Pivotal role of microRNA-33 in metabolic syndrome: A systematic review

Mojgan Gharipour[(1)], Masoumeh Sadeghi[(2)]

Review Article

Abstract

Metabolic syndrome (MetS) is a major public health concerns and increase in the incidence of MetS caused a rise in the rates of global morbidity, and mortality due to cardiovascular disease and diabetes. Lifestyle modification, a healthy diet, and pharmacological treatment and bariatric surgery are recommended in order to control this syndrome. Molecular mechanisms of metabolic disorders are essential in order to develop novel, valid therapeutic strategies. MicroRNA-33 plays imperative regulatory roles in a variety of biological processes including collaboration with sterol regulatory element-binding protein (SREBP) to maintain cholesterol homeostasis, high-density lipoprotein formation, fatty acid oxidation, and insulin signaling. Investigation of these molecules and their genetic targets may potentially identify new pathways involved in complex metabolic disease processes, improve our understanding of metabolic disorders, and influence future approaches to the treatment of obesity. This article reviews the role of miRNA-33 in metabolic syndrome, and highlights the potential of using miRNA-33 as a novel biomarker and therapeutic target for this syndrome.

Keywords: MicroRNA-33, Insulin Resistance Syndrome X, Regulatory Role

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Introduction

Metabolic syndrome (MetS) is characterized by the clustering of several risk factors such as dyslipidemia, hypertension, insulin resistance, and central obesity. Moreover, this condition increases the risk of cardiovascular disease (CVD) and type 2 diabetes mellitus.[1-5] MetS is considered as a major health problem, and presents an impressive therapeutic challenge.[1,3,5-10] The prevalence of MetS, based on the National Cholesterol Education Program (NCEP) definition, is high and has recently been estimated in adults around the world to be 15.5%, in the U.S. 23.7%, Russia 17.6%, and in Finland 13.7%.[11] Published data showed that the prevalence of MetS is relatively higher in the Middle East regain than other parts; for example, it is 66% in Oman, and 29.9% in Turkey, and in Iran it was reported from 24.1% to 38.9%.[5,12-14] Increase in the incidence of MetS has caused a rise in the rate of global morbidity, and mortality due to cardiovascular disease and diabetes.[15] Lifestyle modification, a healthy diet, and pharmacological treatment are recommended for controlling this syndrome.[1] However, the evidences showed that greater role of genetic determinates than environmental factors on incidence of MetS.[16-18] It is well documented that failure of function in up and down regulation of regulatory genes and enzymes lead to MetS.[19] However, there is controversy about the role of genes in up and down regulation; for example, genome-wide association studies have demonstrated numerous genes and regions, which are susceptible to individual MetS risk factors such as hypertension, obesity, and diabetes.[18,20-22] However, family studies did not find any genetic loci mediate clustering of MetS components.[16,23-25]

The most recent studies have discovered new molecules named microRNA, which play a crucial role in controlling metabolic and homeostasis pathways. Latest findings have demonstrated the remarkable role of small non-coding RNAs (microRNAs; 19–22 nucleotides) in the post-transcriptional regulation of a number of genes and their involvement in many pathological states, such as diabetes, atherosclerosis, and cancer.[26] MicroRNAs (miRs) have been indicated as potential novel biomarkers for many pathological states, consequent to their tissue specific expression and

1- PhD Candidate, Isfahan Cardiovascular Research Centre, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Associate Professor, Cardiac Rehabilitation Research Centre, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Masoumeh Sadeghi, Email: m_sadeghi@cc.mui.ac.ir

association with clinic pathologic variables.[27] Investigation of these tiny molecules and their genetic targets may potentially identify new pathways involved in complex metabolic disease processes, improving our understanding of metabolic disorders and influencing future approaches to the treatment of MetS.

Materials and Methods

We reviewed English-language MEDLINE publications from 2007 through 2013 for experimental, observational, and clinical studies on the relation between metabolic syndrome and microRNA. Search terms of metabolic syndrome included insulin resistance syndrome X, syndrome X, dysmetabolic Syndrome X, Reaven syndrome X, syndrome X, Reaven, metabolic cardiovascular syndrome, cardiovascular syndromes, and metabolic cardiovascular. In addition, search terms of microRNA-33 included miRNAs-33, miRNA-33, micro RNA-33, RNA Micro, MicroRNA-33, primary microRNA-33, microRNA, pri-miRNA-33 Temporal RNA-33, pre-miRNA-33. Approximately 47 papers were reviewed. Based on the relevance, strength, and quality of the design and methods, 37 publications were selected for inclusion in the study.

As this topic is very novel, we reviewed all studies that were done on animals, cell culture, or humans. We reviewed all observational studies as we did not find any randomized trials of either parallel or crossover design. For overall objective evaluation, the design and quality of individual studies, the consistency of findings across studies, and the biologic plausibility of possible mechanisms evaluated the strength of the evidence.

Results

Studies were done to find the role of microRNA were not homogeny; therefore, we were not able to perform meta-analysis.

MicroRNA-33(miR-33)

The most recent investigations demonstrated that miR-33 plays a key regulatory role in the initiation and progression of atherosclerosis.[28,29] MiR-33 mediated regulation in the metabolic pathways such as lipid metabolism (cholesterol homeostasis, HDL biogenesis, and fatty acid, phospholipids, and triglyceride, and bile acid metabolism), inflammatory response, insulin signaling, and glucose homeostasis.[28]

MiR-33, as an intronic microRNA located within the sterol regulatory element-binding protein (SREBP) genes, is one of the master regulators of cholesterol and fatty acid metabolism. Recently, Moore et al.[30] and Fernández-Hernando and Moore,[31] in their studies, showed that miR-33 regulates cholesterol efflux and high-density lipoprotein (HDL) formation, fatty acid oxidation, and insulin signaling. These results describe a model in which miR-33 works in concert with its host genes to ensure that the cell's metabolic state is balanced, thus highlighting the clinical potential of microRNAs as novel therapeutic targets for treating MetS.[26]

Mir-33a and Mir-33 b in humans

Other researchers provided identification within the intronic sequences of the SREBP genes in organisms ranging from drosophila to humans.[32-34]

MiR-33a and miR-33b differ in only 2 nucleotides in the mature form and have the same targets; they differ in their patterns of evolutionary conservation. MiR-33a is encoded within intron 16 of the human SREBP-2 gene and is conserved in many animal species. In humans two miR-33 genes are present as miR-33b, which is located in intron 17 of the SREBP-1 gene on chromosome 17, and miR-33a, which is presented in intron 16 of the SREBP-2 gene on chromosome 22.

Fatty acid oxidation and insulin signaling in hepatic cell lines inhibits by over expression of miR-33a and –b. While inhibition of endogenous miR-33a and -b increases these two metabolic pathways. Therefore, they interestingly showed that miR-33a and -b regulate pathways controlling three of the risk factors of metabolic syndrome, namely levels of HDL, triglycerides, and insulin signaling, and suggest that inhibitors of miR-33a and -b may be useful in the treatment of this growing health concern.

Role of miR-33a and miR-33 b in MetS

In the hepatocytes, lipoprotein uptake increased in conditions of low intracellular cholesterol or in presence of statins. Inducing SREBP-2, increases endogenous cholesterol biosynthesis. SREBP-1, induced by insulin resistance or hyperinsulinemia, leads to increased fatty acid and triglycerides synthesis. The activation of SREBPs induces miR-33a and -b expression, leading to decreased HDL cholesterol levels by targeting ATP-binding cassette, sub-family A (ABC1), member 1 (ABCA1), reduced insulin signaling by targeting insulin receptor substrate 2 (IRS2), and reduced cellular β-oxidation by targeting different fatty acid oxidation enzymes. Therapeutic inhibition of miR-33 might result in increased plasma HDL cholesterol levels, reduced very low density lipoprotein (VLDL) secretion, and increased insulin signaling, thus improving the prognosis of patients with metabolic syndrome.

MiR-33 and Sterol Regulatory

Fernández-Hernando et al. demonstrated that inhibitors of miR-33 in vitro and in vivo relieve

repression of these genes resulting in up-regulation of the associated metabolic pathways.[35] It is well known that hypertriglycemia in MetS is caused by the insulin-induced increase in sterol regulatory element-binding protein 2 (SREBP-2) mRNA and protein levels.[31,35,36] For the first time, Horie et al. showed that miR-33 modulates the expression of genes involved in cellular cholesterol transport in mice lacking miR-33.[37] They showed that miR-33 is a key regulator of HDL synthesis by mediating cholesterol efflux from cells to apolipoprotein A (ApoA)-I.[37,38] Horie et al.[37] Rayner et al.[39] showed that antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. Conversely, silencing of miR-33 in vivo increases hepatic expression of ABCA1and plasma HDL levels. Thus, miR-33 appears to regulate both HDL biogenesis in the liver and cellular cholesterol efflux. Therefore, an effective strategy for increasing plasma HDL cholesterol and fatty acid oxidation, and prevention of atherosclerosis is necessary.[31]

MiR-33 and fatty acid metabolism

MiR-33a and -b target key enzymes involved in the regulation of fatty acid oxidation, including Carnitine O-acetyltransferase, carnitine palmitoyltransferase 1A, hydroxyacyl-CoA-dehydrogenase, Sirtuin-6 (SIRT6), and AMP kinase subunit-α. Additionally, miR-33a and -b target the insulin receptor substrate 2, an essential component of the insulin-signaling pathway in the liver. Over expression of miR-33a and -b reduces both fatty acid oxidation and insulin signaling in hepatic cell lines, whereas inhibition of endogenous miR-33a and -b increases these two metabolic pathways. Notably, miR-33 also inhibits translation of several transcript encoding proteins involved in fatty acid oxidation including carnitine palmitoyltransferase 1a (CPT1A), Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), beta subunit (HADHB), and Carnitine O-octanoyltransferase (CROT), thereby reducing fatty acid degradation. Ramírez et al. demonstrated that increase in SREBP activity leads to cholesterol and fatty acid accumulation and the down regulation of their own processing pathway.[26]

MiR-33 regulates fatty acid oxidation and insulin signaling

Gerin et al. showed that overexpression of miR-33a and -b reduces fatty acid oxidation and leads to the accumulation of triglycerides in human hepatic cells and in the fat body of miR-33 transgenic flies.[32] Previous works revealed an attractive responsibility for miR-33a and -b in glucose metabolism; as miR-33a and –b overexpression reduces IRS2 levels and inhibits the activation of downstream messenger cascades. Consistent with these findings is the finding that miR-33b over expression reduces insulin-induced 2-deoxyglucose uptakes in hepatic cells, suggesting that miR-33 plays a key role in regulating insulin signaling.[32]

Conclusion

The documented involvement of microRNAs in glucose and lipid metabolism has provided strong evidence in support of their role as key players in the regulation of complex metabolic pathways. Additionally, miR-33 represents an ideal target for future therapies. Although much remains to be learned concerning the role of miRNAs in regulating lipid homeostasis and insulin signaling, these results highlight the potential of miRNAs in the treatment of diseases.

Conflict of Interests

Authors have no conflict of interests.

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