Review article

# CIRCULAR RNA – MIRNA MEDIATED INTERACTION IN MYOCARDIAL INFARCTION

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**ABSTRACT**

Circular RNA (circRNAs) belong to the long non-coding RNA family, but unlike the linear RNA in circular RNA, the 3' and 5' end in the RNA molecule are joined together, forming their circular structure. Until recently, circRNAs have been believed to be a side product of splicing, but now it is known that they have a wide range of biological functions, from regulators of gene expression to regulators of other non-coding RNAs - microRNAs (miRNAs). CircRNAs have the potential of being therapeutic targets and biomarkers for diseases. There are little data and only several investigations about this type of RNAs in myocardial infarction in humans.

This review summarizes the role of some new circRNA – miRNA interactions in the development of Myocardial Infarction.

**Keywords:** CircRNAs, miRNAs, myocardial infarction,

**INTRODUCTION**

According to their nucleotide size, there are two types of non-coding RNA (ncRNAs): small ncRNAs (<200nt) and long non-coding RNAs (lncRNAs) (>200nt) [1]. CircularRNAs (circRNAs) are a class of ncRNAs with structure in the form of a closed-continuous loop. These molecules are resistant to Ribonuclease R (RNase/R) enzyme activity [2], which explains their better stability in comparison with the linear structure of lncRNAs. Due to their stable levels and widespread expression, circRNAs are well conserved in the liver, stomach, lung, saliva, exosomes and blood [3-6]. Therefore, they could play an important role as diagnostic and prognostic biomarkers in a variety of diseases [7-11]. The participation of circRNAs has been recently discovered in cardiovascular diseases (CVDs) such as myocardial infarction (MI) and heart failure (HF). [2, 12] However, there is less information about their role in cooperation with miRNAs in the pathophysiology of these diseases.

The aim of this review is to present the participation of certain circRNAs in cardiovascular diseases, and thus it summarizes the role of circRNA – miRNA interactions for the development of MI.

**Characteristic and role of circRNAs**

Unusual with their circular covalently bonded structure, high stability and resistance to exonucleases, circRNAs biogenesis, functions and application are an active area of research. Currently, it is known that the precursor mRNA back-splicing process generates circRNAs and, more specifically, ecircRNAs (exonic circular RNAs) and EIciRNAs (exonic-intronic circular RNAs) [13]. Several biogenesis mechanisms have been proposed: lariat driven circularization (exon skipping model); intron pairing driven circularization (direct back-splicing model); RBP driven circularization [14, 15]. Inside the cell, circRNA localization determines their functions **(Fig.1)**.

For instance, circRNAs with retained introns (ciRNAs, EIciRNAs) probably regulate gene transcription as they are found mainly in the nucleus [16, 17] and ecircRNAs occurring in the cytosol are likely to be involved in post-transcriptional regulation as alternative splicing regulation. [17, 18] Some cytosolic circRNAs were associated with polysomes, containing IRES and ORF, allowing them to be translated into small peptides and proteins despite lacking of poly(A) tail and a 7-methylguanosine cap [19-21]. Furthermore, circRNAs bind proteins and this function gives rise of numerous speculations like circRNAs are a transport vehicle for proteins or induce allosteric changes, regulating protein function. [7, 22] The most studied circRNA function is miRNA sponging since miRNAs are involved in the regulation of nearly all cellular processes like cell differentiation, proliferation, migration and apoptosis. [23] Multiple miRNAs can be regulated by one circRNA, or one circRNA can have multiple sites for one miRNA. [24, 25] At the same time, it seems that not all circRNAs function as miRNA sponges. [26] However, the network circRNA-miRNA-mRNA could reveal novel mechanisms in various

**Fig 1.** circRNA functions. The most known circRNAs function is a sponge for miRNAs. Other circRNAs functions include sponging of RBP (RNA binding proteins), modulation of gene transcription and template for protein translation. circRNAs are promising biomarkers for many diseases.
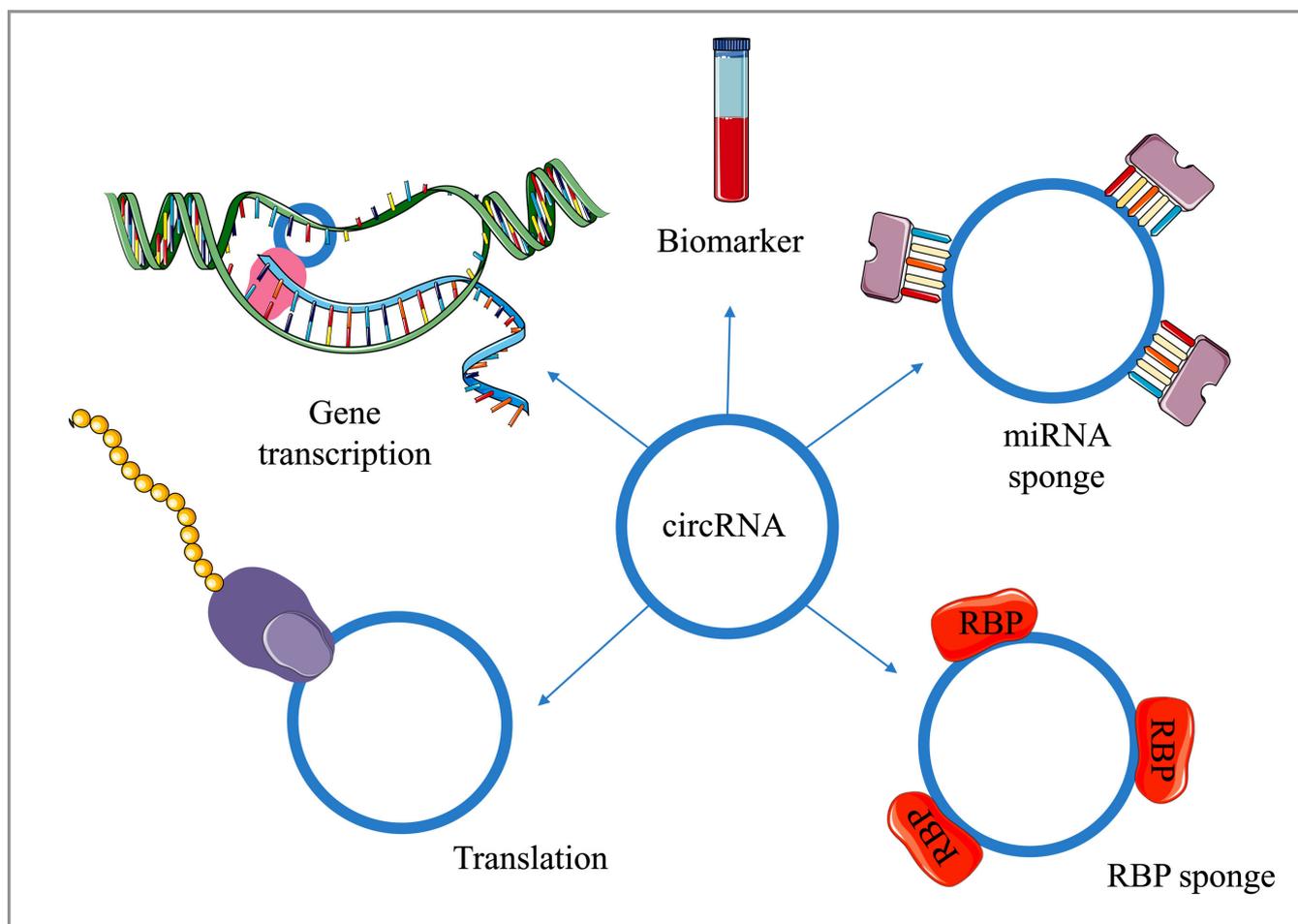


human diseases and be used for possible therapeutic strategies. Moreover, circRNAs appear to be promising non-invasive biomarkers since they are found in liquid samples as cerebrospinal fluid, saliva, blood and urine. Their up or down-regulation could be used for diagnosis, prognosis, therapy selection and monitoring. [27]

**Myocardial Associated CircRNA (MICRA) – miR-150**

Myocardial Associated CircRNA (MICRA) is a circRNA that has an impaired blood excretion after MI or ischemic reperfusion injury. MICRA was examined in a clinical study [28], and its predictive value in left ventricular (LV) dysfunction was evaluated. The study established that expression levels of MICRA in the blood of 642 patients with acute MI were lower compared to the healthy control individuals. Furthermore, lower values of MICRA were associated with a decreased left ventricular ejection fraction. For this reason, the authors consider it a possible predictor of LV dysfunction. [28]

In a more recent clinical study [29], MICRA was examined in whole blood in 472 patients with acute MI at the time of reperfusion, and ejection fraction was determined 4 months after. The result was the same patients

with a reduced ejection fraction 4 months after the incident had lower MICRA values than those with a preserved ejection fraction. [29]

The connection between MICRA and miRNA has been described for miR-150. [30,31] MICRA probably inhibited acting as a sponge for miR-150 [29]29. It is believed that miR-150 serves as a cardiac remodeling controller, and lower levels of miR-150 were found in patients with LV hypertrophy and LV rupture after acute MI. [31]

**Mitochondrial Fission and Apoptosis CircRNA (MFACR) – miR-652-3p**

In a study using mouse cultured primary cardiomyocytes subjected to anoxia/reoxygenation (A/R), the negative role of MFACR in the regulation of mitochondrial fission and cardiomyocytes apoptosis is demonstrated. [32] *In vivo* in a mouse model of MI and ischemia-reperfusion injury tissue levels of both MFACR and MTP18 were elevated in comparison with healthy hearts, and inhibition of MFACR lead to decreased cardiomyocyte apoptosis and infarct size. [32] It is reported that circRNA binds and acts as a sponge of miR-652-3p *in vivo*. MiR-652-3p regulates the expression of MTP18 (a nuclear-encoded mitochondrial membrane pro-

tein) and suppresses its level. This protein is known to regulate mitochondrial fission and apoptosis. *In vitro*, in a mouse cell model of MI, expression levels of MFACR and levels of MTP18 were elevated in cardiomyocytes in the A/R condition with a significant increase in cell apoptosis. [32] The axis MFCAR/miR-652-3p/MTP18 is formed, and probably MFCAR plays a crucial role in apoptosis regulation. [32] These results show the potential role of MFCAR in the pathogenesis, and the development of MI should not be underestimated.

### CircRNA_081881 - miR-548

Another circRNA_081881 appears promising for a precise diagnosis of acute MI. Plasma levels of circRNA_081881 were more than ten-fold downregulated in patients with acute MI in comparison with healthy volunteers. [33] This circRNA is thought to play its biological role by controlling the expression of PPARy protein (heart protective protein). This protein is so far with a not very clear role in cardiomyocytes. CircRNA_081881 controls its expression by sponging miR-548. [34] This way, plasma levels of PPARy protein are also downregulated in patients with AMI. [33]

### CircRNA transcribed from the sodium/calcium exchanger 1 (ncx1) gene (NCX1) -– miR-133a-3p

This circRNA plays a crucial role in the regulation of apoptosis in terms of myocardial infarction and ischemia-reperfusion injury. In an interesting study, tissue samples for NCX1 in mouse models of myocardial infarction are upregulated, furthermore slicing of NCX1 attenuates cardiomyocytes apoptosis [35]35. NCX1 promotes apoptosis via sponging miR-133a-3p, thus preventing inhibition of the translation of a gene called CDIP1. The last one encodes the production of pro-apoptotic protein cell death-inducing p53-target protein 1 (CDIP1). [35] The authors also observed overexpression of NCX1 and CDIP1 in mouse cardiomyocytes with an induced ischemia-reperfusion injury. A knockdown of NCX1 in heart tissues attenuates apoptosis and reduced levels of the protein CDIP1. [35] This circRNA may serve in future diagnosis as a therapeutic target in terms of myocardial infarction and ischemia induced injury.

### CircRNA antisense to the cerebellar degeneration-related protein 1 transcript (Cdr1as) – miR-7

In an interesting study, the authors used mouse models of MI and ischemia-reperfusion injury36. They examine the cell expression of Cdr1as, miR-7 and PARP (poly(ADP-ribose) polymerase), which is a trigger of apoptosis. CircRNA Cdr1as and miR-7 were co-overexpressed in increased infarct size and in cardiomyocytes after ischemia-reperfusion injury. In the infarct region, there was increased apoptotic activity. High levels of miR-7 lead to a reduction of PARP and reversing of cell apoptosis, while overexpression of Cdr1as leads to upregulation of PARP in vivo and increased infarct size. [36] It is thought that this is because Cd1as is

sponging miR-7 and positively regulates the expression of PARP. [37] Cdr1as has the potential to be inhibiting the target of heart apoptosis.

### CircRNA tetratricopeptide repeat domain 3 (circ-Ttc3) – miR-15b

Circ-Ttc3 serves as a sponge of miR-15b in mouse hearts. [38] In a study, authors explore the expression of circ-Ttc3 and miR-15b in mouse cardiomyocytes by analyzing *in vivo* myocardial infarction and *in vitro* ischemia-reperfusion injury. They find out overexpression of both RNAs in myocardial infarction and in ischemia-reperfusion injury. The depressed circ-Ttc3 leads to the enhancement of apoptosis, and overexpression of miR-15b promotes apoptosis. Taking together those observations, the authors conclude that circ-Ttc3 might play a protective role for the cardiomyocytes in terms of myocardial infarction and ischemia-reperfusion injury. [38]

### Nuclear factor 1 B-type (NFIB) circRNA – miR-433

NFIB could attenuate cardiac fibroblastic activity post-MI via sponging miR-433. [39] In the same study, the authors investigate the expression of NFIB in heart samples of mouse models of myocardial infarction. They find out that the expression of NFIB is downregulated 8 - 10 weeks after MI. To find its biological role, mouse fibroblastic activity was stimulated through TGF-â (Transforming growth factor â - cytokine that stimulates fibroblast proliferation). Under those conditions, overexpression of NFIB attenuated cardiac fibroblast proliferation, while inhibition promoted it. The effect of NFIB is mediated because of the deactivation of miR-433, which promotes myofibroblastic differentiation in murine post-MI models. [40] In conclusion, NFIB–miR-433 axis may serve as a promising therapeutic option for attenuating cardiac fibrosis.

### Microtubule-actin crosslinking factor 1 (MACF1) crcRNA – miR-500b-5p

In a recent study [41], cardiac tissue levels of MACF1 are significantly downregulated in a mouse model of myocardial infarction in comparison with the control group 2 weeks after the infarction. [41] MACF1 was downregulated in primary cardiomyocytes subjected to ischemic injury. [41] Moreover, overexpression of MACF1 during in vivo experiment led to reduced myocardial infarct size and showed improved left ventricular ejection fraction. [41] It was assumed that this effect was due to reduced apoptotic activity. In the myocardial tissue and in primary cardiomyocytes exposed to ischemic injury, overexpression of miR-500b-5p was detected. [41] This miRNA is believed that is targeting the *EMP1* gene, which is involved in the control of cell death. [42-44] Overexpression of MACF1 reduced the expression of miR-500b-5b via upregulation of EMP1 (epithelial membrane protein 1). [41] Thus the authors concluded that MACF1 could act as a sponge for miR-500b-5p. [41] In conclusion, MACF1 seems like a promis-

ing therapeutic option in MI through the possible modulation of the miR-500b-5p/EMP1 axis.

### Hsa_circ_0090876, transcribed from LAS1L gene (LAS1L) circRNACirc_LAS1L – miR-125b

The expression of circ_LAS1L and its potential pathophysiological role is studied in 30 patients with acute MI. [45] In patients with acute MI and in CFs, circ_LAS1L expression was significantly decreased. [45] The authors assumed that this cicrRNA might play an important role in MI. In fact, overexpression of circ_LAS1L led to inhibition of target gene, which encodes expression of collagen I and collagen III. In this way, circ_LAS1L could have antifibrotic potential. [45] Circ_LAS1L probably exhibited its biological function through sponging and inhibition of miR 125-b. [45] There are iterature data that miR-125b may have fibrosis-promoting potential [46, 47], although it could also have a protective role for cardiomyocytes. [48] In patients with MI, miR-125-b was overexpressed. [45] It was assumed for its function to downregulate the secretion of SFRP5 (frizzled-related protein 5), a protein that inhibited CF proliferation and migration and promoted apoptosis. 45 On the other hand, overexpression of circ_LASIL inhibited the activity of miR-125b and promoted the expression of SFRP5. [45] Circ_LASIL may have therapeutic antifibrotic activity through modulation of miR-125-b – SFRP5 pathway. However, more investigations are needed.

## CONCLUSION

The potential connection between circRNA and miRNA in terms of MI is an opportunity to discover more about the regulatory mechanisms and the pathomorphological manifestations of the diseases. The interaction between both types of RNAs reveals a new field of examining the development and progression of MI. Moreover, it has the potential to be used for diagnostic, prognostic and therapeutic purposes.

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