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MicroRNA in cardiac arrhythmias

MikroRNA w zaburzeniach rytmu serca

Mateusz Polak, Katarzyna Mizia-Stec

First Department of Cardiology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland
Leszek Giec Upper-Silesian Medical Centre, Katowice, Poland

Abstract

The aetiology of cardiac arrhythmias, especially atrial fibrillation (AF), is complex and needs further evaluation. The predisposition to arrhythmias may have a genetic origin, and recently more attention is paid to the role of microRNA (miRNA). MiRNAs are small, non-coding RNA molecules with properties that inhibit messenger RNA and regulate most biological processes in cells. MiRNAs play a key role in the development of the cardiovascular system, where the regulatory function of the miRNAs is essential for the proper organogenesis of the cardiovascular system. MiRNA is also responsible for the control of the expression of genes involved in the rhythm and function of the heart, including the regulation of cardiac cell proliferation, expression of ion channels and their function, regulation of inflammatory processes, apoptosis, and fibrosis. It has been shown that differences in the levels of circulating miRNAs in the blood correlate with various arrhythmias. A large number of relations between the change in miRNA expression and an increased risk of specific arrhythmia have been established. The greatest number of such relations was discovered for AF. The available data describing changes in the atria of the heart predisposing to AF and intensifying during long-term AF indicates the need to search for biomarkers. Identifying the role of the miRNAs in the pathogenesis of arrhythmias is a major step in the development of new diagnostic and therapeutic tools.

Key words: microRNA, arrhythmia, atrial fibrillation

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Introduction

The aetiology of atrial fibrillation is complex and still far from full explanation. Genetic predisposition, comorbidities, and structural or electrical remodelling of the atria are responsible for the pathogenesis and maintenance of arrhythmic readiness among patients [1]. The predisposition to atrial fibrillation may have a genetic basis, hence increased attention is paid to the potential ability of microRNA (miRNA) to regulate genes responsible for the onset and progression of atrial fibrillation. MiRNAs are molecules with properties that inhibit messenger RNA (mRNA) and regulate most biological processes in cells [2].

In clinical practice, miRNA can be used to identify both patients with an increased risk of atrial fibrillation and assess the risk of thromboembolism during already documented arrhythmias. The available indirect data, describing structural changes or conduction disturbances in the atria of the heart predisposing to atrial fibrillation and increasing during long-term atrial fibrillation, indicate that there is a need to identify biomarkers that are the result of individual mechanisms and identify patients at risk.

Address for correspondence: Mateusz Polak MD, I Katedra i Klinika Kardiologii Górnośląskiego Centrum Medycznego im. prof. Leszka Gieca, Śląski Uniwersytet Medyczny w Katowicach, ul. Ziołowa 47, 40–635 Katowice, Poland, e-mail: mateuszpiotrpolak@gmail.com

The biogenesis and function of microRNA

MiRNAs are small, non-coding RNA molecules consisting of 19 to 25 nucleotides. The main function of miRNA is the regulation of post-transcriptional gene expression. A single miRNA can affect many mRNAs and therefore influence gene expression. Genes affected by miRNA are often involved in a functional interacting pathway [3].

The transcription of miRNA takes place in the nucleus by RNA polymerase II. The primary miRNA is then cleaved by RNase III endonuclease Drosha into precursor-miRNA. In the cytoplasm, pre-miRNA is cleaved by the RNase III endonuclease Dicer to approximately 22 nucleotides double-stranded miRNA. The guide strand is then incorporated into the RNA-induced silencing complex (RISC) and creates mature miRNA, while the other strand is degraded [4]. Alternatively, pre-miRNAs can be processed independently of the Drosha complex through the direct splicing of introns [5].

The connection with the RISC, allows miRNAs to affect target mRNA resulting in inhibition of translation or mRNA degradation [6]. The effect depends on binding complementation. Perfect complementation with miRNA and mRNA results in degradation of the transcript. While imperfect complementation leads to inhibition of translation [7]. The overview of miRNA biogenesis and function is presented in Figure 1.

The role of microRNA in the heart evelopment

MicroRNAs play a vital role in the development of the cardiovascular system. Tissue-specific deletion of genes that are directly involved in miRNA biogenesis in mice (like Drosha or Dicer) led to death during early gestation. The complete lack of regulatory function of miRNA in mice embryos resulted in fatal developmental defects in the cardiovascular system. On the other hand, the knockout of particular miRNAs in mice resulted in much lower lethality [8]. This observation illustrates the function of miRNA, which is more of smooth regulation than a binary inhibiting or activating gene expression [9].

MicroRNA expression studies have proved that only 18 miRNAs constitute about 90% of the total cardiac miRNA. It is still to be proved, that only a few main miRNAs contribute to cardiac development and function or there is a group of lesser miRNAs that play a vital role in addition to the main 18 miRNAs [10].

The most abundant miRNAs in cardiomyocytes are miR-1 and miR-133, which role is the promotion of mesoderm differentiation in embryonic stem cells. However, they seem to have different roles later in cardiac development, where miR-1 promotes cardiomyocyte differentiation and miR-133 inhibits it [11]. MiR-1 also regulates

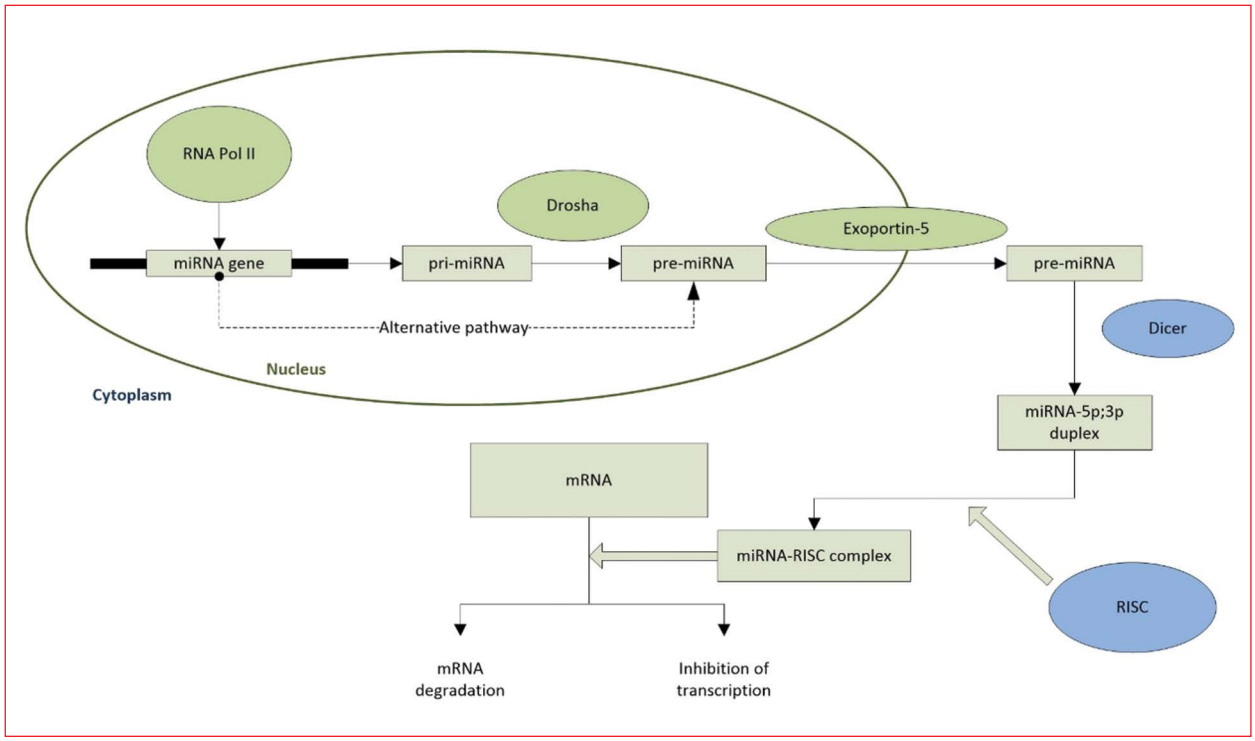

Figure 1. Schematic representation of miRNA biogenesis and function. Description in the text; mRNA — messenger RNA; miRNA — microRNA; RISC — RNA-induced silencing complex

the expression of Irx5 and Hand2, which are transcription factors. The Hand2 protein is directly involved in the development of the outflow tract and right ventricle, whereas the role of Irx5 protein is to regulate the expression of potassium channel genes and therefore influences the cardiac ventricular repolarization. The deletion of miR-1 led to ventricular septal defects [12]. MiR-133 affects the activity of transcription factors that plays a vital role in cell cycle progression: serum response factor, responsible for the regulation of genes involved in cardiac and smooth muscle differentiation, and cyclin D2, involved in the control of cardiomyocyte proliferation [13].

Contractile protein expression is also regulated by miRNA. MiR-208a, miR-208b, and miR-499 control the myosin genes. These miRNAs are encoded in the introns of alpha- and beta-myosin heavy chains genes [14]. The other miRNAs involved in heart development belong to the miR-15 family, which are miR-15a/b, miR-16- one-half, miR-195, and miR-497. MiR-195 inhibits cardiomyocyte proliferation after birth via up-regulation. Overexpression of this miRNA leads to ventricular hypoplasia and septal defects. MiR-15b is responsible for the level of adenosine triphosphate (ATP) in cardiac cells by controlling the adenosine diphosphate/ /ATP exchanger in mitochondria [15].

The role of microRNA in atrial fibrillation

Cardiac arrhythmias represent a wide group of disturbances in the cardiac rhythm. The pathophysiology of particular arrhythmias is usually complex. MicroRNAs represent a variable group of molecules regulating the expression of genes involved in heart rhythm and function, including regulation of cardiac cell proliferation, expression of ionic channels and their function, regulating inflammation, apoptosis, and fibrosis processes [16]. The mechanisms in which miRNAs may influence the cardiomyocyte creating the substrate for arrhythmias are presented in Figure 2.

The connection between miRNAs function and the risk of occurrence of cardiac arrhythmia seems also indisputable. The differences in levels of blood circulating miRNAs are strictly associated with various cardiac arrhythmias, especially AF (Table 1). MiR-1 and miR-133 play a vital role in the pathophysiology of non-AF arrhythmias. In subjects with a decreased level of miR-1, the supraventricular tachyarrhythmias were more common, whereas an elevated level of miR-133 was connected with ventricular tachycardia [17]. Also, the expression of the hyperpolarization-activated cyclic nucleotide-gated channel (HCN) gene family is under the control of miR-1 and miR-133. These channels are found in pacemaker cells in atriums and ventricles and overexpression of HCN support arrhythmogenic mechanisms [18]. Increased miR-1 however had been documented in ischemic rat hearts, where it contributes to the slowdown of cardiac conduction and is associated with ischemic arrhythmias [19].

The abnormalities in the levels of many other miRNAs have been linked to AF. Deregulated expression of miR-29 resulted in fibrosis and has been found to contribute to

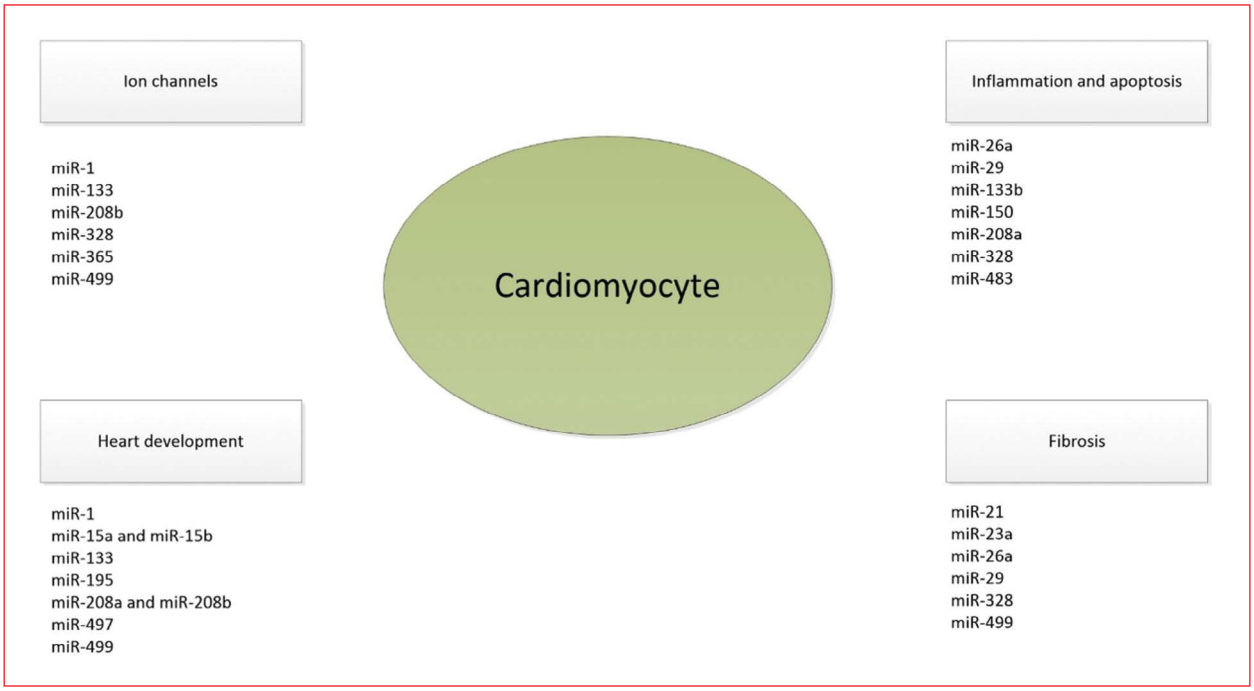

Figure 2. The mechanisms in which miRNAs may influence the cardiomyocyte create the substrate for cardiac arrhythmias. Description in the text

Table 1. The association between change in expression of microRNAs and cardiac arrhythmias [15, 26]

MicroRNA	Change	Associated arrhythmia
miR-1	Underexpression	SVT
miR-1	Overexpression	VT
miR-21	Overexpression	AF
miR-23a	Underexpression	AF (postoperative)
miR-26a	Underexpression	AF (postoperative)
miR-30d	Underexpression	AF
miR-133	Overexpression	VT
miR-133	Underexpression	AF
miR-150	Underexpression	AF
miR-208b	Overexpression	AF
miR-212	Overexpression	AF
miR-328	Overexpression	AF
miR-483	Overexpression	AF (postoperative)
miR-499	Overexpression	AF
miR-590	Underexpression	AF

AF — atrial fibrillation; SVT — supraventricular tachycardia; VT — ventricular tachycardia

apoptosis, because of increased expression of mRNAs encoding fibrosis-promoting proteins [20].

Atrial fibrosis has emerged as an important pathophysiological contributor and has been linked to AF recurrences. Another miRNA that is strongly involved in the regulation of connective tissue proliferation in atria is miR-21. With an increased level of miR-21 in transgenic mice models, cardiac fibroblasts deregulate the extracellular signal-regulated pathway and mitogen-activated protein kinase pathway. Malfunction of these pathways led to uncontrolled growth factors secretion fibroblasts proliferation, resulting in cardiac hypertrophy and fibrosis [21].

Detailed analysis of blood specimens from patients with AF indicated a significant decrease in the level of miR-150, both in platelets and in serum. The study showed a three times lower level of platelet miR-150 and one and half times in serum compared to the control group without a history of AF [22]. There is a considerable suspicion that decreased level of miR-150 may be related to AF development, which was thought to be associated with inflammation, fibrosis, and increased platelet function.

An increased level of miR-208b was also found in cardiac tissue samples from human and animal specimens with AF. An increased level of this miRNA inhibits the function of the sarco-endoplasmic reticulum Ca^{2+}-ATPase 2 leading to conduction disturbances and therefore to AF [23]. Also, the risk of postoperative AF can be related to the level of circulating miRNAs. Increased serum levels of miR-483 were associated with a higher risk of postoperative AF. On the other hand, AF occurred more often in patients with low levels of miR-23a and miR-26a after coronary bypass grafting surgery [24].

It is assumed that miRNAs may also regulate atrial remodelling by regulation of calcium channel protein expression. Overexpression of miR-328 was found in atrial tissue of patients and animal specimens with AF. In mice models, a prominent level of miR-328 enhanced AF vulnerability, while knockdown of miR-328 seems to have protective properties. Targeting both subunits of cardiac L-type calcium ion channel, miR-328 can be a potential effector in AF development [25].

Increased concentration of miR-499 also was found in the atrial tissue of patients with AF. By regulating the expression of the Ca2+-activated potassium ion channel, miR-499 may take its part in atrial fibrosis and remodelling and therefore induce AF [26].

The level of miRNA can also differ in new-onset AF. In their study da Silva et al. [27] compared the level of particular miRNAs in patients with acute new-onset AF and a control group. Patients with new-onset AF presented a significantly increased level of miR-133b, miR-328, and miR-499 in serum than patients with controlled AF or without AF. As pointed out before, these miRNAs participated in the regulation of genes that were involved in apoptosis and fibrosis processes. On the other hand, the expression of miR-21 was significantly lower in patients with well-controlled AF compared to the new-onset AF group. And therefore, it was proved that increased expression of miR-21 promotes fibrosis, while decreased expression prevents it.

The role of microRNA in ventricular arrhythmias

Ventricular arrhythmias (VA) can manifest as ventricular premature beats, ventricular tachycardia, or ventricular fibrillation. There is evidence that supports the relation between miRNAs and VA, especially in ischemic heart models. Increased levels of miR-1 and miR-133 were associated with an increased risk of VA [28]. Researchers have shown on animal models that overexpression of miR-1 and miR-133 led to increased depolarization and repolarization time and therefore creating the conditions for VA development. However, decreased concentration of these miRNAs was connected to supraventricular arrhythmias and AF, respectively. Age-associated low levels of miR-1 and miR-133 contribute to the overexpression of HCN2 and HCN4, and abnormal cardiac electrical activity [29]. The association between change in expression of particular miRNAs and cardiac electrical activity is presented in Table 2.

The overexpression of miR-208a in cardiovascular patients is proven to be associated with increased oxidative stress, inflammation, and apoptosis. A recent study showed a significant increase in the expression of miR-208a in

Table 2. The association between change in expression of particular microRNAs and cardiac electrical activity [26]

MiRNA	Change	Effect
miR-1	Overexpression	QRS ↑, QT ↑, VA
miR-1	Underexpression	Conduction block
miR-1-2	Knockout	QRS ↑
miR-133	Overexpression	QRS ↑, QT ↑
miR-208a	Knockout/Underexpression	Conduction block
miR-208a	Underexpression	Conduction block
miR-365	Overexpression	QT ↑
miR-365	Underexpression	QT ↓

VA — ventricular arrhythmia

heart failure, VA, and myocardial infarction patients when compared to the control group [30]. The increase in miR-208a was in pair with apoptotic and inflammation factors, like BAX and TNF-α, thus revealing miR-208a's potential role in these processes.

Another analysis of human cardiomyocytes identifies miR-365 as the main miRNA to regulate ventricular repolarization. Researchers show that elevation of miR-365 significantly prolongs QT, whereas underexpression of this miRNA significantly reduces QT interval. In cardiomyocytes from short-QT syndrome patients, an important level of miR-365 was able to normalize QT time, whereas inhibition of miR-365 normalized prolonged QT in long-QT syndrome cells. The study confirmed miR-365-dependent regulation of repolarizing ionic potassium current [31].

There is also evidence suggesting that the influence of mRNA on cardiac arrhythmias can differ in different ages. Recently polish researchers showed that in the paediatric population with supraventricular arrhythmias levels of miR-1 were significantly higher than in the control group. Furthermore, patients with VA had significantly lower miR-133 expression levels [32]. These results stand opposite to previous paediatric studies, where subjects with supraventricular tachycardia had lower miR-1 expression levels, while those with VA presented with higher expression of miR-133 [33].

Conclusions

The main function of miRNAs is the regulation of gene expression. It is done by inhibiting the process of translation of mRNAs through interaction with the three untranslated regions of specific mRNAs [32]. Numerous studies and research have shown that miRNAs play a vital role in the development and progression of various heart diseases, including cardiac arrhythmias. miRNAs are involved in cardiovascular pathophysiology and their expression is altered in various cardiovascular diseases, not only cardiac arrhythmias. Many factors such as active potential abnormalities, structural remodelling, ion channel abnormalities, inflammation and apoptosis, and promotion of fibrosis are related to genes that are under the control of miRNAs [35].

MiRNAs also seem to be a new generation of potential biomarkers. The list of miRNAs identified in human blood is increasing constantly. There are some specific miRNAs identified for use in specific diseases, which require validation in larger studies. They also may contribute additional value to biomarkers that we have available currently, or even serve as independent prognostic factors and disease monitoring tools [36].

Currently, there are no suitable biomarkers for the primary diagnosis of AF, such as the circulating natriuretic peptides for heart failure or troponins for myocardial infarction. However, the properties of the circulating MiRNAs make them an attractive biomarker for the early diagnosis of numerous diseases, including AF [37].

MiRNA studies represent an attractive and promising field of investigation. Identifying and understanding the role of miRNAs is a major step in the development of new therapeutic and diagnostic tools. The miRNAs are key molecules in arrhythmia, so their intervention and regulation have become a new target for the treatment of diseases [38]. The encouraging results of miRNA applications in experimental settings and reports of negligible toxicity to healthy tissues suggest that these molecules have the considerable therapeutic potential [39].

AF is the most common cardiac arrhythmia in adults worldwide. AF is associated with high morbidity and mortality, which puts a significant burden on patients, public health, and the healthcare system [40]. As a result, there is an urging need to search for a reliable marker for AF prediction and miRNAs seem to be a group of substances with the potential for this role.

Conflict of interest

The authors declare no conflict of interest.

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Streszczenie

Etiologia zaburzeń rytmu serca, a zwłaszcza migotania przedsionków (AF), jest złożona i wymaga dalszych badań. Podłoża do rozwoju arytmii dopatruje się między innymi w czynnikach genetycznych, a coraz większą uwagę zwraca się na rolę, jaką może odgrywać mikroRNA (miRNA). MikroRNA to małe, niekodujące cząsteczki RNA o właściwościach hamujących informacyjny RNA i regulujących większość procesów biologicznych w komórkach. MikroRNA odgrywają istotną rolę w rozwoju układu sercowo-naczyniowego, gdzie funkcja regulatorowa miRNA jest konieczna dla prawidłowej organogenezy układu sercowo-naczyniowego. MikroRNA odpowiada także za kontrolę ekspresji genów zaangażowanych w rytm i funkcję serca, w tym regulację proliferacji komórek serca, ekspresję kanałów jonowych i ich funkcję, a także regulację procesów zapalnych, apoptozy i włóknienia. Udowodniono, że różnice w poziomach miRNA krążących we krwi ściśle korelują z różnymi zaburzeniami rytmu serca. Ustalono liczne korelacje między zmianą ekspresji miRNA a zwiększonym ryzykiem wystąpienia określonej arytmii. Najwięcej takich zależności odkryto dla AF. Dostępne dane opisujące zmiany w przedsionkach serca predysponujące do AF i nasilające się w przebiegu długotrwałego AF wskazują na potrzebę poszukiwania biomarkerów będących wypadkową poszczególnych mechanizmów. Identyfikacja roli miRNA w patogenezie zaburzeń rytmu serca to ważny krok w rozwoju nowych narzędzi diagnostycznych i terapeutycznych.

Słowa kluczowe: mikroRNA, arytmia, migotanie przedsionków

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