

Oxidative-Stress-Responsive MicroRNAs in Heart Injury

Subjects: Pathology

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Reactive oxygen species (ROS) are important molecules in the living organisms as a part of many signaling pathways. However, if overproduced, they also play a significant role in the development of cardiovascular diseases, such as arrhythmia, cardiomyopathy, ischemia/reperfusion injury (e. g. myocardial infarction, heart transplantation), and heart failure. As a result of oxidative stress action, apoptosis, hypertrophy, and fibrosis may occur. MicroRNAs (miRNAs) represent important endogenous nucleotides that regulate many biological processes including those involved in a heart damage by oxidative stress. Oxidative stress can alter the expression level of many miRNAs. These changes in miRNA expression occur mainly via modulation of Nrf2, sirtuins, NFAT/calcineurin, or NF-κB pathways. Up to now, several circulating miRNAs have been reported to be potential biomarkers of ROS-related cardiac diseases including myocardial infarction, hypertrophy, ischemia/reperfusion, and heart failure, such as miRNA-499, miRNA-199, miRNA-21, miRNA-144, miRNA-208a, miRNA-34a, etc. On the other hand, a lot of studies are aimed at using miRNAs for therapeutic purposes. This review points to the need for studying the role of redox-sensitive miRNAs to identify more effective biomarkers and develop better therapeutic targets for oxidative stress-related heart diseases.

Keywords: cardiovascular diseases ; miRNA ; oxidative stress ; ischemia/reperfusion injury ; transplantation

1. Introduction

Since 2001, miRNAs have been recognized as biomarkers and possible therapeutic targets for the diagnosis and treatment of diseases ^[1]. One of the biggest advantages for using miRNAs as biomarkers is their stability under many different conditions. MiRNAs can be stored at room temperature, frozen, or thawed ^[2]. Bioavailability of miRNA is another great advantage. MiRNAs can be isolated from various biological materials, like from peripheral blood, fresh and frozen tissues, or formalin-fixed, paraffin-wax-embedded samples, but also from saliva, epithelium of the skin, or hair ^{[3][4]}. Difficulties in the use of therapeutically altering miRNAs lie in their non-specificity— single miRNA can target many genes and influence more than one gene expression, so they could affect also other pathways in the organisms ^[5]. MiRNAs impose a relatively modest effect on their target, reflecting that individual mRNAs are targeted by multiple miRNAs, while the cellular proteome might be able to compensate the absence of a single miRNA ^[6].

2. Development

Manipulation of RNA using miRNA mimics and antagomirs holds significant therapeutic potential for treating a variety of diseases. With recent technological advances, identification and validation of potential therapeutic miRNA targets are readily available ^[1]. Treatment of diseases by modulation of selected miRNAs in the organisms is based on two approaches. First, miRNA mimics is an approach for gene silencing due to generating synthesized artificial double-stranded miRNA-like RNA fragments. These molecules are able to bind to target mRNA and suppressed genes ^[7]. The second approach uses antagomirs, chemically designed oligonucleotides. These oligonucleotides specifically inhibit target miRNA by binding to them, which leads to reduction of RISC activation and to upregulation of genes ^{[8][9]}. MiRNAs could be modulated also by miRNA sponges (target mimicry), masking, and erasers. MiRNA sponges contain a binding site for the miRNA family, leading to the blocking of the activity of miRNAs ^{[10][11]}. Masking is based on the occupation of the binding site on target mRNA by oligonucleotides ^[12]. Erasers are oligonucleotides complementary to specific miRNA, leading to inhibition of its function ^[13]. However, delivery of anti-miRNAs and miRNAs in vivo may prove to be challenging ^[1].

Oxidative stress is one of the important contributing factors in cardiovascular disease genesis and development. Excessive ROS production has a significant impact on the pathogenesis of cardiovascular diseases related to atherosclerosis, cardiomyopathy, ischemia/reperfusion, and heart failure. Published literature highlights the increasing importance of studying the role of redox-sensitive miRNAs to identify more effective biomarkers and develop better therapeutic targets for oxidative-stress-related diseases. It is necessary to define the roles of individual miRNAs and their

important targets, to determine their potential for possible diagnosis/treatment of cardiovascular disorders. Although a number of targets of oxidative-stress-responsive miRNAs have been identified, e.g., Nrf2, SIRT1, and NF-κB, future studies are still needed to determine further potential targets and their links to cardiovascular disease. MiRNA may be a promising novel tool and means in the clinical diagnosis, prognostic evaluation, and even therapeutic intervention of oxidative-stress-related CVD. The knowledge of the crosstalk between miRNAs, ROS, and cardiovascular diseases can contribute to new therapeutic approaches based on the suppression of ROS effects, with the potential to ameliorate or prevent the progression of cardiovascular diseases. However, several studies are still required to validate the present findings before the application of miRNA in clinical practice.

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