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Review article

Metabolic switch during adipogenesis: From branched chain amino acid catabolism to lipid synthesis☆

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ABSTRACT

Fat cell metabolism has an impact on body homeostasis and its proper function. Nevertheless, the knowledge about simultaneous metabolic processes, which occur during adipogenesis and in mature adipocytes, is limited. Identification of key metabolic events associated with fat cell metabolism could be beneficial in the field of novel drug development, drug repurposing, as well as for the discovery of patterns predicting obesity risk. The main objective of our work was to provide comprehensive characterization of metabolic processes occurring during adipogenesis and in mature adipocytes. In order to globally determine crucial metabolic pathways involved in fat cell metabolism, metabolomics and transcriptomics approaches were applied. We observed significantly regulated metabolites correlating with significantly regulated genes at different stages of adipogenesis. We identified the synthesis of phosphatidylcholines, the metabolism of even and odd chain fatty acids, as well as the catabolism of branched chain amino acids (BCAA; leucine, isoleucine and valine) as key regulated pathways. Our further analysis led to identification of an enzymatic switch comprising the enzymes Hmgcs2 (3-hydroxy-3-methylglutaryl-CoA synthase) and Auh (AU RNA binding protein/enoyl-CoA hydratase) which connects leucine degradation with cholesterol synthesis. In addition, propionyl-CoA, a product of isoleucine degradation, was identified as a putative substrate for odd chain fatty acid synthesis. The uncovered crosstalks between BCAA and lipid metabolism during adipogenesis might contribute to the understanding of molecular mechanisms of obesity and have potential implications in obesity prediction.
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1. Introduction

Obesity has been identified as a major risk factor for chronic diseases, such as cardiovascular disease, hypertension, dyslipidemia, hyperglycemia [1], type 2 diabetes, insulin resistance [2,3], and some types of cancer [4] including colon [5], breast [6] and prostate cancer [7], as well as an increased risk of premature death [8]. Thus, identification of markers predicting the risk of obesity as well as determination of drug targets could strongly benefit the health system. Studies on obesity have recognized several factors including genetic background [9], interplay between environment and genetics [10] as well as epigenetic mechanisms [11] to be associated with this multifactorial disorder. Further understanding of obesity and its co-morbidities could be provided by metabolomics, enabling a global overview on metabolic processes in the body, which simultaneously reflect the sum of gene expression, protein abundance, and environmental influence [12]. Lately, metabolomics applied to a human cohort for the investigation of the metabolic difference between obese and lean individuals revealed a possible origin of insulin resistance associated with obesity [13]. This study highlighted that an increase in plasma branched chain amino acid (BCAA) concentrations is a hallmark of adult obese individuals. The BCAAs have also been shown to contribute to obesity-associated insulin resistance [13]. In contrast, a study with obese children and children with type 2 diabetes indicated down-regulation in the plasma BCAA levels compared to healthy lean subjects [14,15]. Clearly, BCAA metabolism is altered in obesity; however, our current understanding how it is regulated and cross-linked to other pathways has not been fully elucidated.

This discrepancy could be associated with the dynamics of fat cell turnover [16]. It has been shown that the number of fat cells is settled during childhood and adolescence and is constant in adulthood of lean and obese individuals, independent of weight loss or gain [16]. Consequently, differences in fat cell fates of children/adolescents and adults could have direct impact on the diverse patterns in their metabolism, since adipocytes are involved in synthesis and secretion of several hormones [17] and thereby contribute to energy homeostasis [18]. Thus, an increased adipocyte size and/or number results in an increase of molecules released by adipocytes including e.g. adipokines, free fatty acids, and inflammatory mediators, which affect other tissues such as liver, muscle, or neural connections leading to co-morbidities of obesity [3,19].

Exploration of ongoing metabolic changes during adipogenic cell differentiation and in mature adipocytes might facilitate the identification of metabolic pathways and biomarkers useful for obesity prediction and identification of novel drug targets.

However, possibilities to perform mechanistic and functional analyses in the whole organism are limited, and therefore we and others applied analyses on the molecular basis of adipogenesis in cell culture.

The adipogenic cell differentiation process has been already investigated with different omics tools, particularly transcriptomics [20–22], proteomics [23–25], and recently metabolomics [26]. However, more specific insight into the regulation of metabolic pathways can be gained by combining different omics technologies. For example, metabolomics and genomics have already been successfully applied by us in human studies (mGWAS) [12,27–29] and generated new hypotheses for biomedical and pharmaceutical research [29].

In the present study we combined for the first time metabolomics and transcriptomics in order to provide a comprehensive overview on adipogenesis and fat cell metabolism using the murine 3T3-L1 cell culture model. Our main goal was to reveal interconnected pathways and biomarkers for adipogenesis to further facilitate the identification of targets useful in prediction and therapies of obesity.

We found associations between BCAA degradation products and intermediates of the cholesterol synthesis as well as even and odd chain fatty acid metabolism. The metabolic signatures of adipogenesis observed in our study further support the BCAAs as important players in fat metabolism and highlight odd-chain fatty acids and glycerophospholipids as novel biomarkers of adipogenesis. Furthermore, differences in BCAA metabolism between children/adolescents and adults observed previously [13–15], might be associated with the process of adipogenesis [16]. Therefore, a decreased BCAA level in children might suggest increased formation of fat cells and simultaneously serve as a biomarker for obesity prediction. The metabolic pathways of BCAA catabolism and glycerophospholipid synthesis should be considered as potential drug targets preventing obesity.

2. Materials and methods

2.1. 3T3-L1 Preadipocyte culturing and differentiation into adipocytes

3T3-L1 cells (murine preadipocytes) obtained from the American Type Culture Collection (ATCC) were grown at 37 °C in a 5% CO_2 humidified atmosphere in growth medium DMEM (High Glucose (4.5 g/L); PAA Laboratories), supplemented with 10% fatal bovine serum (FBS; PAA Laboratories), 100 IU/mL penicillin, and 100 mg/mL streptomycin (Invitrogen).

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