Biologia Serbica, 2022, 44(1): 11-17 DOI: 10.5281/zenodo.7075087

Minireview

Change of transcriptomic signature in subcutaneous adipose tissue induced by weight loss

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Accepted: 1 August 2022 / Published online 15 September 2022

Summary. Obesity is a chronic disease underlined as one of greatest public health challenges in 21st century that significantly increase the risk of developing diabetes, cardiovascular diseases, liver disease and cancer. Current strategies in obesity prevention focus on the lifestyle changes, calorie-restriction diets, pharmacological and surgical interventions. Although obese subjects share some phenotype characteristics, others can be significantly different. For example, up to 30% of obese patients are metabolically healthy and do not display the "typical" metabolic obesity-associated complications. These phenotype difference also lead to variation in success rate of treatments among different individuals. Since obesity cannot be looked at as one simple pathological entity, we need novel tools to define different phenotypes of obesity in order to improve stratifications of patients and facilitate the development of personalized treatments. The use of next-generation sequencing enables comprehensive view on interaction between different genes, and the discovery of novel pathways that are dysregulated in different pathophysiological processes. So far, this approach has identified novel coding and non-coding regions of DNA that are implicated in the development and progression of obesity and help to identify potential tissue-specific biomarkers that could be used for successful predictions of intervention outcomes. Another interesting layer of information that recently is being explored is related to the modifications of RNA and its implications in adipose tissue physiology. Animal as well as human studies have confirmed critical role that some RNA modification play in the dysfunctionality of adipose tissue in obesity. Future efforts should aim to integrate transcriptomics data with other omics (genomics, epigenomics, proteomics and metabolomics) through the use of machine learning algorithms in order to get more holistic view and deeper understanding of different obesity phenotypes.

Keywords: adipose tissue, epitranscriptomics, obesity, transcriptomics.

INTRODUCTION

Obesity is a chronic disorder that develops due to imbalance between energy intake and expenditure. Individuals are classified as obese if their body mass index (BMI) is over 30 kg/m2, while overweight people fall into BMI range of 25–30 kg/m2. World health organization (WHO) underlined obesity as one of greatest public health challenges in 21st century (Lobstein and Brinsden 2020). Obesity is already responsible for 10–13% of deaths in different parts of the European region (www.worldobesity.org). In 2010, obesity accounted for more than 1 million deaths and 12 million life-years of ill health in Europe alone (Hruby et al. 2015). By 2025, WHO predicted that obesity prevalence will reach 18% in men and surpass 21% in women (Lobstein and Brinsden 2020). Unfortunately, the latest data from Serbia (2016) shows that obesity prevalence in man already reached predicted values (17.6%) and in women is close to the predicted target (18%) (Hruby et al. 2015). Obesity increases the risk of developing several non-communicable diseases: diabetes, cardiovascular diseases, liver disease and several types of cancer, as well as risk of developing more than one of these diseases (co-morbidity)

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(Hruby et al. 2015). Previous studies have suggested that obesity alone contributes to 80% of all type 2 diabetes mellitus, 35% of ischemic heart disease and 55% of hypertension among European adults (Cuschieri et al. 2016). Obesity is also one of the key factors involved in the development of metabolic syndrome. Furthermore, recent events related to the Covid-19 pandemic pointed out the significance of obesity as aggravating comorbidity, attributing the higher risk of mortality of obese patients infected with SARS-CoV-2 virus (Anderson et al. 2020). Current data on health care expenses suggest that the whole of Europe spends between 1.9% and 4.7% of the total annual health care costs and 2.8% of the annual hospital costs in dealing with overweight or obese patients (von Lengerke et al. 2011). According to OECD analysis obese people use 2.4 times more health care service, undergo more surgery, stay longer in hospital and require more expensive and complex treatment than healthy-weight individuals. Obesity accounts for more than 70% of all treatment costs for diabetes, almost a quarter of treatment for CVD and 9% of cancer disease (GBD 2015 Obesity Collaborators et al. 2017).

Considering pandemic character of obesity, current strategies in obesity prevention focus on the promotion of healthy eating and encourage physical activity through the involvement of state and local organizations, business and community leaders, and school, childcare, and healthcare professionals. In addition to the outlined strategies, in cases of sever and persistent obesity, more radical approaches should be considered. So far, several pharmacotherapy options are approved as an addition to lifestyle changes, but its use leads to only modest weight reduction. Other weight loss treatment possibilities include calorie-restriction diet, bariatric surgery, and intragastric balloon placement. These approaches aim to induce significant weight reduction, but also to improve metabolic status in treated patients. Although different treatments lead to sufficient effects, it is evident that there is vast deviation in success rate of treatments among different individuals (Cefalu et al. 2015). Consequently, there are growing numbers of demands for using individualized approach to therapy and interventions that facilitate adherence to diet. "Deep phenotyping" of obese individuals through identification of additional molecular mechanisms and factors responsible for obesity and/or ineffectiveness of obesity treatment may help in selecting the most appropriate therapeutic strategies for each patient.

ADIPOSE TISSUE

Morphologically speaking adipose tissue is classified as white (WAT), brown (BAT) and beige adipose tissue (Chait et al. 2020). Apart from being energy depot, WAT plays an important endocrine role through secretion of adipokines that act in autocrine, paracrine and endocrine fashion (Chait et al. 2020). Secretome of WAT is complex, and adipokines that were widely studied including adiponectin, leptin, IL-6, resistin, omentin are shown to have numerous effects of different organs and tissues. Adipose tissue is comprised of numerous different cell types of which only one third are adipocytes, and others are fibroblasts, endothelial cells, macrophages, lymphocytes, stromal vascular cells and pre-adipocytes. Complex interplay between these different cell types is essential for understanding obesity development and progression, as well as other obesity-related complications such as atherosclerosis, insulin resistance, type 2 diabetes etc.

WAT can be classified according to its anatomical localization to subcutaneous (SAT) and visceral (VAT) adipose tissue (Chait et al. 2020). SAT is primarily localized to upper and lower body depots in humans, and is the most prominent WAT depot in lean, healthy subjects, making up 80% of all adipose tissue (Reddy et al. 2019). This type of adipose tissue acts as a buffer for excess energy intake during times of limited energy expenditure (Freedland et al. 2004). However, SAT capacity to store excess of fat is limited. Thus, when its storage capacity is exceeded, fat starts to also accumulate in VAT. VAT includes mesenteric fat (MWAT, contiguous with digestive organs in the viscera), omental fat (OWAT, an apron of fat that stretches over the intestines, liver, and stomach), and retroperitoneal fat (RWAT, surrounding the kidneys) (Chusyd et al. 2016). Near proximity of VAT to the vital organs makes it more potent influencer on their metabolic functions and as such is essential part of pathophysiological mechanisms of obesity. In addition, it is worth mentioning that SAT can be also subdivided into upper regions located primarily in the trunk, and lower located in the gluteo-femoral regions (Chait et al. 2020). Similar to VAT, abdominal SAT is more implicated in mechanisms that lead to vital organ malfunction during progression of obesity.

BAT takes up fatty acids from the circulation and generating heat through the activity of specific proteins that uncouple ATP production via ATP synthase and oxidative phosphorylation. In this way BAT takes part in the non-shivering thermogenesis (Cannon et al. 2004). Although it was previously believed that BAT plays important metabolic roles only in infants, it has recently been shown that adults have functional and inducible levels of BAT that respond to cold and sympathetic nervous system activation and redirects flow of excessive fat from ectopic lipid storage (Cypess et al. 2013). Similar to WAT that secretes adipokines, BAT synthesizes and secretes "batokines" such as fibroblast growth factors, neuregulin 4, VEGF, and cytokines such as IL-6 (Lee et al. 2019) Considering that BAT represents a small part of adipose tissue in humans its endocrine potential is relatively unknown, but it is hypothesized that its contribution to the metabolic health may be significant.

Recently, the third type of adipose tissue was recognized and described as beige fat, which is defined as the presence of brown adipocytes within classic WAT depots. Although beige fat shares some phenotype features with BAT, it is worth mentioning that beige fat is physiologically distinct from BAT, with differential expression of certain genes involved in metabolism, inflammation, and transcription (Walden et al. 2012). Different stimuli (cold exposure, exercise, bariatric surgery, linoleic acid, short-chain fatty acids, capsaicin, green tea extract, thiazolidinediones, and β-adrenergic receptors) can promote process of so-called WAT browning, which includes increase of beige fat within WAT (Chait et al. 2020). Currently, the efforts are made to explore if browning of WAT can be used as therapeutic approach to improve metabolic control and fight obesity.

DYSFUNCTION OF ADIPOSE TISSUE IN OBESITY

Obesity is characterized by excessive expansion of white adipose tissue (WAT) resulting from increased adipocyte size (hypertrophic adipocytes) and number (hyperplastic adipocytes) mostly localized under the skin (SAT) and between the organs within the abdominal cavity (VAT). During obesity development, adipocytes are exposed to the complex interplay between inflammation, oxidative stress and metabolic dysfunction that slowly leads to the loss of their physiological phenotype (Manna et al. 2015). In contrast to lean healthy adipose tissue, hypertrophic adipose tissue is characterized by excessive fat accumulation that promotes series of changes on transcriptional and post-transcriptional levels, leading to endoplasmatic reticulum stress and significant shift in adipocyte secretome towards proinflammatory profile (increased secretion of IL6 and TNFα, decreased secretion of adiponectin) (Manna et al. 2015). Furthermore, adipocytes promote formation of proinflammatory M2 macrophages by activating key cellular pathways (e.g., TLR-4 signaling pathway) (Chait et al. 2020). The activated M2- macrophages further induce a prominent inflammatory milieu in the adipose tissue and trigger the master mediators of inflammation in the adipocytes and attenuate cellular insulin sensitivity, ultimately causing insulin resistance. These local effects are then translated to the systematic level due to endocrine nature of adipokines and their significant influence on functions of other organs such as liver, muscles and heart, which represents one of the links between obesity and cardiometabolic diseases. Taking into account these systematic effects that dysfunctional adipocytes can induce, it is important that obesity treatments lead not only to body weight reduction, but also to improvement of metabolic status and reduction of risks for cardiovascular comorbidities.

Intriguingly, up to 30% of obese patients are metabolically healthy and do not display the "typical" metabolic obesity-associated complications (Blüher et al. 2014). Adipose tissue expansion in such patients is achieved by recruiting and differentiating adipose precursor cells rather than infiltrating fat into mature adipocytes (Patel et al. 2013; Longo et al. 2019). On the contrary, in obese patients with disturbed metabolic homeostasis, SAT becomes dysfunctional due to alterations in the precursor cell commitment leading to adipocyte hypertrophy, decreased adipogenesis and angiogenesis (Patel et al. 2013; Longo et al. 2019). When the storage capacity of SAT is exceeded, further caloric overload leads to fat accumulation in both ectopic tissues and visceral depots (Patel et al. 2013; Longo et al. 2019). In addition, fat accumulation is accompanied with increased local inflammatory response and oxidative stress that is gradually translated to the systemic level through endocrine effects of adipokines leading to impaired glucose metabolism, dyslipidemia, elevated blood pressure and the development of metabolic syndrome (Heymsfield et al. 2017).

It is becoming more and more evident that obesity cannot be looked at as one simple pathological entity if better therapeutic strategies ought to be developed. We need to go beyond this classical approach and use novel tools to define different phenotypes of obesity in order to improve stratifications of patients and facilitate the development of personalized treatments.

CHANGES OF TRANSCRIPTIONAL SIGNATURE IN ADIPOSE TISSUE DURING WEIGHT LOSS

Analysis of gene expression profiles through the use of latest technological advancements such as next-generation sequencing and appropriate bioinformatics algorithms enabled more comprehensive view on interaction between different genes, and the discovery of novel pathways that are dysregulated in different pathophysiological processes. So far, this approach has been used to explore changes in the transcriptome of adipocytes not only to discover novel pathological players in the development of obesity, but also to define specific phenotypes of patients that would be good/poor responders to the certain treatment (Fig. 1).

In the study by Armenise et al. (2017), the transcriptome of overweight and obese, nondiabetic subjects, from the DiOGenes (Diet, Obesity and Genes) study was analysed. The subjects were treated with 8-week low calorie diet and a 6-months weight-maintenance diet. Biopsies of abdominal SAT from 191 patients was analysed with RNA sequencing in order to identified genes that were differentially expressed and associated with clinical outcomes after the treatment. In

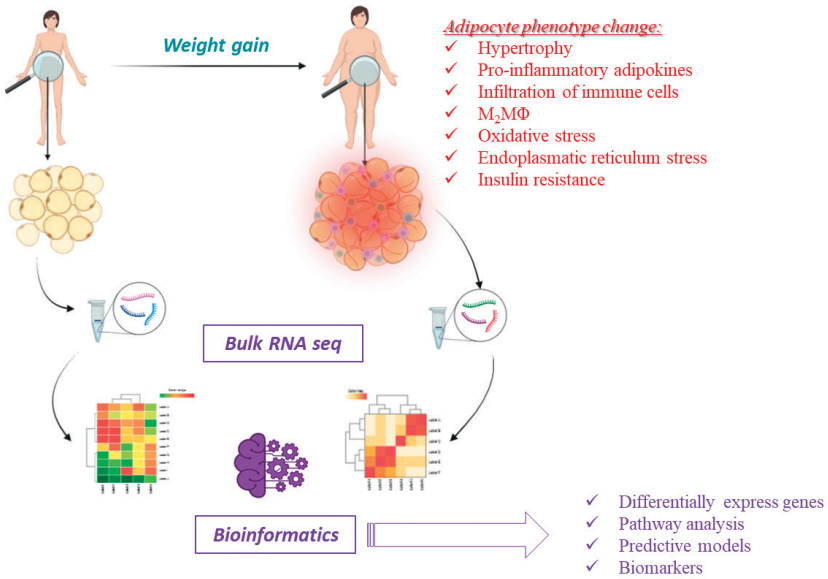

Fig. 1. Transcriptomic analysis of adipose tissue enables more comprehensive phenotype characterization.

addition, it was investigated if gene expression changes could help in distinguishing responders from non-responders. They have identified 1173 genes differentially expressed during the treatment. The following pathway analyses showed that the 350 genes were associated with BMI changes, 33 genes were associated with Matsuda index values, as well as that these genes are mostly enriched in lipid and glucose metabolism pathways. They have also developed a prediction model based on clinical changes during the low-calorie diet in combination with baseline gene expression (area under the curve 0.87), showing that proposed biomarkers can outperform standard clinical models for classification of weight maintainers and help in improving clinical models for prediction of glycemic control.

In the small-scale study by González-Plaza et al. recruited patients were morbidly obese women (n = 8) with low and high insulin resistance undergoing bariatric surgery with 2-year follow up (González-Plaza et al. 2016). Microarray analysis of SAT identified numerous differentially expressed genes that were associated with inflammation and cancer, later being especially enriched in the groups of patients with high insulin resistance. Observed downregulation of inflammatory pathways suggests that bariatric surgery can reverse obesity-induced inflammation. This favourable influence on inflammatory status was also confirmed by Kerr et al. who observed downregulation of pro-inflammatory genes, even five years after bariatric surgery despite of the weight regain (Kerr et al. 2020).

Regarding the obesity as a risk factor for cancer, González-Plaza et al further hypothesized that this can be related to effects of endocrine signals that originate from distal adipose tissues on tumor cells, which may significantly disrupt local metabolic homeostasis. Rey et al. also identified numerous deregulations of coding and non-coding oncogenes of adipose tissue in severely obese subjects (Rey et al. 2021). In this study, diabetic conditions were associated with a high number of oncogenic-associated long non-coding RNAs, and the authors particularly emphasized that long non-coding RNAs could be new players in the adipogenic deregulations concerning both cancer and diabetes. Thus, it seems important to consider interplay between adipose and cancer tissue as a potential therapeutic target.

It is quite intriguing that weight loss induced by different treatments can lead to completely opposite changes in adipocyte's phenotype. Standardized bioinformatics analysis of four independent weight-loss studies explored influence of low-calorie diet and bariatric surgery on differential mitochondrial gene expression in SAT (van der Kolk et al. 2021). Based on the results of this study, diet-induced weight loss lead to downregulation, while bariatric surgery leads to the upregulation of mitochondrial oxidative metabolism, with the strongest effect being observed in mitochondrial DNA encoded mRNA. Although mechanisms behind these differences are far from known, it is evident that these data open new doors for utilizing molecular mechanisms in SAT that could lead to the development of better, more patient-oriented weight-loss interventions.

EPITRANSCRIPTOMIC REGULATION OF ADIPOSE TISSUE FUNCTION

Epitranscriptomics explore another layer of phenotype complexity related to the post-transcriptional modifications of RNA transcripts that influence the fate and functions of

RNA. In the past several years, N6-methyladenosine (m6A) RNA modification was identified as the most abundant epitranscriptomic alteration that plays a role in the regulation many intracellular processes, including mRNA splicing, translation, and degradation as well as miRNA biogenesis (Sweaad et al. 2021). M6A modifications have been identified on coding and noncoding RNAs including ribosomal and transfer RNA, small nuclear RNA, long noncoding RNAs and circular RNAs. The key players in m6A RNA modifications are enzymes termed writers (m6A methyltransferases, such as METTL3 and METTL14), erasers (m6A demethylases, such as fat mass and obesity-associated protein (FTO) and α-ketoglutarate-dependent dioxygenase alkB homolog 5 (ALKBH5)), and readers (m6A-binding proteins, YT521-B homology domain (YTHDF2) and the insulin-like growth factor-2 mRNA-binding protein (IGF2BP)) (Wu et al. 2021).

RNA modifications play important roles in the regulation of adipose tissue functions. So far, it has been suggested that m6A RNA modifications regulate adipose tissue expansion and lipid metabolism, mediate browning of white adipose tissue, influence self-renewal and differentiation of pluripotent stem cells and controls terminal differentiation of preadipocytes (Wu et al. 2021). High-fat diet in mice upregulates the expression of FTO leading to decrease in m6A levels and adipose tissue expansion and adipogenesis (Zhou et al. 2015). Treatment with betain that acts as methyl donor, antagonise this effect via FTO downregulation and increase in m6A levels (Zhou et al. 2015). The similar effect was achieved in weanling piglets during excessive supplementation with branched-chain amino acids which significantly decreased m6A levels and the expression of acetyl-coenzyme A carboxylase alpha and fatty acid synthase in adipose tissue (Heng et al. 2020). Curcumin supplementation also showed beneficial effects through attenuation of lipopolysaccharide-induced hepatic lipid metabolism disruption and enhanced m6A modification in the liver (Lu et al. 2018). Epigallocatechin gallate, catechin from green tea, inhibits adipogenesis and increase m6A levels in 3T3-L1 cell lines by decreasing stability of FTO and delaying the G1/S phase transition and cell cycle progression in an m6A-YTHDF2-dependent manner (Wu et al. 2018). In line with these data from animal studies, Rønningen et al. showed significant associations of m6A regulators with obesity in humans (Rønningen et al. 2021). Namely, it was found that the expression levels of the writer vir-like m6A methyltransferase associated (VIRMA) and the reader YTHDC1 in SAT of obese individuals were significantly downregulated compared to the lean individuals. In addition, VIRMA SAT expression levels corelated with BMI, percentage of body fat, maximal adipocyte diameter in SAT and leptin serum levels. Since there is sufficient evidence that m6A modifications could be a critical link between dietary nutrients and obesity, it is evident that epitrascirptomic mechanisms should be explored further as a potential target for interventions.

FUTURE PERSPECTIVES

Although currently there are lot of initiatives to fight obesity pandemic, epidemiological predictions suggest that percentage of obese will continue to rise. From 2020 to 2050 obesity and related disease will decreases worker productivity, lowers gross domestic product and reduce life expectancy by three years across EU and other developed countries. Moreover, responses to obesity treatments vary considerably, and often are unpredictable. In the New York Obesity Research Center Weight Loss Program (NYORC) program 9% of participants actually gained weight over 1 year, even though the program took place under highly controlled and supervised conditions (Cefalu et al. 2015). This underlines the urge to find novel, more efficient interventions and therapeutic approaches, and to establish tools for better phenotyping of obese individuals and prediction of treatment outcomes.

So-called bulk RNA sequencing gave good insights in significance of different pathways and dysregulation of genes in obesity. However, novel transcriptomic techniques can give deeper insights in the complexity and heterogeneity of adipose tissue. Single cell RNA sequencing is a technique combines cell sorting with RNA sequencing in order to get the information of gene expression profiles on the single cell level. Another useful tool that could increase our knowledge of tissue heterogeneity, but also about localization of RNAs within the cells is spatial transcriptomics. Deeper insights in adipose tissue heterogeneity and the discovery of novel cell types within the adipose tissue could be helpful in discovering new pathological players that could be targeted with specific interventions.

Considering that obesity is a very complex disease that involves interplay between multiple organs, in order to unravel different pathological mechanisms, it might be good to go beyond and above traditional view and surpass oversimplification of the subject. Systems biology is approach that gives holistic view through complex mathematical modelling and integration of data from different omics such as genomics, epigenetics, transcriptomics, proteomics and metabolomics. Through machine learning and artificial intelligence it is possible to overlayer data from different omics in order to find causal relations between certain targets. This can lead to development of multi-marker models that can better represent the complexity of the disease and help determine specific phenotypes of obese subjects that could be applied in clinical settings for better prevention and more successful interventions.

ACKNOWLEDGMENTS

This research was funded by the Ministry of Education, Science and Technological Development, Republic of Serbia through Grant Agreement with University of Belgrade-Faculty of Pharmacy No: 451-03-68/2022-14/200161.

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