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MIRNA-133A IN ACUTE MYOCARDIAL INFARCTION: MUCH MORE THAN A CARDIAC BIOMARKER

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Abstract: Ischemic heart disease is a leading cause of morbidity and mortality worldwide. Infarct size is the single most important predictor of adverse ventricular remodeling, and it is linearly dependent upon the amount of myocardial salvage by reperfusion. Lack of timely reperfusion, due to ineffective treatment or delayed presentation, leads to an unfavorable prognosis. Micro Ribo Nucleic Acids (miRNAs) are small non-coding RNAs ~22 nucleotides in length that function as guide molecules in RNA silencing. Targeting most protein-coding transcripts, miRNAs are involved in nearly all developmental and pathological processes in animals. The biogenesis of miRNAs is under tight control, and their dysregulation is associated with many human diseases. In cardiac diseases, including myocardial infarction (MI), expression of cardiac miRNAs is markedly altered which leads to deleterious effects associated with heart injury, arrhythmia, increased apoptosis, fibrosis, hypertrophy, and tissue remodeling. In acute MI, circulating levels of cardiac miRNAs are significantly elevated making them a promising diagnostic marker for early diagnosis of acute MI. The great cardio-specific capacity of these miRNAs is very helpful for enhancing regenerative properties and survival of stem cell and cardiac progenitor transplants and for reprogramming of mature non-cardiac cells to cardiomyocytes. in this review we will illustrate the role of miRNA-133a in human heart and its therapeutic implications.

Keywords:
Acute STEMI, myocardial remodeling, miRNA-133a.

Introduction

1- MicroRNA-133a (miR-133a) in the Heart .

Certain miRNAs may be expressed in a tissue-specific pattern, such as cardiac miRNAs , miR133a which are abundantly expressed in the myocardium. MiR-133a is transcribed from the same chromosomal loci as miR-1. In addition, miR-133a play a key role in promoting cardiogenesis, heart function, and pathology. miR-133a predominantly control the early stages of cardiogenesis by directing the commitment of embryonic stem cells and mesodermal precursors to the cardiac-specific muscle lineage, in the heart, miR-133a also mediate cardiac conductance and automaticity by regulating all phases of the cardiac action potential(1).

2- MiR-133a as a Potential Diagnostic Biomarker of Acute MI .

In contrast, the expression level of miR-133a in serum is elevated significantly in patients with acute myocardial infarction (AMI) or with unstable angina pectoris, Additionally, miR-133a levels in serum are significantly related to all-cause mortality in acute coronary syndrome (ACS) patients(2). In 2011, Kimura et al. first measured the levels of circulating miR-133a associated with cardiovascular diseases, and demonstrated that the levels of circulating miR-133a are elevated early after the onset of chest pain when there is no up-regulation in serum creatine phosphokinase (CK or CPK) or cardiac Troponin T (cTnT), . Increased levels of circulating miR-133a are found in exosomes, which implies that the living myocardium may be the source of circulating miR-133a . Moreover, elevated levels of circulating miR-133a are strongly associated with AMI diagnosis. In addition to traditional markers for clinical prognosis in AMI patients, the concentration of miR-133a may also provide prognostic information, perhaps even earlier than these traditional markers(3) .

3- MiR-133a Reduces Hypoxia-Induced Apoptosis in Cardiac Myocytes .

MiR- 133a is an apoptosis suppressor in myocardial ischemic post conditioning (IPost), inhibiting TAGLN2, HSP60, HSP70, Apaf-1, caspase-3/8/9 expression, and promoting antiapoptotic protein Bcl-2 expression (4). Ischemia and reperfusion injury (I/R injury) increases apoptosis via elevated

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expression of pro-apoptotic genes like caspase-9, and reduces miR-1 and miR-133 levels. In contrast, IPost upregulates miR-133a, which decreases caspase-9 expression,and, consequently, decreases apoptosis of cardiomyocytes under I/R injury. Thus, myo-miRNAs miR-1 and miR- 133a may play an important role in IPost protection by regulating apoptosis-related genes, such as caspase-9 (5).

4-MiR-133a Over-Expression Protect Against Cardiac Fibrosis Post-MI .
The main determinants of tissue fibrosis are an activated transforming growth factor-b (TGF-b) signaling cascade and the accumulation of increased extracellular matrix (ECM) proteins such as fibronectin (FN1) and collagen 1 alpha 1 V (COL4a1) (6). MiR-133a, along with other transcription factors can induce myocardial trans differentiation of cardiac fibroblasts by inhibiting TGF-b signaling or the expression of certain factors that promote fibrosis, such as snail-1 expression (7)

5 -MiR-133a Represses Cardiac Hypertrophy .
MiR-133a has potential regulatory roles in cardiac hypertrophy. Activation of NFAT nuclear factor of activated T cells-mediated hypertrophic signaling is a key regulatory response to hypertrophic stimuli. NFATc4, a hypertrophy associated mediator, is a negatively regulated target of miR- 133a (8). Additionally, in vitro over-expression of miR-133 could inhibit cardiac hypertrophy. In contrast, inhibition of miR-133 by 'decoy' sequences induces hypertrophy, which is more pronounced than hypertrophy generated with common inducers. In vivo inhibition of miR-133 by a single transfection of an antagomir causes sustained and marked cardiac hypertrophy. RhoA, a GDP-GTP exchange protein regulating cardiac hypertrophy; Cdc42, a signal transduction kinase involved in hypertrophy; and Nelf-A/WHSC2, a nuclear factor implicated in cardiogenesis, have been identified as specific targets of miR-133 (9).

6- MiR-133a Promotes Regeneration and Cardiac Programming Post-MI
Regeneration of the infarcted heart with new, functional cardiomyocytes remains challenging, but promising. Transplantation of cardiac stem cells (CSCs) or progenitor cells has been regarded as a potential therapeutic option for myocardial
infarction patients. At present, cell therapy approaches with various types of mature or stem cell patients have produced modest improvements. Among them, resident CSCs/CPCs are a promising option. The great beneficial cardiac-specific effect of cardiac miRNAs including miR- 133a is very helpful for enhancing the regenerative properties and survival of transplanted stem cells and cardiac progenitor cells, and for reprogramming mature noncardiac cells to cardiomyocytes (1). .

7- MiR-133a and Stem Cell Transplantation in MI .
MiR-133a can be utilized in stem cell therapies for MI to augment the survival of grafted cells and increase treatment effectiveness, possibly by enabling more transplanted stem cells to differentiate into healthy cardiomyocytes,
or by contributing additional cardioprotective benefits. Similarly, the survival rate and ability of transplanted cells to resist host-mediated immune responses may
also be strengthened by employing exosomes derived from MSCs that overexpress indoleamine 2,3-dioxygenase1 ,(1) .

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