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Review

MicroRNAs: Emerging roles in adipogenesis and obesity

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ABSTRACT

Obesity is a serious health problem worldwide associated with an increased risk of life-threatening diseases such as type 2 diabetes, atherosclerosis, and certain types of cancer. Understanding the molecular basis of adipogenesis and fat cell development in obesity is essential to identify new biomarkers and therapeutic targets for the development of anti-obesity drugs. Recent computational and experimental studies have shown that microRNAs (miRNAs) appear to play regulatory roles in many biological processes associated with obesity, including adipocyte differentiation and lipid metabolism. In addition, many miRNAs are dysregulated in metabolic tissues from obese animals and humans, which potentially contributes to the pathogenesis of obesity-associated complications. The discovery of circulating miRNAs has highlighted their potential as both endocrine signaling molecules and disease markers. The potential of miRNA based therapeutics targeting obesity is highlighted as well as recommendations for future research which could lead to a breakthrough in the treatment of obesity.

Contents

1. Introduction

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems [1]. Obesity is a leading preventable cause of death worldwide, with increasing prevalence in adults and children, and authorities view it as one of the most serious public health problems of the 21st century [2]. Obesity is stigmatized in much of the modern world (particularly in the Western world), though it was widely perceived as a symbol of wealth and fertility at other times in history, and still is in some parts of the world [1,3].

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In 2013, the American Medical Association classified obesity as a disease.

Obesity and the associated metabolic syndrome represent a major public health issue, and present a formidable therapeutic challenge [4]. The obese transition leads to a deviation away from the main function of adipose tissue that of effective and appropriately controlled fat storage and release, and adipose tissue dysfunction in obesity predisposes to the metabolic consequences of obesity, such as insulin resistance, diabetes and cardiovascular disease [5]. A greater understanding of the molecular mechanisms underlying obesity and adipose tissue dysfunction will be required if we are to identify novel therapeutic targets.

MicroRNAs (miRNAs) are a novel group of small (approximately 22 nucleotides) non-coding RNAs that have emerged as important regulators of mRNA expression. Recent findings indicate that microRNAs (miRNAs) are involved in the regulatory network of many biological processes, including cell differentiation, animal development, metabolism, tumorigenesis and other diseases [6–11], through post-transcriptional regulation of transcription factors and/or other genes. Several miRNAs were reported to be expressed in adipocytes of mammals and seem to play a role in the regulation of adipogenesis even with potential impact on adipogenesis dysfunctions (Tables 1 and 2).

2. MiRNA and biological function

MiRNAs are found in all multicellular organisms from plants to humans and in many instances are highly conserved through evolution and therefore likely to be important for normal cellular function. For the few miRNAs of which function have been uncovered, they are important regulators of various aspects of developmental control in both plants and animals, including cell fate determination and differentiation, cell proliferation, cell death, fat metabolism, neuronal patterning, hematopoietic differentiation, immunity, and control of leaf and flower development [12–14].

MiRNAs can be derived from individual miRNAs genes, introns of protein-coding genes, or from polycistronic transcripts that often encode multiple, closely related miRNAs. In animals, miRNAs are synthesized from primary miRNAs (pri-miRNAs) in two stages. The first step is the nuclear cleavage of the pri-miRNA, which liberates 60–70 nt stem loop intermediate, known as the miRNA precursor, or the pre-miRNA. This processing is performed by the Drosha RNase III endonuclease, which cleaves both strands of the stem at sites near the base of the primary stem loop [15]. This pre-miRNA is actively transported from the nucleus to the cytoplasm by Ran-GTP and the export receptor exportin-5 [16,17]. The nuclear cut by Drosha defines one end of the mature miRNA. The other end is processed in the cytoplasm by the enzyme Dicer, also an RNase III endonuclease. These form a transient, double-stranded miRNA of 22 nucleotides in length. The miRNA duplex is then incorporated into a multicomponent protein complex known as RNA-induced silencing complex (RISC), which contains the Argonuate (AGO) protein [18,19]. During the functional process, one strand is rapidly removed and degraded, the other strand of the miRNA duplex is selected as a mature miRNA. The mature miRNA negatively regulate gene expression through translational repression or mRNA cleavage, which depends on the extent of complementarity between the miRNA and its target. If the target mRNA has perfect complementarity to the miRNA-armed RISC, the mRNA will be cleaved and degraded, or it will repress productive translation if the mRNA does not have sufficient complementarity to be cleaved but does have a suitable constellation of miRNA complementary sites [20,21] (Fig. 1).

Table 1
MiRNAs associated with adipogenesis in mammals.

miRNA	Functions	Targets	References
miR-143	↑Adipogenesis	ERK5	[29,30,33,34]
miR-17-92	↑Adipogenesis	RB2/P130	[38]
miR-103	↑Adipogenesis	–	[29,31,36,37]
miR-21	↑Adipogenesis	TGFBR2, STAT3	[46,47]
miR-519d	↑Adipogenesis	PPARα	[36]
miR-200	↑Adipogenesis	–	[50]
miR-210	↑Adipogenesis	TCF7L2	[41]
miR-30a/d	↑Adipogenesis	RUNX2	[42–44]
miR-30c	↑Adipogenesis	PAI-1, ALK2	[44]
miR-204/211	↑Adipogenesis	RUNX2	[45]
miR-375	↑Adipogenesis	–	[48]
miR-146b	↑Adipogenesis	SIRT1	[52]
miR-27	↓Adipogenesis	PPARγ	[53–55]
miR-130	↓Adipogenesis	PPARγ	[57]
Let-7	↓Adipogenesis	HMGA2	[31]
miR-448	↓Adipogenesis	KLF5	[59]
miR-138	↓Adipogenesis	EID-1	[60]
miR-155	↓Adipogenesis	C/EBPß, CREB	[61]
miR-145	↓Adipogenesis	IRS1	[62]
miR-224	↓Adipogenesis	EGR2	[63]

3. Overview of adipogenesis

Adipogenesis is the process by which cells from the adipose tissue proliferate, differentiate and convert into cells able to assimilate lipids [22]. There are two important stages of adipogenesis: commitment and differentiation [23].

Commitment is the process in which the pluripotent stem cells located in the vascular stroma of adipose tissue respond to signal(s) to go through determination into preadipocytes. Once pluripotent fibroblasts commit to the adipose lineage (preadipocytes), they can be induced to form adipocytes [23]. Adipocyte differentiation is an ordered multistep process requiring the sequential activation of several groups of transcription factors [24–26], including CCAAT/enhancer binding protein (C/EBP) gene family, peroxisome proliferator activated receptor-γ (PPARγ), Krüppel-like factors (KLFs) and sterol regulatory element binding protein (SREBP). Hormones and growth factors that affect adipocyte differentiation, such as insulin [27] and insulin-like growth factor [28], transfer external growth and differentiation signals to differentiating adipocytes. While it is accepted that this complex process is tightly controlled by a combination of multiple transcription factors and extracellular hormones, little is known about the precise mechanisms of adipogenesis.

4. Role of microRNAs in adipogenesis

In mammalian cells, the miRNAs can affect the regulation of adipogenesis in different steps, and perform different roles such as a proadipogenic factor or as an antiadipogenic factor (Fig. 2).

4.1. MiRNAs that enhance adipogenesis

MiR-143 has been shown to increase during human and murine preadipocyte differentiation [29–32] and inhibition of miR-143 inhibited differentiation in cultured human preadipocytes [29], whereas ectopic overexpression by transfection enhanced triglyceride accumulation in differentiating 3T3-L1pre-adipocytes [32]. MiR-143 seems to inhibit the expression of the gene ERK5 (extracellular-signal-regulated kinase 5), which does not have a defined role in adipogenesis [29]. MiR-143 is upregulated in mesenteric adipose tissue and associated with weight gain in high-fat diet-induced obese mice [33], but other studies have found that miR-143 is downregulated in epididymal adipose tissue from ob/ob mice compared with wildtype mice [32] and is downregulated in adipose tissue samples from obese humans [34], a discrepancy that may have been caused by the different fat depots sampled or the different models of obesity used. Recently, it is found that Fgf7, a member of the fibroblast growth factor family, is a putative target of miR-143 [35]. Fgfy may function as a fine-tuning molecule in the adipogenic process. In the same time, it is reported that knock down of miR-143 does not yield significant changes in phenotype with in vivo approaches

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