FTO Intronic SNP

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Contributors: Endre Kristóf , Rini Arianti , Abhirup Shaw , Attila Vámos , Zoltan Vereb
Submitted by: Endre Kristóf

Definition

Browning of white adipose tissue shifts adipocytes from energy storage white to energy expenditure beige types. The balance between the two adipocyte populations in white adipose tissue is highly determined by noncoding variants of the Fat mass and obesity-associated (FTO) locus which has the strongest association with obesity. The rs1421085 FTO risk allele results in a loss of ARID5B repression of IRX3 and IRX5 which promotes excess white adipocyte formation. Recent studies have revealed the presence of brown adipose tissues at several anatomical sites in humans including the deep-neck (DN). We found that the characteristic gene expression profile and associated pathways of DN brown adipocytes were determined by partially overlapping effects of tissue site specific commitments of the stem cells, PPARγ stimulation and the FTO status of donors. The presence of FTO rs1421085 risk alleles had a strong influence, manifested during differentiation, on browning resulting in compromised expression of metabolic and mitochondrial genes as well as pathways which are decisive in thermogenesis.

1. History

Brown and beige adipocytes play a major role in maintaining the constant core body temperature of hibernating, small, and newborn animals, as well as in humans without shivering[1][2]. Their heat production is mainly mediated by uncoupling protein 1 (UCP1), a mitochondrial carrier protein, which uncouples ATP synthesis from the respiratory chain activity[1][3]. The stimulation of thermogenesis leads to increased energy expenditure that can ameliorate the energy balance during obesity and type 2 diabetes mellitus[4][5].

In adult humans, specific adipose depots are enriched in brown adipocytes; these expanse to 1–1.5% of total body mass and are mostly found in the perirenal, deep-neck (DN), and paravertebral regions[6]. It is still unrevealed whether these thermogenic fat depots represent the classical brown or the beige type of adipocytes by origin and function, even after recent intense studies of DN tissue, which could be compared to paired subcutaneous (SC) fat samples[7][8][9][10].

Genome-wide association studies (GWAS) have identified fat mass and obesity-associated, *FTO* as a gene predisposing to obesity[11]. The 2-oxoglutarate dependent dioxygenase enzyme, encoded by the proposed*FTO* gene, is a member of a family of DNA repair enzymes which plays an important role in fatty acid metabolism and post-translational modifications in addition to the repair mechanism[12]. SNPs appearing in the exons of the gene modify the activity of the enzyme, however, the exact molecular mechanism remained unknown[13]. Overexpression of FTO in mice resulted in a significant increase in fat mass in abdominal white adipose tissue when mice were fed either with a normal or a high-fat diet, as well as an increase in food intake[14]. SGBS human preadipocytes deficient in this enzyme had elevated UCP1 expression and uncoupled respiration, without any changes in mitochondrial mass or structure when they were differentiated to white adipocytes[15].

2. Development

The ratio of brown and white adipocytes is partially determined during the early differentiation of mesenchymal progenitors into adipocyte subtypes, which is strongly influenced by genetic predisposition[16]. A recent GWAS of body fat distribution identified 98 independent adiposity loci which potentially could affect the appearance of thermogenic fat[17]. In a detailed study by Claussnitzer et al. it has been described that single nucleotide polymorphism (SNP) rs1421085 underlies the genetic association between the FTO locus and obesity and the presence of the C risk-allele of the FTO locus results in a cell autonomous, IRX3 and IRX5 dependent shift in the gene expression programs toward white instead of brown adipocyte with lipid-storage and a decrease in thermogenesis. When the T/T healthy genotype is carried at the rs1421085 position, the ARIDB5 repressor is able to bind to this site not allowing IRX3 and 5 expression which allows adipocyte precursors to be committed for browning differentiation[18]. In parallel, IRX5 knockout mice had reduced fat

mass and were protected from diet-induced fat accumulation. In addition, IRX5 knockdown increased the mitochondrial respiration in isolated murine adipocytes[19]. On the contrary, it was also shown that IRX3 promotes the browning of white adipocytes as directly bound to *UCP1* promoter and its rare variants are associated with human obesity risk[20].

3. Influences

We screened and compared global gene expression patterns by RNA sequencing of human adipose-derived stromal cells (hASCs)-derived white and brown (in response to sustained PPARγ stimulation) differentiated adipocytes. The hASCs were isolated from paired DN and SC adipose tissue samples of nine donors, three of each FTO rs1421085 genotype: T/T-risk-free, T/C-heterozygous, and C/C-obesity-risk. DN adipocytes displayed higher browning features and characteristic differentially expressed gene patterns revealing associated pathways which were highly expressed (thermogenesis, interferon, cytokine, retinoic acid) or downregulated (particularly extracellular matrix remodeling) as compared to SC ones. In our study, *IRX3* was significantly higher expressed in samples with FTO obesity-risk alleles that support its suppressive role in thermogenesis. Interestingly, DN progenitors and differentiated adipocytes had also lower expression of the IRX family members, including *IRX1-3* and *5-6* as compared to SC adipocytes, irrespective to their FTO allele status, which suggests that an FTO rs1421085 SNP-independent mechanism in DN samples suppresses *IRX* gene expression. Finally, we found that the expression of metabolic, mitochondrial, and thermogenic genes, with *SLC2A4*, *EHHADH*, *PPARGC1A*, *CPT1B*, and *FABP4* as prominent network stabilizers, was strikingly compromised by the FTO rs1421085 genotypes of the progenitors.

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Keywords

adipocyte browning;deep-neck;FTO obesity-risk allele;thermogenesis;obesity;mitochondria