MicroRNAs: components of an integrated system controlling cardiac development, physiology, and disease pathogenesis

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See reviews in this series by Fazi and Nervi,\textsuperscript{21} Thum \textit{et al.},\textsuperscript{22} Yang \textit{et al.},\textsuperscript{23} and Urbich \textit{et al.}\textsuperscript{24}

Protein-encoding sequences comprise \(<1.5\%\) of the human genome.\textsuperscript{1} Nevertheless, a considerable fraction (\(\sim 90\%\)) of the genome is effectively transcribed.\textsuperscript{2} Therefore, most of the transcriptional output of the genome of higher organisms seems to consist of non-coding (nc) RNAs, i.e. RNA that is not translated into a protein end product.\textsuperscript{3} It is now clear that much of this genomic output is not just transcriptional background noise of ‘junk’ DNA but an intricate RNA-based network constituting a level of regulation that appears as important as posttranscriptional protein modification. Only a limited number of ncRNA species predominately maintaining basic biochemical processes, such as ribosomal RNA and transfer RNA, have been analysed in depth, but other types of ncRNAs have now been identified and are being studied.\textsuperscript{4} These ncRNAs regulate the gene expression process at many of its steps, from the epigenetic level down to translation, through a variety of mechanisms (Figure 1).\textsuperscript{5} ncRNA has also been implicated in surprising areas, such as the integrity of cellular structure,\textsuperscript{6} and many other fascinating functions probably await discovery.

The thought that RNA might be involved in the control of gene expression first arose in the late 1960s: RNAs were hypothesized to specify which genes were turned on and off in eukaryotic cells with a mechanism based on the base-pairing rules of Watson and Crick.\textsuperscript{7} Nonetheless, this theory was buried in oblivion probably as a result of the exciting discovery of protein transcription factors. However, in the past few decades, convincing evidence has emerged that RNA is, in fact, more than simply an intermediary between DNA and protein. Several classes of ncRNA are now known that have a fundamental role in the control of gene expression: whereas long ncRNAs control dosage compensation and genomic imprinting,\textsuperscript{5} one class of small ncRNAs, micro (mi)RNAs, is predicted to regulate at least one-third of all human genes.\textsuperscript{8} These approximately 22 nucleotide ncRNAs, together with their associated proteins, act in gene silencing pathways through the regulation of mRNA stability and protein translation.

Unexpected findings had been obtained in experiments with plants during the late 1980s and early 1990s in which certain genes were to be overexpressed: occasionally, instead of the expected increased gene expression, down-regulation was observed.\textsuperscript{9–11} This finding was later confirmed in the nematode, \textit{Caenorhabditis elegans}, the species in which key breakthroughs in RNA silencing would be made: for example, that double-stranded (ds)RNA is the trigger for mRNA destruction\textsuperscript{12} and that dsRNA is converted into small RNAs, called short-interfering (si)RNA, to mediate silencing phenomena with a mechanism termed RNA interference.\textsuperscript{13}

In parallel with the discovery of how exogenously introduced RNA, i.e. siRNA, could mediate gene expression, reports were being published that would pave the way for the discovery of their endogenous counterpart, namely miRNA. Two independent studies published in 1993 reported that \textit{lin-4}, a heterochronic gene controlling the timing of development of nematodes, does not code for a protein but produces small RNA transcripts, complementary to the 3’-untranslated region of \textit{lin-14} mRNA.\textsuperscript{14,15} The subsequent inhibition of \textit{lin-14} translation provided the explanation of the mechanism of the heterochronic switch. Several years later, the connection between miRNAs and siRNAs was made when Dicer, the enzyme converting dsRNA into siRNAs, was shown to convert pre-miRNAs into mature miRNAs.\textsuperscript{16–18}

Since then, the function of miRNAs in developmental biology of higher organisms, including mammals, has been established.\textsuperscript{19} Moreover, a remarkable number of publications have linked miRNA to physiological processes and to pathologies such as cancer.\textsuperscript{20} In comparison to other fields, the elucidation of the role of miRNAs in the cardiovascular system is in its infancy, but the studies published...
to date underscore the fundamental role that miRNA has on many aspects of biology of the heart and vasculature. In this review focus of the Journal, four review articles highlight the current understanding we have gained in the role of miRNA in cardiovascular biology. First, Fazi and Nervi21 detail miRNA biogenesis and function and demonstrate the importance of miRNA in the development of muscle, nervous, and blood tissues. Then, Thum et al.22 summarize the role of miRNA in cardiac developmental biology and in a fundamental aspect underlying heart diseases, i.e. hypertrophic growth. Yang et al.23 focus on the role of miRNAs in electrophysiology, another important area of heart biology. Finally, Urbich et al.24 report on aspects of vascular biology, which so far have not been specifically translated to the heart but that are nonetheless essential in the development and treatment of ischaemic diseases.

It is now obvious that the complexity of an organism is not limited to the number of different protein-coding genes and the interaction of their products but, rather, to the exquisite intricacies of the entire interactome, which includes ncRNAs as an integral and probably prevailing part.25 In this complex regulatory network, microRNAs are just one of the players. The few recent studies reviewed in this review focus just start to scrape the surface of this control system in the heart. Much more work lies ahead not only to understand the role of miRNAs and the regulation of their expression and maturation but also to discover the function of other ncRNAs in the heart. The identification of these components and the elucidation of mechanisms of these complex interactions require the development of powerful high-throughput technology and computation algorithms capable of integrating data from all parts of this machinery. Future studies will increase our awareness of the complexity of gene expression control and of the role played by miRNA in particular.

References