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REVIEW

The clinical potential of adipogenesis and obesity-related microRNAs

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Abstract Obesity is a growing health problem commonly associated with numerous metabolic disorders including type 2 diabetes, hypertension, cardiovascular disease, and some forms of cancer. The burden of obesity and associated cardiometabolic diseases are believed to arise through complex interplay between genetics and epigenetics predisposition, nutrition, environment, and lifestyle. However, the molecular basis and the repertoire of obesity-affecting factors are still unknown. Emerging evidence is connecting microRNAs (miRNAs) dysregulation with adipogenesis and obesity. Alteration in miRNAs expression could result in changes in the pattern of genes controlling a range of biological processes including inflammation, lipid metabolism, insulin resistance and adipogenesis. Hence, understanding exact roles of miRNAs as well as the degree of their contribution to the regulation of adipogenesis and fat cell development in obesity would provide new therapeutic targets for the development of novel and effective anti-obesity drugs. The objective of the current review is to: (i) discuss some of the latest development on relevant miRNAs dysregulation mainly in human adipogenesis and obesity, (ii) emphasize the role of circulating miRNAs as new promising therapeutics and attractive potential biomarkers for treating obesity and associated risk factor diseases, (iii) describe how dietary factors may influence obesity through modulation of miRNAs expression, (iv) highlight some of the actual limitations to the promise of miRNAs as novel therapeutics as well as to their translation for the benefit of patients, and finally (v) provide recommendations for future research on miRNA-based therapeutics that could lead to a breakthrough in the treatment of obesity and its associated pathologies.

Introduction

Obesity represents a major public health challenge in developed and developing countries [1] and has dramatically increased during the past decades across all age groups. The etiology of obesity is multifactorial involving complex interplay between genetics and epigenetic predisposition, nutrition, environment, and lifestyle [2,3]. Several studies have indicated that obesity is associated with altered adipose tissue metabolism which increases

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the risk of life-threatening diseases such as diabetes, hypertension, cardiovascular disease (CVD) and certain types of cancer [4–6].

The adipose tissue is a critical regulator of systemic energy homeostasis by acting as a caloric reservoir. In humans, there are two major types of adipose tissue: white adipose tissue (WAT), and brown adipose tissue (BAT) [7]. The two tissues differ at the functional, as well as the morphological and molecular levels. WAT is an active endocrine organ, contains single, large lipid droplets occupying the majority of cell volume and accumulates surplus energy mainly in the form of triacylglycerols, whereas BAT is characterized by multilocular lipid droplets and high mitochondrial content and dissipates energy directly as heat (thermogenesis).

Chronic imbalance between intake of calories consumed and the calories expended results in the accumulation of excess energy and dysfunctional adipose tissue which can lead to a metabolic disease state. In fact, the majority of patients with obesity have impaired adipose tissue function. Moreover, in obesity; excess of WAT is closely linked to metabolic complications such as insulin resistance and type 2 diabetes mellitus (T2DM) [7]. At the cellular level, obesity is often characterized by increased fat mass ascribed to the hypertrophy and hyperplasia of adipocytes [8] and energy storage in adipose tissue [9]. These characteristics are further associated with changes in circulating adipokines, free fatty acids, inflammatory mediators, and most importantly impaired whole body insulin sensitivity [10,11]. Therefore, extensive efforts have been recently made to better understand the molecular mechanisms underlying adipogenesis and adipose tissue dysfunction which contribute to metabolic dysregulation associated with obesity.

Adipogenesis is the process by which multipotential mesenchymal stem cells (MSCs) commit to become adipocyte precursor cells which then differentiate into lipid assimilating cells [10,11,12] (Fig. 1). This process is known to occur in two distinct stages: the first one being the commitment stage, in which MSCs commit to becoming pre-adipocytes, and the second one being the terminal differentiation phase [13,14,15], in which, pre-adipocytes acquire the machinery for lipid synthesis and transport, insulin action, and secretion of adipocytes-specific proteins. Impaired adipogenesis and consequent adipocyte dysfunction result in excess free fatty acid release, and promote systemic inflammation, insulin resistance and abnormal storage of surplus lipids in non-adipose tissues where it causes lipotoxicity [16,17]. Such conditions may contribute to the development of diabetes, fatty liver and cardiovascular complications associated with obesity.

A variety of molecular regulatory factors including circulating hormones, transcription factors, growth factors, and processes involving signaling pathways have been shown to regulate adipogenesis [18]. For instance, adipogenesis has been shown to be tightly controlled by a complex network of transcription factors including the peroxisome proliferator-activated receptor (PPARγ), and the CCAAT/enhancer binding proteins (C/EBPs) [19–22]. The pro-adipogenic factor PPARγ, a key regulator of adipocyte differentiation, activates lipogenic genes such as those of aP2/fatty acid binding protein 4 (FABP4), fatty acid synthase (FAS), and GLUT4 [23,24] as well as genes encoding lipid droplet-related proteins; perilipin and cidec/FSP27 [25,26]. Other factors have also been found to play a critical role in adipogenesis such as adiponectin. These players have been shown to determine MSCs terminal fate and may be responsible for the formation of mature adipocytes [27,28].

The process of adipogenesis is further controlled by complex signaling pathways interaction including, but not limited to those initiated by Wnt/β-catenin, TGFβ/BMPs/SMADs, IGF-1 and insulin [29,30], hedgehog, notch1, JAK/STAT, MAPK and phosphatidylinositol-3 kinase (PI3K)Akt [15,28,31]. Reports implicate Wnt members and their effector β-catenin signaling in the regulation of adipogenesis [32–35]. In this sense, numerous members of Wnt family were shown to inhibit early stages of adipogenesis [34].

Notch1 signaling is another pathway of great importance in adipogenesis regulation. Notch1 activation inhibits adipose progenitor cells differentiation including MSCs [36–38]. This observation was confirmed by another study reporting that Notch1 decreases the expression of various proadipogenic genes such as *PPARγ*, *aP2*, and adiponectin [39]. More recently, it was shown that Notch1 signaling is also important in mature adipocytes development and function, beige adipocytes formation and energy metabolism [40–42]. Furthermore, inhibition of Notch gene expression during MSCs differentiation was shown to promote adipogenic differentiation of human bone marrow derived MSCs and induce autophagy of MSCs through PTEN-PI3K/Akt/mTOR pathway [43].

The transforming growth factor β (TGFβ) superfamily members, TGFβ and BMPs, have also been found to regulate the differentiation of different cell types including adipocytes [44]. For instance, TGFβ has been shown to promote osteogenic differentiation, while at the same time, inhibit adipogenic differentiation of human MSCs (hMSCs) under various experimental conditions [45]. In line with this observation, a previous study reported that transgenic overexpression of TGF-β impairs the development of adipose tissue [46]. Mechanistically, TGF-β inhibits adipocyte differentiation by interacting with C/EBP and repressing its transcriptional activity [47]. Furthermore, TGF-β/SMAD signaling pathway was also shown to be involved in the regulation of cell differentiation [48,49], and thus considered as potential therapeutic target for obesity.

Hedgehog (Hh) signaling pathway is another important modulator of stem cell differentiation processes, including adipogenic differentiation [50,]. Various studies have revealed the role of Hh signaling during MSCs differentiation [51,52]. For instance, Fontaine et al. [52] reported that Hh signaling alters adipocyte maturation of hMSCs by targeting the expression of C/EBPα and PPARγ2.

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