Research focused on microRNAs: a link between myocardial remodeling and growth during pathological processes and physical exercises

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Chronic heart failure has been classified as a global epidemic of the 21st century according to the recent report of American Heart Association Statistics Committee and Stroke Statistics Subcommittee (1). This diagnose is on the rise despite the recent advances in cardiovascular experimental and clinical sciences. More than 2% of the European population suffers from it and 30–40% of patients die within 1 year after receiving the diagnosis. Even with the very best of modern therapy, heart failure is still associated with an annual mortality rate of 10%, and it consumes 2% of the National Health Service budget in United Kingdom (2).

Chronic heart failure is a complex clinical syndrome characterized by inability of the heart to pump enough blood to meet the metabolic demand of organs and tissues. This abnormal state may be a result of a number of cardiac pathologies or injuries. But it is also complex of genetic, neurohumoral, inflammatory a metabolic changes that modify function of cardiomyocytes, and cardiac non-myocyte cells such as fibroblasts, mast cells, endothelial cells, macrophages, etc. There are many reasons and ways how a human heart can fail (3,4).

Our knowledge of the mechanisms that regulate gene expression has increased considerably in recent years. Gene expression requires specific transcription factors—proteins that activate or inhibit transcription from genomic DNA to messenger RNA (mRNA) by binding to promoter or enhancer regions of genes. MicroRNAs have emerged as one of the central players of gene expression regulation. The implications of miRNAs in the pathological processes of cardiovascular system have recently been recognized, representing the most rapidly evolving research field. Then, joint microRNAs gene expression regulation together with not long ago published results of the ENCODE project (Encyclopedia of DNA Elements) can dramatically improve understanding of the genetic programs governing myocyte etiology and should inform the development of regenerative treatments (5-7). MicroRNAs are 18–25-nucleotide noncoding RNAs that are known to regulate gene expression by binding to mRNAs, causing the mRNA degradation or translational inhibition of targeted transcripts. A growing body of evidence suggests that genome-encoded regulatory RNA molecules such as miRNAs regulate many processes seen in heart failure development like cell proliferation, cell death, changes in metabolism, structure, function and also neuronal activation (8,9).

The exact biological functions of microRNAs in association with heart diseases are still not fully understood. Also it should be noted that a lot of controversies exist among different scientific studies focused on this topic. For example Cheng *et al.* (10) showed that knockdown of

microRNA-21 relieves cardiomyocyte hypertrophy, whereas the study from Tatsuguchi *et al*. (11) group demonstrated the opposite. The study by Carè *et al*. (12) clearly indicates that microRNA-133 is an antihypertrophic factor and downregulation of microRNA-133 alone is sufficient to induce cardiac hypertrophy. However, the study reported by van Rooij *et al*. (13) suggests that microRNA-133 does not cause any morphological changes of cardiomyocytes indicative of hypertrophic growth. Moreover, among the seven studies focused on the role of microRNA-133, two reported downregulation of miR-133 in hypertrophy (12,13), three failed to observe this change (10,14,15), one found it upregulated (16). Collectively, with respect to hypertrophy, it is evident that in addition to the muscle-specific, microRNAs miR-1, miR-133, and miR-208, other microRNAs, including miR-195, miR-21, miR-18b, etc., also play an important role. It appears that multiple microRNAs are involved in cardiac hypertrophy and each of them can independently determine pathological processes inside the heart. Regarding the course of these specific microRNAs and their mRNA targets expression, they could potentially become promising therapeutic targets and/or therapeutic means. Their active or passive release into the bloodstream and subsequently into the urine could also be possibly used for detection of heart damage, which would make microRNA serum and urine levels important diagnostic markers (17-19).

Recent years, many studies have proven a key role of microRNAs in the regulation of physiological adaptation to the exercise, such as skeletal muscle and cardiomyocyte hypertrophy, mitochondrial biogenesis, vascular angiogenesis and metabolic processes. Numerous tissue-specific miRNAs are released into circulation during and after the exercise and reflect the acute response to physiological stimulus, which is summarized in a recent article published by Polakovičová *et al*. (20). Exercise training has been recommended as an adjuvant intervention for the prevention and treatment of cardiovascular diseases. Exercise training can lead to physiological cardiac growth including an increase in cardiomyocyte size and markers of proliferation. Exercise-induced physiological cardiac growth is different from pathological hypertrophy. Understanding how exercise induces cardiac growth may help to identify novel therapeutic targets to mitigate the adverse cardiac remodeling in response to pathological stress. Some newly described microRNA molecules as miR-17-3p might serve as a novel therapeutic target for enhancing cardiac survival and regeneration in association with physical exercise (21).

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Footnote

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