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Editorial: Dietary Lipid Absorption

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The composition of dietary fat influences tissue fatty acid composition, which in turn impacts cellular function through a number of different processes. This includes changes in signaling, lipid metabolism, and transcriptional activities that normally function to maintain intracellular fatty acid homeostasis. The consumption of high levels of dietary fat in excess of caloric expenditure is linked with obesity and the disruption of normal homeostatic mechanisms governing lipid metabolism. Data from the Centers for Disease Control and Prevention show that obesity (defined as a BMI≥30) represents a considerable health concern in the United States. Of particular note is that for adult men, the prevalence of obesity was 33% in 2006; the prevalence for adult women was slightly higher at 35%. Obesity is also of concern for children and adolescents where in 2006, 16% were considered obese (above the 95th percentile of the 2000 BMI-for-age growth charts).

Statistics released by the American Heart Association show that the rise in obesity correlates with high low-density lipoprotein-cholesterol (LDL-C) levels. In 2004, nearly 33% of adults in the United States (age 20 and older) had LDL-C levels of 130 mg/dL or higher. Obesity is associated with disturbances in lipid metabolism including triglycerides, free fatty acids and lipoprotein cholesterol. One common finding in obese individuals is elevated levels of circulating free fatty acids that in turn increases fatty acid internalization and ectopic accumulation of triglycerides. Such disturbances in normal lipid

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metabolic homeostasis are associated with changes in fatty acid oxidation, accumulation of reactive oxygen species, the synthesis of ceramide and ER stress. The correlation between chronically elevated plasma free fatty acids and triglycerides and low highdensity lipoprotein-cholesterol (HDL-C) levels with the development of obesity, insulin resistance and cardiovascular disease has led to the hypothesis that decreases in pancreatic insulin production, cardiac failure, arrhythmias, and hypertrophy are due to aberrant accumulation of lipids in these tissues. This Special Issue of *Immunology, Endocrine and Metabolic Agents in Medicinal Chemistry*, with a focus on dietary lipid absorption, is particularly timely given the obesity epidemic and comes from many of the leading experts in fatty acid and sterol transport. These review articles cover five general areas: [1] Fatty acid transport, with a focus on fatty acid translocase (CD36) and members of the fatty acid transport protein (FATP) family; [2] sterol transport, with a focus on Niemann-Pick C1-Like 1 (NPC1L1) and ATP binding cassette transporters G5 and G8 (ABCG5/ABCG8); [3] intracellular fatty acid trafficking, with a specific focus on liver fatty acid binding protein (L-FABP); [4] therapeutic properties of n-3 polyunsaturated fatty acids; and [5] chylomicron synthesis with a focus on regulation and the role of apolipoproteins.

Articles by Nassir and Abumrad and Black *et al.* summarize recent research into defining the molecular mechanisms involved in fatty acid transport, particularly at the level of the plasma membrane. Most of the data indicate this process consists of both diffusive and protein-mediated components. In the context of dietary lipid absorption, Nassir and Abumrad present a current view of fatty acid translocase (CD36), which is expressed in the proximal intestine and thought to function in coordinating absorption of fatty acids and cholesterol for optimal chylomicron formation and secretion. The article by Black *et al.* summarizes current our understanding of the fatty acid transport protein (FATP) family members, which in some instances appear to associate with long chain acyl CoA synthetase (Acsl). One operational strategy governing the transport of fatty acids proceeding through FATP and Acsl is vectorial acylation whereby fatty acids are transported and concomitantly activated to CoA thioesters for further

metabolism. As pointed out in these two articles, proteins involved in intestinal fatty acid transport, specifically CD36 and FATP, represent potentially important and accessible targets for the management of hyperlipidemia by reducing absorption of dietary lipid. Along these lines, high throughput strategies have been employed to select for small molecule inhibitors of FATP, but with caveat that disrupting fatty acid import of systemic trafficking pathways may have unfavorable consequences (*ref* Black *et al.*). The relatively high frequency of polymorphism in the CD36 gene and the corresponding high incidence of CD36 deficiency in some populations suggest this protein may contribute to individual variations in lipid absorption and processing and thus like FATP may be an especially attractive drug target (*ref* Nassir and Abumrad).

Brown and Yu review the current state of knowledge regarding the function of Niemann-Pick C1-Like 1 (NPC1L1) and ATP-binding cassette transporters G5 and G8 (ABCG5/ABCG8), which represent opposing apical intestinal cholesterol transporters. NPC1L1 is essential for intestinal cholesterol absorption and protection against excessive biliary sterol loss while ABCG5/ABCG8 is critical for promoting biliary cholesterol secretion in the liver and is likely to provide a direct role in intestinal disposal of sterols. Both NPC1L1 and ABCG5/ABCG6 represent therapeutic targets aimed at reduction of circulating LDL-C, which represent a major risk factor for the development of atherosclerotic cardiovascular disease. Of particular note is the compound ezetimibe currently in clinical use, which specifically targets NPC1L1 and reduces intestinal cholesterol absorption.

Intracellular fatty acid trafficking in liver and intestine is controlled in large part by fatty acid binding protein, L-FABP. As reviewed by Newberry and Davidson, of particular importance is the finding that members of the FABP multigene family serve as important metabolic sensors that regulate fatty acid trafficking and metabolic compartmentalization. Studies using *L-Fabp−/−* mice are consistent with the notion that L-FABP provides an important role in modulating hepatic fatty acid trafficking in response to augmented lipid mobilization from adipose stores. The *L-Fabp−/−* mice are also protected against obesity and hepatic steatosis when fed a high saturated fat diet or a high saturated

fat diet containing cholesterol, but not when fed a high fat diet containing polyunsaturated fat (*ref* Newberry and Davidson). These observations are of particular interest as they suggest the lipid sensing functions of L-FABP may, in part, be dependent upon specific fatty acid species. L-FABP appears to regulate processes in both intestinal and hepatic fatty acid trafficking through specific diet-gene interactions thus providing an important link in the pathogenesis of diet-induced obesity and hepatic steatosis.

The articles by Kim *et al.* and Calder present current research findings showing dietary n-3 polyunsaturated fatty acids (PUFA) exhibit anti-inflammatory bioactive properties, compared to n-6 PUFA. The n-6 PUFA arachidonic acid is the precursor of inflammatory eicosanoids including prostaglandin E_2 and leukotriene B_4. The n-3 PUFAs eicosapentaenoic acid and docosahexaenoic acid inhibit arachidonic acid metabolism to inflammatory eicosanoids and give rise to mediators that are antiinflammatory (*ref* Calder). As pointed out in the article by Kim *et al.* there are multiple mechanisms by which n-3 PUFAs exert these affects, particularly in the context of the immune cell response. The putative targets of anti-inflammatory n-3 PUFAs include cytokine production, antagonism of n-6 PUFA metabolism, binding to nuclear receptors as ligands, and the alteration of signaling protein acylation. Work by Kim *et al.* has extended this further by showing n-3 PUFAs function in the coalescence of lipid rafts resulting in specialized signaling platforms at the plasma membrane. Given the anti-inflammatory properties of n-3 PUFAs they may be of therapeutic use in a variety of acute and chronic inflammatory settings, including inflammatory bowel diseases and asthma, but it is clear that additional clinical trails are required (*ref* Calder).

The final two articles by Ji *et al.* and Mansbach address the process formation of chylomicron formation s following fatty acid absorption, which includes and summarizes new findings in regarding the synthesis and secretion of chylomicrons that distribute absorbed dietary lipid. Ji *et al.* describe the roles of the various lipid esterifying enzymes in the metabolism of the absorbed partial glycerides and fatty acids and detail the formation of chylomicrons and very low-density lipoprotein. The article by Mansbach provides additional information

detailing how triacylglycerol (TAG) crosses the endoplasmic reticulum and is incorporated into the developing chylomicron through a two-step process involving apolipoprotein B48. In this latter article, there is discussion regarding the regulation of pre-chylomicron transport vesicle generation through the action of PKCζ. Ji *et al.* point out in their article that a thorough understanding of combined processes involved in intestinal lipid absorption provides an invaluable framework of information to address obesity and hyperlipidemia.

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