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miRNAs in the development of left ventricular remodeling and post-myocardial infarction heart failure

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Abstract

Acute myocardial infarction (AMI) induces unfavorable left ventricular remodeling (LVR), a complex process which involves molecular, cellular, and geometrical alterations leading to important changes in heart structure and function. Heart failure (HF) is a frequent complication of AMI and it remains a serious clinical, epidemiological and economic problem. Despite advances in the therapy and the management of HF, still many patients suffer from severe symptoms. The underlying molecular mechanisms of the post-AMI LVR are not yet fully understood. Many studies have indicated that dysregulation of microRNAs (miRNAs) molecules expression led to the changes in several pathological processes occurring in the heart, which are associated with post-AMI transition from cardiac hypertrophy to failure. In this review, we summarize the current knowledge on the role of miRNAs in the regulation of basic processes, such as excessive myocardial fibrosis, pathological cardiomyocyte hypertrophy and myocardial cell apoptosis. Moreover, the significance of circulating miRNAs as prognostic, non-invasive biomarkers in the prediction of LVR and HF development after AMI has also been discussed. In conclusion, miR-29 family members (miR-29a, miR-29b), miR-150 and miR-30a-5p represent different groups of miRNAs, but all of them are involved in the regulation of the fundamental processes associated with post-AMI LV dysfunction and occurrence of HF. Furthermore, these miRNAs molecules may serve as a potential therapeutic target during disease progression.

Keywords: acute myocardial infarction; circulating microRNAs; heart failure; left ventricular remodeling; prognostic biomarkers.
1. Introduction

Acute myocardial infarction (AMI) is a life-threatening condition and it remains the frequent cause of heart failure (HF) [1-2]. AMI is associated with unfavorable left ventricular remodeling (LVR), which affects cardiac function and increases the risk of HF occurrence [3]. An example of an unfavourable remodeling of LV after AMI might be bendopnea, which is connected with changes in ventricular filling and it is one of the symptoms of chronic heart failure [4]. The molecular processes involved in the pathogenesis of HF following AMI include extensive myocardial damage, repetitive ischemia and impairment of myocardial contractility, chronic activation of neuroendocrine systems and extracellular matrix remodeling [1, 5]. According to the literature, one-third of ST elevation myocardial infarction patients develop LVR [6]. Left ventricular systolic dysfunction and other adverse changes in consecutive stages of HF are often worse. In clinical practice, for many years, natriuretic peptides (especially NT-proBNP), have been a well-known tool used to assess LV systolic dysfunction and to diagnose and monitor the effectiveness treatment in patients with HF [7]. Some studies have reported that 70% of patients who develop HF after AMI die within 7.6-year period [8]. HF remains the leading hospital admission diagnosis in patients over 65 years old [9]. Based on the Framingham Heart Study, a 5-year mortality rate is 45–60% [10-11]. Early forecasting of adverse LVR and the occurrence of HF following AMI is essential to improve morbidity and mortality outcomes. Despite advances in the identification of biomarkers associated with LVR, the ideal biomarker for an early and reliable prediction of the risk of developing post-AMI HF is still to be found [12].

MicroRNAs (miRNAs, miRs) belong to the best characterized class of non-coding RNA family. For several years, growing interest in miRNAs’ biology in cardiovascular research has been observed. Some miRNAs are highly expressed in the heart and in many studies the significance of miRNAs in cardiac development, physiology and disease has been
investigated [13-15]. Increasing evidence indicates that upregulation and downregulation of miRNAs can be considered as a detector of environmental changes in heart disease and HF, through their causative and protective role, so important for modulating metabolic pathways [16]. The development of new therapy procedures became possible because of the engagement of the scientific community in the attempt to explain the pathophysiology of cardiovascular disease through thorough miRNA molecules research as a potential therapeutic target [17]. Currently a resounding interest in circulating miRNA molecules has been observed, due to their role, both as promising diagnostic as well as prognostic biomarkers for various pathological processes occurring in the heart, including the development of LVR and post-AMI HF.

2. microRNAs – origin, structure, function and regulation

miRNAs belong to a class of small (~22 nucleotides long), single-stranded, evolutionarily conserved molecules. These non-coding RNAs act as posttranscriptional gene regulators through target mRNA translation inhibition or the promotion of mRNA degradation [17-19]. Due to broad target interactions, miRNAs participate in the regulation of a wide range of biological processes, e.g.: programmed cell death, metabolism, immune responses, cell proliferation, differentiation organogenesis, and many others [19-21].

In accordance with the miRBase Sequence Database (version 22.1), more than 2000 known human miRNAs are documented [22]. It has been estimated that more than 60% of human protein-coding genes are targeted by single miRNA [23].

The microRNA biogenesis pathway consists of complex processes occurring in nucleus and cytoplasm (Figure 1). First of them, located in the nucleus, leads to the generation of long primary miRNAs (pri-miRNAs), which are generally transcribed by RNA polymerase II [24-27]. miRNAs genes can be expressed as independent transcripts (intergenic miRNA),
polycistronic transcripts that often encode multiple miRNAs, or they can be embedded in introns of protein-encoding mRNAs (intragenic miRNA) [28]. Pri-miRNAs are hundreds to thousands of nucleotides long, they contain an active miRNA in a stem-loop structure. Pri-miRNAs molecules are processed in the nucleus by a microprocessor complex consisting of ribonuclease III Drosha and DiGeorge Critical Region 8 (DGCR8) to form a 60-100-nucleotides long hairpin-shaped precursor miRNAs (pre-miRNAs) [29-30]. Pre-miRNAs are transferred from the nucleus into the cytoplasm by the shutter Exportin 5 [30-31]. In the cytoplasm pre-miRNAs are processed by RNAase III type endonuclease Dicer to small double-stranded duplex containing the mature miRNA (18-25 nucleotides long) [30]. Functional miRNAs are finally coupled to Argonaute 2 protein (Ago2) and then incorporated into RNA-induced silencing complex (RISC) [27]. The mechanism of mRNA regulation by miRNA depends on the degree of sequence complementarity between the miRNA and 3′UTR motif in the target mRNA gene [32]. The extent of base-pairing determines their mode of action: translation inhibition and/or augmented mRNA degradation, both pathways resulting in the effective downregulation of the target gene expression. Some miRNAs may also promote mRNA transcription [17, 33]. It is worth of emphasizing that an individual miRNA can regulate the expression of multiple target genes and they are also controlled by many factors and molecular mechanisms themselves, creating complex system of mutual interactions [34-36].

The understanding of the complexity of mechanisms taking part in miRNA expression regulation will be essential in explanation of the pathogenesis and treatment of cardiovascular diseases arising from dysregulated gene expression.
3. miRNAs and myocardial infarction

Myocardial infarction (MI) is an effect of myocardial ischemia, resulting in its necrosis. Due to the lack of oxygen, the reduced blood flow to the heart may lead to the damage of cardiomyocytes. The above processes are usually caused by the rupture of the atherosclerotic plaque in the coronary vessels [37].

The role of tissue-specific miRNAs both in physiological and pathological conditions has been documented. miRNAs are critical regulators which participate in almost all aspects of cardiovascular diseases. During MI many of miRNA molecules are released from cardiomyocytes into the bloodstream [38-39]. Cellular miRNAs can be transported into circulation in microvesicles, exosomes, and apoptotic bodies or associated with miRNA-protein complexes with Ago2 or nucleoplasmin, as well as HDL-miRNA complexes [23]. Circulating miR-1, miR-133a, miR-133b, miR-208a, miR-208b and miR-499 are frequently associated with MI. miR-133a, miR-133b and miR-1 are strongly expressed in heart and skeletal muscle, whereas miR-499 and miR-208a are only cardiac-specific [27, 38, 40-41].

miR-1 is one of the most upregulated miRNAs, whereas miR-133a is downregulated in rats’ hearts upon acute myocardial ischemia/reperfusion [42]. Yin et al. [43] have reported that after ischemic preconditioning expression of miR-1, miR-21 and miR-24 were significantly elevated in the heart. The increased miRNA levels thereafter trigger cardiac protection by upregulating endothelial nitric oxide synthase and also heat-shock protein 70, and heat-shock transcription factor 1 [43].

The results of our previous studies [44] have demonstrated that miR-208a molecules are released into the circulation (3-fold increase vs. control) during AMI, even before the appearance of traditional biomarkers of cardiomyocyte necrosis: cTnI and CK-MBmass. The highest expression of miR-208a (90-fold increase vs. control) was observed in the third hour after reperfusion. Plasma expression of miRNA-208a correlated with cTnI concentration and
also with the concentration of CK-MBmass. These results clearly indicate that miRNA-208a molecules which were present in plasma had been released from cardiac myocytes. After 24 hours, their expression decreased to the level observed at the time of admission [44]. Contradictory results were presented by Zile et al. [45], who observed a three-fold increase in miRNA-208 expression in comparison to control, only until the 5th day after an AMI. Maximum expression occurred on day 28th and the increased expression continued for the next 90 days [45]. This late plasma expression of miR-208a was associated with the development of HF in these patients. The presented studies seem to suggest that there are at least two different mechanisms of miR-208 molecule release from cardiomyocytes. In the early phase of MI, miR-208a may be released in microvesicles formed during myocardial ischaemia. The late release is probably associated with the damage of cardiomyocytes and/or their apoptosis.

4. miRNAs and heart failure

Cardiac remodeling is an adaptive myocardial change that maintains the hemodynamic balance under the influence of external stimuli. When these causative factor continue such remodeling becomes an irreversible process leading to HF [30]. The pathological ventricular remodeling is characterized by three main features: extensive fibrosis, pathological cardiomyocytes hypertrophy and myocardial cell apoptosis [17] (Table I). miRNA molecules involved in the processes mentioned above with reverse direction of mechanism of action: anti- and pro- are shown in Table I.

Table I. miRNA molecules involved in heart failure development.
4.1. Excessive myocardial fibrosis

The balance between collagen synthesis and degradation is essential for myocardial extracellular matrix (ECM) homeostasis. Activated fibroblast synthesize collagen which is then degraded by matrix metalloproteinases [17]. In several studies it has been documented, that miRNAs molecules play regulating role in collagen metabolic pathways. miR-24, miR-29, miR-30, miR-31 and miR-133 are major anti-fibrotic miRNAs [30] (Table I). miR-133 and miR-30 take part in the regulation of connective tissue growth factor expression (CTGF) [46-47], a key molecule in the fibrotic process, which induces the synthesis of ECM [17]. It has been observed that increased expression of miR-133 and miR-30 may reduce CTGF synthesis leading to decrease collagen deposition [46].

The pro-fibrotic miRNAs include miR-21 and miR-125b (Table I). miR-21 is expressed exclusively in cardiac fibroblasts and it can promote the proliferation and fibrosis of fibroblasts [30]. Sygitowicz et al. [48] demonstrated an increase in miR-21 expression in the serum of patients with symptomatic heart failure, which was independent of disease severity. The increase in miR-21 expression did not correlate with NT-proBNP concentration, but was significantly associated with an increase in serum concentration of galectin-3, which is a biomarker of fibrotic process [48]. Similar results were obtained by Roy et al. [49]. They observed elevated miR-21 expression in the ischemic-reperfused myocardium. In study performed by Jaffre et al. [50] downregulated miR-21 expression not only inhibits fibrosis but also prevents cardiac hypertrophy caused by thoracic aortic coarctation.

4.2. Pathological cardiomyocyte hypertrophy

Cardiomyocyte hypertrophy occurs in multiple pathological conditions, such as chronic overload, ischemic injury and neurohormonal imbalance as a part of early adaptive reaction. However, this process may lead to cardiomyocyte death. Pathological concentric
hypertrophy of cardiomyocytes is an independent risk factor and an indicator of poor prognosis in HF patients [37]. Multiple molecular mechanisms are involved in the occurrence of pathological cardiomyocyte hypertrophy, especially the Ca$^{2+}$-dependent pathway and the phosphatidylinositol 3-kinase pathway [51-52]. Multiple miRNAs can affect the Ca$^{2+}$-dependent pathway. miR-1, miR-9, miR-26 and miR-133 exhibit anti-cardiac hypertrophy effects [30] (Table I). It has been established that in a rat model, miR-1 inhibits cardiomyocyte hypertrophy [30, 51]. In our previous study [48], we demonstrated downregulated expression of circulating miR-1 in patients with symptomatic heart failure. The degree of miR-1 expression decreased with the severity of NYHA class. This effect was greater in patients in NYHA class IV than those in NYHA class II/III. In our other studies [53-54], we also observed significant negative correlation between decreasing expression of miR-1 and serum NT-proBNP concentration and also left ventricular hypertrophy.

4.3. Myocardial cell apoptosis

Multiple miRNAs are associated with the regulation of myocardial cell apoptosis (Table I). miR-101a, miR-200a, miR-330 and miR-320 are the key miRNA molecules involved in induction of myocardial cell apoptosis [30]. It has been established that downregulated expression of miR-200a leads to increase expression of β-catenin and cyclin D1 involved in the cell proliferation via activation of the E-cadherin and Wnt/β-catenin signaling pathways [55]. miR-330 by inhibition of Akt phosphorylation induces myocardial cell apoptosis [56]. miR-101a may decrease the expression of Mcl-1, an important protein of anti-apoptotic family of Bcl-2 [57]. Pro-apoptotic action of miR-320 is connected with its effects on the important cardioprotective heat shock protein 20 [58]. The contrary to the above effect is an anti-apoptotic effect which is exerted by: miRNA-30, miRNA-199 and miRNA-206 [30].
5. Circulating miRNAs in the development of LVR and HF

Several studies have reported an association between circulating miRNAs levels and the development of LV dysfunction and HF [45, 59-70] (Table II). In this review, twenty one dysregulated miRs were identified as potential biomarkers for LVR and HF occurrence following AMI. miRs molecules, frequently connected with these processes (including miR-1, miR-21, miR-24, miR-27a, miR-29a/b, miR-101, miR-133a, miR-208a/b; Table II), are well-known due to the fact that their relationship with cardiovascular diseases has been confirmed. Some of them are involved in pathological processes during HF development and were listed in Table I. It is noteworthy that in recent studies the role of other types of miRs (e.g.: miR-34a, miR-150) in post-infarction LVR has also been confirmed. Among selected types of miRs there are also new miRs biomarkers (e.g.: miR-30a-5p, miR-1254) in case of which the information about the function in LVR and HF pathogenesis is, so far, limited, but which seem to have a promising prognostic value.

Table II. Circulating miRNAs after AMI in patients who develop LVR and HF.

The expression of some miR-29 family members (miR-29a, miR-29b) has been reported as prognostic biomarkers in LVR development and HF [45, 59, 63]. miR-29 family appears to have biological importance to ECM remodeling of heart by activating Wnt signaling pathway [71]. Target prediction analysis revealed that mRNA for miR-29 were involved in cardiac fibrosis processes, the encoding of collagen isoforms type I alpha 1 and 2, collagen type III alpha 1, matrix metalloproteinase 2, and others [47, 72-73]. Furthermore, miR-29 family members are also involved in the regulation of cell proliferation, differentiation, and apoptosis [73]. It was demonstrated by van Rooij et al. [72] that in mice model and in human cardiac tissue samples the expression of all three members of the miR-29 family (miR-29a, miR-29b, miR-29c) was decreased in border region of the infarcted heart. Further analysis performed by van Rooij et al. [72] and Kriegel et al. [73] also confirmed that the downregulated expression
of miR-29 takes part in the process of cardiac fibrosis. Research conducted on isolated mice cardiac fibroblasts with transforming growth factor has shown downregulated expression of miR-29a, miR-29b, and miR-29c [72-73]. Other studies [74] confirmed that decreased miR-29a expression may play an important role in cardiac fibrotic tissue due to the regulation of vascular endothelial growth factor-A and mitogen activated protein kinase signaling pathway. The circulating level of miR-29a was significantly reduced in AMI patients with low left ventricular ejection fraction, indicating its essential role in the occurrence of unfavorable LVR after AMI [63]. On the other hand, one may hypothesize that the upregulation of miR-29a expression early after AMI may be associated with limitation or inhibition of cardiac fibrosis or with promotion of ECM degradation, leading to more extensive LVR [45]. Grabmaier et al. [59] showed that elevated expression of miR-29b early after AMI and throughout follow-up was related with the anti-fibrotic effects. Thus, the upregulation of miR-29b could reflect a favorable outcome in regard to adverse LVR in post-AMI patients. However, the above mechanisms remain to be confirmed in further large-scale clinical and animal studies.

The prognostic significance of miR-150 in post-infarction LVR has also been confirmed [64, 69-70]. The function of miR-150 in the heart is still poorly understood. miR-150 can be actively secreted by monocytes under various conditions [75]. miR-150 can be involved in various mechanisms through which it can play a protective role against myocardial injury, cardiac hypertrophy or myocardial fibrosis. The cardioprotective functions of miR-150 were confirmed in a mice model of AMI, by regulating monocytes accumulation [75]. Another studies, performed by [76-77], showed that the upregulated expression of miR-150 in the heart may lead to inhibition of cardiac hypertrophy and fibrosis via regulating of serum response factor and transcription factor c-Myb. Moreover, the potentially cardioprotective effects exerted by miR-150 may be related to the direct suppression of pro-apoptotic genes: zinc-binding transcription factor induced by ischemia and pro-inflammatory ATP receptor in
cardiomyocytes [78]. On the other hand, the downregulation of circulating miR-150 is associated with hypertrophy, LV ruptures and unfavorable LVR after AMI [64, 69]. miR-150 is involved in LVR through the inhibition of the expression of its target genes: C-reactive protein and adrenergic receptor beta 1 [69]. The association between miR-150 and sepsis was also observed, which suggests its relation with inflammatory processes [79]. Due to the fact that inflammation is engaged in the development of post-infarction LVR, further studies are needed to determine the role of miR-150 as an inflammation-associated miR.

The overexpression of miR-30a-5p is related to LV dysfunction after AMI [68]. Circulating miR-30a-5p can be a novel prognostic biomarker. *In silico* functional analysis has shown that targets genes for miR-30a-5p are probably involved in metabolic pathways associated with cardiovascular pathogenesis (e.g. Wnt signaling pathway, calcium modulating pathway, fibroblast growth factor signaling) [68]. Some studies have demonstrated upregulation of miR-30a expression in patients with AMI [80], LV hypertrophy and HF [81]. Pan et al. [81] published results in which they presented that miR-30a is involved in cardiomyocytes autophagy by regulating its target gene beclin-1. It has also been confirmed that decreased expression of miR-30a-5p and miR-30c-5p may be associated with the regulation of apoptosis in skeletal myoblasts cells [82].

6. Conclusion and future perspectives

MicroRNAs indicate their promising potential as unique molecular markers that more precisely than the current biomarkers used in clinics (such as natriuretic peptides and/or galectin-3) illustrate sequences of metabolic pathways leading from myocardial infarction to heart failure. Hence, there is a need to identify the different types of miRNA molecules involved in the initiation and development of the disease. The current state of knowledge seems to suggest that family members miR-29 (miR-29a, miR-29b), miR-150 and miR-30a-
5p may be useful molecular markers in predicting the patient's clinical status. The miRNA molecules shown represent different groups of miRNAs, but all of them are involved in the regulation of basic processes such as cardiac fibrosis, apoptosis, autophagy and inflammation associated with left ventricular dysfunction after MI and HF development. It should be emphasized, however, that it is necessary to continue clinical and animal studies to confirm both their pathophysiological function in the heart after myocardial infarction and their usefulness in clinical practice. This is also important because of the potential role of these miRNAs as an important therapeutic target in patients with developing heart failure.

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Table I. miRNA molecules involved in heart failure development.

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<th>Fibrosis</th>
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<th>Apoptosis</th>
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Table II. Circulating miRNAs after AMI in patients who develop LVR and HF.

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Figure 1. miRNA biogenesis and function.

RISC – RNA-induced silencing complex; Ago2 – Argonaute 2 protein; ORF – open reading frame.