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# miRNA-208a 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-208a in human heart and its therapeutic implications.

**Keywords:** Acute STEMI, myocardial remodeling, miRNA-208a

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## INTRODUCTION

### 1-miRNA-208a in cardiogenesis

In the heart muscle, the myosin heavy chain (MHC) is the major contractile protein comprising α- and β-isoforms. The proportion of isoforms could change during heart development. β-MHC is mainly expressed in late fetal life while α-MHC is preferentially expressed in the adult. Cardiac expression of miRNA-208a and miRNA-208b also vary in parallel with α-MHC and β-MHC expression. miRNA208b is predominantly expressed in the fetal myocardium while its expression drops in the adult heart. In contrast, miR-208a expression rises during cardiogenesis achieving top levels in adulthood. The switch from the predominant miRNA-208b expression to preferential expression of miRNA-208a occurs post-natally suggesting that both miRNAs share the same targets. Compared with rodents, miRNA-208a is the predominant miRNA-208a isoform that is expressed in humans and large animals. (1)

### 2- miRNA- 208a in heart function

Overexpression of miRNA-208a in cardiomyocytes leads to hypertrophy; and is associated with increased β-MHC expression and miR-208-dependent down-regulation of THRAP1 and myostatin, which both act as hypertrophy repressors. In addition, miRNA-208a upregulation in hypertrophic hearts leads to abnormalities in cardiac rhythm and fibrosis and is associated with reduced expression of cardiac-specific transcription factors (GATA and homeodomain-only protein (HOPX)) and junctional protein connexin-40 involved in intercellular conductance. (1)

### 3-miRNA- 208a as a marker of myocardial infarction

The miR-208a family is composed of miRNA-208a, miRNA-208b, and miRNA-499 encoded by α-cardiac muscle myosin heavy chain gene (α-MHC/Myh6), β-MHC/Myh7, and Myh7b, respectively, which plays a vital role in regulating muscle myosin content, myofiber identity, and muscle performance. It is well known that tissue and cell specificity is crucial character to miRNAs. Analyzing distribution of miRNAs by quantitative real-time polymerase chain reaction (qPCR) in various organs, including the heart, brain, kidney, lung, liver, and skeletal muscles, revealed that miRNA-208a is exclusively expressed in the heart. (2)

High level of circulating miRNA-208a family has been discovered in coronary artery disease that can serve as a potential biomarker. The plasma miRNA-208a level analyzed by qPCR showed greater sensitivity and specificity in identifying myocardial injury than other miRNAs. miRNA-208a level in plasma was not increased in response to cardiac hypertrophy, other causes of troponin elevation as acute or chronic kidney disease, stroke and trauma. miR-208a was also closely correlated to circulating cardiac troponin I (cTnI) which is a sound biomarker for myocardial injury. (2)

miR-208a was undetectable in plasma from healthy people, non-coronary heart disease (CHD), or CHD people (patient with unstable angina), but it was elevated within 4 h after the onset of symptoms in 100 % of the MI patients while only 85% of these patients have a cTnT elevation. (3)

### 4- miRNAs in acute myocardial ischemia/ reperfusion injury (IRI)

A large number of studies have shown early changes in myocardial expression of miRNAs (either increasing or decreasing) in response to acute myocardial IRI, they act via activation or inhibition of a number of proteins which have been implicated as downstream targets for miRNA in the setting of acute myocardial IRI. As expected, many of the downstream target's impact on cell death pathways such as apoptosis, autophagy, and more recently necroptosis. (4)

In an experimental study **Zhang *et al* 2018,** found that the elevated miRNA-208a expression enhanced the injury

of cells and promoted cell apoptosis. miRNA-208a directly target 3'UTR of CHD9 and negatively regulated CHD9 expression. Overexpression of CHD9 rescued IRI that was enhanced by miRNA-208a mimic transfection. miRNA-208a was positively related with activation of Notch/NF-B signal pathways via CHD9. They concluded that, miRNA-208a was a cardiac enriched miRNA and CHD9 is a direct target of miRNA-208a, which was also related with Notch/NFB signal pathway during IRI. miRNA-208a has the potential to be a biomarker for early diagnosis of IRI and might be used as a treatment target in treatment of ischemic heart disease. (5)

**5- miRNA- 208a as a marker of myocardial fibrosis**

It was found that miRNA-208a can increase endoglin expression in cardiac myoblasts and in volume-overloading heart failure to modulate myocardial fibrosis. Endoglin is a membrane glycoprotein that is a coreceptor of transforming growth factor (TGF)-b1 and TGF-b3. Endoglin is a potent mediator of profibrotic effects of angiotensin II on cardiac fibroblasts and can modulate the effect of TGF-b1 on extracellular matrix synthesis. These data indicate that endoglin may play an important role in fibrogenesis in cardiac remodeling. (6)

It's also found that Overexpression of miRNA-208a led to apparently hypertrophic growth by inhibiting thyroid hormone-receptor-associated protein-1 (THRAP-1) and myostatin, both in vivo and in vitro. A Clinical study found that myocardial miR-208a was upregulated in patients with HF compared to those with non-failing heart. Upregulated miR-208a from patients with dilated cardiomyopathy (DCM) was negatively correlated to left ventricular ejection fraction (LVEF) but positively associated with left ventricular end-systolic volume index (LVESVI). In this study miRNA-208a was associated with clinical outcomes and it was a strong independent predictor of cardiac death in the follow-up study. (2)

**6-Role of miRNA in follow up after PCI**

It was found that the miRNA-208 level was higher in patients with 2 or 3 stenosed coronary vessels than in those with only one stenosed coronary vessel, indicating that miRNA-208 may be predictive for the degree of coronary injury. (7)

Also, miRNA-208 level remarkably decreased 24 h after PCI in acute myocardial infarction (AMI) patients. Thus, successful clinical interventions can lower miRNA-208 expression in AMI patients, suggesting that miRNA-208 is useful for assessing the effective myocardial reperfusion following myocardial ischemia in AMI patients and thus is valuable for the evaluation of early clinical interventions. Therefore, miRNA-208 can play a role in monitoring clinical conditions. (7)

**7-Therapeutic implications of miRNA 208a**

In one study, it was found that therapeutic inhibition of miRNA-208a by subcutaneous delivery of anti-miRNA-208a leads to 225 gene regulated response in hypertension- induced heart failure in Dahl hypertensive rats compared with the 325 targets regulated response after MI especially at the site of infarction more than the remote myocardium. They concluded that anti miRNA-208a effect not only depends on the dose but also it depends on the type and the level of the stress, and its dose dependently prevents pathological myosin switching and cardiac remodeling, while improving cardiac function, overall health, and survival. (8)

It was found that early modulation of miRNA-208a in the diabetic heart induces alterations in the downstream signaling pathway leading to cardiac remodeling and that therapeutic inhibition of miR-208a may be beneficial in preventing diabetes-induced adverse remodeling of the heart. (9)

A therapeutic miRNA MGN-9103 by miRagen Therapeutics is under trials for the treatment of chronic heart failure. It targets miRNA-208a that is required for cardiac hypertrophy, fibrosis, and myosin switching. (10)

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