

MicroRNAs and Cardiovascular Disease: Small Signals and Big Opportunities!

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Ind J Car Dis Wom 2020;5:15–17

We sometimes underestimate the influence of little things!
— Charles W. Chesnutt

Only ~2% of the human genome actually codes for genes involved in protein synthesis.¹ A large portion of the genome has repetitive deoxyribonucleic acid (DNA) sequences whose function is not completely understood. There is a notable portion of ~5% of the genome that codes for microribonucleic acids (microRNAs or miRNAs). These are short noncoding RNA segments that suppress gene expression by posttranscriptional modification of messenger RNA (mRNA) causing mRNA cleavage or suppressing its translation, which is a key step in protein synthesis. miRNA biology and their role in cardiovascular disease have been reviewed previously in detail.² Primary miRNAs are long segments of nucleotides transcribed from non-protein-coding segments of the DNA, and these serve as the precursors for preliminary miRNAs. At this point the preliminary miRNAs are transported from the nucleus to the cytoplasm where they undergo further processing into the immature miRNA. The immature miRNA is a double-stranded RNA, which loses a strand to leave a guide strand, or single-stranded miRNA, which then interacts with and regulates the function of mRNA in the RNA-induced silencing complex (RISC). An important aspect of miRNA biology is that these nucleotide segments can be transported outside the cytoplasm of the cells they were originally transcribed in, and modulate multiple genes in different tissues while having variable degrees of suppression across these tissue types.^{2–5}

An accumulating body of evidence has revealed characteristic expression patterns of specific miRNAs in a multitude of cell types in cardiovascular system, such as endothelial

cells, inflammatory cells, and myocytes.² This has spawned research into potential diagnostic, prognostic, and therapeutic applications of miRNA and inhibitors of miRNAs (anti miRNAs or antagomirs) in a variety of disease states like heart failure, cardiomyopathy, myocardial regeneration, lipid metabolism, and atherosclerosis.⁵ Despite these advances, this remains a nascent field, and several challenges remain in the application of miRNAs in clinical practice. First, the miRNA regulatory system is quite complex as a single miRNA can suppress multiple genes (often to a varying degree) and one mRNA can have binding sites for multiple miRNAs. Thus, identifying a target miRNA that impacts a specific pathologic step remains challenging. Second, while quantification of miRNAs using the real-time quantitative polymerase chain reaction is reliable, this is labor intensive and not widely available in clinical settings unlike other cardiac biomarkers such as troponin, which have point of care assays. Third, comparing miRNA expression profiles of different subjects or different samples of the same subject can be difficult due to lack of published normal standards. Finally, the majority of miRNAs that have been studied in cardiovascular disease (CVD) are widely expressed and targeting them can entail significant off target adverse effects.^{5,6}

In this issue of IJCDW, Lakkireddy et al studied expression profiles of miRNA-133, miRNA-155, and miRNA-222 in 50 South Asian women (25 cases and 25 controls). The authors found that miRNA-133 and miRNA-222 were elevated in those with CVD. While miRNA-133 was more elevated in those younger than 45 years and with elevated troponin, increased expression of miRNA-222 was noted predominantly in those with troponin <250 ng/L. Despite several limitations of this study, the authors are to be congratulated for their efforts in addressing this glaring gap in knowledge

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DOI <https://doi.org/10.1055/s-0040-1709253>.

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Related Sciences

Published online
April 1, 2020

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particularly from a South Asian perspective. CVD is the leading cause of mortality in India and accounts for 25% of all deaths.⁷ Several studies have demonstrated that South Asians (both living in South Asia and South Asian immigrants to other countries) are at increased risk for CVD that is not completely accounted for by traditional risk factors. Despite this, South Asians remain an underrepresented population in cardiovascular research.⁸ It is well known that miRNA expression profiles are influenced by gender and race in addition to underlying disease processes. Estrogen-mediated regulation of miRNA expression is hypothesized as one of the factors in gender-based differences in the incidence and outcomes of CVD in women compared with men.^{8,9}

Gender-specific variability in miRNA expression is important as it may explain higher incidence of cardiovascular diseases in men compared with age-matched premenopausal women.^{10,11} Estrogen has been described as a protective factor in myocardial ischemia, and has also been shown to regulate miRNA expression. It has been hypothesized that estrogen-regulated miRNAs act to protect against cardiovascular disease while those transcribed from X-chromosomes may have a negative effect on vasculature and myocardium. The change in balance at menopause from higher estrogen regulated miRNAs to X-chromosome linked miRNAs may be the reason behind increased cardiovascular disease risk in postmenopausal females. An example of estrogen-linked miRNA mediated cardioprotective effects is the opposition of classic stimulation of renin-angiotensin-aldosterone system (RAAS) where premenopausal women exhibit vasodilation and increased blood flow while after menopause there is RAAS activation and higher blood pressures compared with age matched premenopausal cohort.¹²⁻¹⁵ Despite rapidly growing research into the role of miRNAs as mediators of gender- and race-related variability in cardiovascular risk and outcomes, this remains largely unstudied in South Asians in general and South Asian women in particular. Therefore, we believe this is a huge step in the right direction. Another strength of the current study is the use of real-time quantitative polymerase chain reaction which despite being labor intensive is considered the gold standard for quantitative comparison of miRNA expression.

This study has several limitations including the relatively small number of subjects studied and more importantly, lack of clinical data pertaining to the nature of CVD, baseline risk factors, therapies being used, and electrocardiographic/echocardiographic findings. The authors studied three different miRNAs that have been implicated in distinct physiologic/pathologic processes in the cardiovascular system. miRNA-133 is one of the more extensively studied miRNAs and is known to be involved in myocyte hypertrophy, cardiac remodeling, and heart failure.¹⁶ It has been shown to be elevated in acute coronary syndrome due to myocyte necrosis but at this time does not offer any diagnostic advantages over established markers like troponin or B-type natriuretic peptide assays. miRNA-155 is a regulator of proapoptotic pathways involved in angiogenesis and is known to influence

vascular consequences of diabetes such as microangiopathy. On the other hand, miRNA-222 is expressed in vascular smooth muscle cells and macrophages, and plays a key role in atherosclerosis and neointimal proliferation.² The expression profiles of miRNAs are therefore significantly influenced by the type of the underlying CVD, presence or absence of hypertension, diabetes, congestive heart failure, ongoing ischemia, and left ventricular remodeling. In the absence of such information that provides the right context, scientific relevance of miRNA expression profiles in this study is too nonspecific and rather unclear.

Despite these limitations, the study provides preliminary evidence of differences in miRNA expression in South Asian women with CVD that must be confirmed and expanded upon with future research. In addition to enhancing our understanding of the pathogenesis, miRNAs can provide us new diagnostic opportunities and treatment tools to address the growing epidemic of CVD in India where pathobiology may differ from that of the Western world.

Conflict of Interest

None declared.

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