Commentary

The FTO Gene, Browning of Adipose Tissue and Omega-3 Fatty Acids

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Body mass index (BMI) is a complex trait with high heritability. In population studies, it is considered a surrogate for obesity [1]. In large genome-wide association studies, the strongest genetic signal for BMI has been the fat mass and obesity-associated (FTO) locus [2]. Eighty-nine genetic variants within introns 1 and 2 of the FTO have been associated with BMI. Browning of adipose tissue has physiological relevance, and disorders of mitochondrial function and brown fat may play a role in pathophysiological aspects of obesity [3]. Browning adipocytes are a key site of energy expenditure; therefore, shifting adipocyte differentiation towards a brown adipocyte-like phenotype may increase energetic efficiency in mammals. Mammals have two types of adipose tissue: white adipose tissue (WAT), which is the most abundant, stores extra calories, and brown adipose tissue, which dissipates energy through mitochondrial uncoupling and the production of heat. Recently, a number of investigators have shown that there is a third type of fat cell, the 'beige' adipocyte. This beige cell transitions between states of energy storage and dissipation. It can be induced and is found in adult humans [4].

The potential importance of the fatty acid composition of dietary fats as a factor that plays a role in adipose tissue development and function has been actively investigated. Over the years, Ailhaud et al. [5], Massiera et al. [6] and Pisani et al. [8] have contributed enormously to understanding the role of arachidonic acid (AA) and its metabolites derived from the cyclooxygenase pathway in increasing WAT proliferation and decreasing browning of WAT. Under isoenergetic isolipidic conditions, inclusion of AA in the diet impaired brite adipocyte recruitment in the subcutaneous WAT compared to mice fed a standard diet [7]. The data of Massiera et al. [6] regarding the fat mass show that perinatal exposure of mice to a high omega-6 [linoleic acid (LA)] fatty acid diet, as it is today in Western diets, results in a progressive accumulation of body fat across generations. This is consistent with the data showing that in humans, overweight and obesity have steadily increased over the last 30–40 years, in addition to occurring earlier in life. Today, there is more obesity in children worldwide than ever before. The inhibitory role of the omega-6 fatty acids (LA + AA) in the browning process of white fat cells has been precisely investigated. Prostaglandin E₂ (PGE₂), a metab-

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olite of AA derived from the cyclooxygenase pathway, favors the formation of energy-storing white adipocytes, and prostaglandin $F_{2\alpha}$ (PGF_{2a}) prevents the formation of energy-dissipating brown-like adipocytes within WAT [8]. AA is highly metabolized in WAT obtained from various sources, diet, or from LA metabolism in the liver or from phospholipids of preadipocytes and adipocytes via phospholipase A2 and from endocannabinoids via fatty acid amide hydrolase and monoacylglycerol lipase activities. High-fat diets rich in omega-6 fatty acids have been shown to increase the risk of leptin resistance, diabetes and obesity in humans and rodents [9, 10], to lower mitochondrial activity and oxygen consumption, and to inhibit PPAR γ target gene expression and mitochondrial uncoupling protein-1 (UCP1) gene expression [8].

Recent studies have focused on the identification and manipulation of brown adipose tissue in humans and the role played by the gut microbiome in energy balance [11]. It appears that there is a close relationship between gut flora and the ability to switch from calorie storage to energy dissipation of brown fat depots. Increases in thermogenesis and browning of WAT results from exposure to colds or diet. Omega-3 fatty acids increase thermogenesis through the expression of UCP1 as well as increase fatty acid oxidation, whereas omega-6 fatty acids LA + AA lead to white fat deposits and obesity [8]. Omega-6 fatty acids inhibit browning of white adipose cells and increase their size and number [8]. Caesar et al. [11] showed that the type of dietary fat (lard or fish oil in rodents) is a major driver of the community structure of the microbiome, affecting both the composition and diversity of the gut microbiome. Their data show that interaction between the gut, microbiota and dietary lipids induces WAT inflammation and establish the gut microbiota as an independent factor aggravating inflammation during diet-induced obesity, and possibly a target to treat metabolic perturbations. Diet affects the composition of the microbiota, which not only reflects dietary changes, but also directly modulates the metabolic function of the host. Alterations in microbiome occur following antibiotic therapy. Transfer of specific bacteria genera can affect body weight, insulin sensitivity, and other metabolic measures. Chevalier et al. [12] showed that cold exposure, like dietary change, leads to changes in the composition of gut microbiota in mice, and when cold-adapted flora are transferred to a germ-free animal, the recipient mouse loses fat mass and has improved insulin sensitivity, which is brought about by a process that involves enhanced browning. These results also suggest that the effect of cold on beige fat recruitment may be relayed, in part through intestinal flora. The increased browning of white fat happens first, followed by an increased absorptive surface in the gut.

Whereas animal studies indicate a protection against obesity [5] by omega-3 fatty acids, human studies have produced conflicting results due to many factors such as not taking into consideration the background diet relative to omega-6 fatty acid content and relying on dietary histories instead of actual determination of omega-6 and omega-3 fatty acids in red blood cell membrane phospholipids [13, 14]. Recently, Wang et al. [15] showed that the risk of being overweight or obese during a mean of 10.4 years of follow-up in the NIH Women's Health Initiative study is inversely associated with the omega-3 fatty acids in red blood cell membrane phospholipids, while the omega-6 fatty acid and the omega-6/omega-3 ratio were positively associated with longitudinal weight gain.

Genome-wide association studies [2, 3] have identified more than 90 loci that contain genetic variants associated with obesity. Many of these variants are in intronic regions. The strongest genetic association with risk to polygenic obesity are single nucleotide variants (SNVs) in introns 1 and 2 of the FTO gene. There are 89 SNVs in FTO introns 1 and 2. Deciphering how these variants regulate gene expression has been difficult. Recently, Claussnitzer et al. [16] reported a strategy and defined the causal SNV and the mechanisms of function in preadipocytes. The authors provide evidence for the rs1421085 T to C SNV to result in a cellular phenotype consistent with obesity in primary human adipocytes, including

decreased mitochondrial energy generation and increased triglyceride accumulation. The data of Claussnitzer et al. [16] show that polymorphic differences in noncoding nucleotide sequences change the basic function of human adipocytes from substrate storage to fuel utilization through enhanced thermogenesis. They established a process by which it is now feasible to test the functionality of noncoding SNVs and their interactions with enhancers and repressors, as well as to test how polymorphisms in SNVs relate to chronic diseases, provide support that browning of white adipose tissue has physiological relevance, and that disorders of mitochondrial function and brown fat may play a role in the pathophysiological aspects of obesity. Their study [16] provided evidence that the risk allele rs1411085 T to C SNV resulted in an increased expression of IRX3 and IRX5 genes in preadipocytes, which shifted the development of these cells toward the ‘white program’ and increased lipid storage, whereas knockdown of IRX3 and IRX5 genes restored thermogenesis in adipocytes from persons at high risk for obesity. Thus, the risk allele functioned similarly to AA metabolites, PGE2 and PGF2a, increasing proliferation of white adipose tissue and decreasing its browning, respectively, whereas the knockdown of IRX3 and IRX5 genes functioned similarly to omega-3 fatty acid metabolites, increasing the browning of the adipose tissue, mitochondrial biogenesis and thermogenesis. The AA metabolites PGE2 and PGF2a lead to increases in white adipose tissue and decreases in the browning process, respectively. Human studies have shown a direct relationship between plasma AA levels and infant body weight, as well as between AA levels in adipose tissue lipids and BMI in children in Cyprus and Crete [17, 18]. In another study, a higher omega-6/omega-3 fatty acid ratio of cord blood plasma was associated with higher subscapular and triceps skinfold thickness and risk of obesity at 3 years of age (BMI ≥95th percentile for age and sex) [19]. Considering the high omega-6/omega-3 fatty acid ratio of Western diets and the role of AA in adipose cell differentiation, proliferation, and decreasing browning of white adipose tissue, further research should include studies on the effects of omega-3 fatty acids in blocking the effects of the risk allele (rs1421085), which appears to be responsible for the association between the first intron of the FTO gene and obesity in humans.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

- 1 Simopoulos AP, Van Itallie TB: Body weight, health, and longevity. *Ann Intern Med* 1984;100:285–295.
- 2 Yang J, Loos RJF, Powell JE, et al: FTO genotype is associated with phenotypic variability of body mass index. *Nature* 2012;490:267–272.
- 3 Locke AE, Kahali B, Berndt SI, et al: Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;518:197–206.
- 4 Rosen ED, Spiegelman BM: What we talk about when we talk about fat. *Cell* 2014;156:20–44.
- 5 Ailhaud G, Massiera F, Weill P, Legrand P, Alessandri JM, Guesnet P: Temporal changes in dietary fats: role of n-6 polyunsaturated fatty acids in excessive adipose tissue development and relationship to obesity. *Prog Lipid Res* 2006;45:203–236.
- 6 Massiera F, Saint-Marc P, Seydoux J, Murata T, Kobayashi T, Narumiya S, Guesnet P, Amri EZ, Negrel R, Ailhaud G: Arachidonic acid and prostacyclin signaling promote adipose tissue development: a human health concern? *J Lipid Res* 2003;44:271–279.
- 7 Pisani DF, Ghandour RA, Beranger GE, Le Faouder P, Chambard JC, Giroud M, Vegiopoulos A, Djedaini M, Bertrand-Michel J, Tauc M, Herzig S, Langin D, Ailhaud G, Duranton C, Amri EZ: The ω6-fatty acid, arachidonic acid, regulates the conversion of white to brite adipocyte through a prostaglandin/calcium mediated pathway. *Mol Metab* 2014;3:834–847.
- 8 Pisani DF, Amri EZ, Ailhaud G: Disequilibrium of polyunsaturated fatty acids status and its dual effect in modulating adipose tissue development and functions. *OCL* 2015;22:D405.

- 9 Nuernberg K, Breier BH, Jayasinghe SN, Bergmann H, Thompson N, Nuernberg G, Dannenberger D, Schneider F, Renne U, Langhammer M, Huber K: Metabolic responses to high-fat diets rich in n–3 or n–6 long-chain polyunsaturated fatty acids in mice selected for either high body weight or leanness explain different health outcomes. *Nutr Metab (Lond)* 2011;8:56.
- 10 Phillips CM, Goumidi L, Bertrais S, Field MR, Ordovas JM, Cupples LA, Defoort C, Lovegrove JA, Drevon CA, Blaak EE, Gibney MJ, Kiec-Wilk B, Karlstrom B, Lopez-Miranda J, McManus R, Hercberg S, Lairon D, Planells R, Roche HM: Leptin receptor polymorphisms interact with polyunsaturated fatty acids to augment risk of insulin resistance and metabolic syndrome in adults. *J Nutr* 2010;140:238–244.
- 11 Caesar R, Tremaroli V, Kovatcheva-Datchary P, Cani PD, Bäckhed F: Crosstalk between gut microbiota and dietary lipids aggravates WAT inflammation through TLR signaling. *Cell Metab* 2015;22:658–668.
- 12 Chevalier C, Stojanović O, Colin DJ, Suarez-Zamorano N, Tarallo V, Veyrat-Durebex C, Rigo D, Fabbiano S, Stevanović A, Hagemann S, Montet X, Seimbille Y, Zamboni N, Hapfelmeier S, Trajkovski M: Gut microbiota orchestrates energy homeostasis during cold. *Cell* 2015;163:1360–1374.
- 13 Buckley JD, Howe PR: Anti-obesity effects of long-chain omega-3 polyunsaturated fatty acids. *Obes Rev* 2009;10:648–659.
- 14 Simopoulos AP: An increase in the omega-6/omega-3 fatty acid ratio increases the risk for obesity. *Nutrients* 2016;8:128.
- 15 Wang L, Manson JE, Rautiainen S, Gaziano JM, Buring JE, Tsai MY, Sesso HD: A prospective study of erythrocyte polyunsaturated fatty acid, weight gain, and risk of becoming overweight or obese in middle-aged and older women. *Eur J Nutr* 2016;55:687–697.
- 16 Claussnitzer M, Dankel SN, Kim KH, Quon G, Meuleman W, Haugen C, Glunk V, Sousa IS, Beaudry JL, Puviindran V, Abdennur NA, Liu J, Svensson PA, Hsu YH, Drucker DJ, Mellgren G, Hui CC, Hauner H, Kellis M: FTO obesity variant circuitry and adipocyte browning in humans. *N Engl J Med* 2015;373:895–907.
- 17 Savva SC, Chadigeorgiou C, Hatzis C, Kyriakakis M, Tsimbinos G, Tornaritis M, Kafatos A: Association of adipose tissue arachidonic acid content with BMI and overweight status in children from Cyprus and Crete. *Br J Nutr* 2004;91:643–649.
- 18 Jensen CL, Prager TC, Fraley JK, Chen H, Anderson RE, Heird WC: Effect of dietary linoleic/alpha-linolenic acid ratio on growth and visual function of term infants. *J Pediatr* 1997;131:200–209.
- 19 Donahue SM, Rifas-Shiman SL, Gold DR, Jouni ZE, Gillman MW, Oken E: Prenatal fatty acid status and child adiposity at age 3 years: results from a US pregnancy cohort. *Am J Clin Nutr* 2011;93:780–788.