suggests genetic diversity in the form of single nucleotide polymorphisms (SNPs) found in several lipid metabolism genes may be a major contributing factor to these epidemiological health disparities (Illig et al., 2010; Kathiresan et al., 2009; Teslovich et al., 2010). Despite the potential inheritance of genetic risk factors for cardiovascular disease and cancer progression, advancements in the new field of metabolomics are yielding promising work to identify metabolic biomarkers of disease that may fuel diagnostic testing and/or predict health outcome. The purpose of this article is to review *de novo* and dietary fatty acid metabolism and highlight the most recent findings in genetic variation found in fatty acid metabolism genes as they relate to dietary fat consumption and various diseases.

## 2. Fatty acids: a biological necessity

Fatty acids are fundamental molecules of cellular biology. Composed of hydrogenated carbons with a carboxyl moiety at the alpha carbon, mammalian fatty acids are divided into three major groups based on the quantity of double bonds found within the carbon chain: saturated fatty acids (SAFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA). SAFA are fully hydrogenated, containing zero double bonds. They are a primary constituent of glycerolipids as well as phospholipids and sphingolipids found in cellular membrane structures. SAFA may also act as post-translational modifiers, thereby dictating the activity and location of cellular signaling proteins. MUFA contain a single double bond, most commonly found between the 9th and 10th carbons from the alpha carbon, and occasionally between the 7th and 8th carbons. MUFA are also primary constituents of cellular membrane structures and glycerolipids. PUFA have more than one, and as many as six, double bonds in their carbon chain. PUFA are found in phospholipids of membrane structures, and may also act as precursors to a variety of lipid signaling molecules. The most unique characteristic of PUFA metabolism is the inability for mammals to synthesize them *de novo*. While mammals express the necessary enzymes to convert carbohydrate and protein-derived carbons into SAFA and MUFA, they lack the desaturase enzymes required for producing the limiting substrate for PUFA synthesis. Therefore, PUFA are considered essential fatty acids that must be acquired from the diet. It is important to note that not only the degree of saturation, but also the carbon chain length can differentiate fatty acids and their biological roles. Within each class of fatty acids the carbon chain length may vary greatly, with as few as 12 and as many as 30 carbons. The chain length of fatty acids in cellular membrane can modify the membrane properties, such as fluidity and formation of microdomains and signaling platforms, ultimately altering susceptibility to cell death or survival (Iwabuchi, Nakayama, Iwahara, & Takamori, 2010; Sassa, Suto, Okayasu, & Kihara, 2012).

Unlike PUFA, SAFA and MUFA may be acquired from the diet or produced *de novo*. Despite identical biochemical structures, it remains unclear whether dietary and *de novo* fatty acids are equivalent or two separate pools of fatty acids used for distinct biological functions in the body. A number of features distinguishing *de novo* and dietary fatty acid metabolism directed questions of why dietary SAFA and MUFA are likely to fall short in compensating for impaired *de novo* fatty acid synthesis. First, the major biological function of fatty acid synthesis is to store energy from carbohydrate-derived carbon precursors as compact fatty acids. This process occurs in the cytosol of cells and is performed by a series of enzymes beginning with the production of acetyl-CoA by ATP citrate lyase (ACLY). Acetyl-CoA is then metabolized by the rate limiting enzyme of the fatty acid synthesis pathway, acetyl-CoA carboxylase 1 (ACACA) to produce the limiting reagent, malonyl-CoA. The multifunctional enzyme, fatty acid synthase (FASN) then produces saturated, short (14:0) to medium (18:0) chain fatty acids by sequentially adding malonyl-CoA to the growing acyl chain through a series of