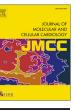
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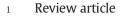
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Bioinformatics of cardiovascular miRNA biology **O4 O6**

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ABSTRACT

MicroRNAs (miRNAs) are small ~22 nucleotide non-coding RNAs and are highly conserved among species. More- 26 over, miRNAs regulate gene expression of a large number of genes associated with important biological functions 27 and signaling pathways. Recently, several miRNAs have been found to be associated with cardiovascular diseases. 28 Thus, investigating the complex regulatory effect of miRNAs may lead to a better understanding of their function-29 al role in the heart. To achieve this, bioinformatics approaches have to be coupled with validation and screening 30 experiments to understand the complex interactions of miRNAs with the genome. This will boost the subsequent 31 development of diagnostic markers and our understanding of the physiological and therapeutic role of miRNAs in 32 cardiac remodeling. In this review, we focus on and explain different bioinformatics strategies and algorithms for 33 the identification and analysis of miRNAs and their regulatory elements to better understand cardiac miRNA 34 biology. Starting with the biogenesis of miRNAs, we present approaches such as LocARNA and miRBase for com- 35 bining sequence and structure analysis including phylogenetic comparisons as well as detailed analysis of RNA 36 folding patterns, functional target prediction, signaling pathway as well as functional analysis. We also show 37 how far bioinformatics helps to tackle the unprecedented level of complexity and systemic effects by miRNA, 38 underlining the strong therapeutic potential of miRNA and miRNA target structures in cardiovascular disease. 39 In addition, we discuss drawbacks and limitations of bioinformatics algorithms and the necessity of experimental 40 approaches for miRNA target identification. This article is part of a Special Issue entitled 'Non-coding RNAs'. 41

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61 62 1. Introduction

MicroRNAs (miRNAs) are highly conserved among different species. They are small ~22 nucleotide non-coding RNAs [9,18,30,46,79,81].

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They have been found to regulate gene expression of a large number 65 of human genes by binding to the 3'-untranslated region (3'-UTR) of 66 messenger RNAs (mRNAs) and also influence protein synthesis 67 through interacting with the protein translation machinery. MiRNAs 68

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are associated with many biological processes and diseases, including 69 70 aging, cardiac function, metabolism and cancer [8,9,15,18,31,46,65,79]. Moreover, a single miRNA can target different mRNAs and a single 7172mRNA can also be regulated by different miRNAs [14,31,57,65], pointing to a complex regulatory network. MiRNAs influence different signaling 73 pathways and are useful as diagnostic markers as well as potential new 74 therapeutic targets for cardiovascular diseases [15]. Cardiovascular dis-7576eases combine together to be the leading cause of death [15]. Several 77 miRNAs have been known to be involved in cardiovascular diseases 78and also play a potential therapeutic role in cardiac remodeling (139 79 cardiac-related miRNAs and their role in cardiovascular diseases extensively reviewed in [22,52]). Specific miRNAs are not only deregulated in 80 various cardiovascular cell types of diseased hearts [77], but also direct-81 82 ly involved in pathologic reactions of the heart. For example, miRNA-1 is associated with myocardial infarction and miRNA-21 and miRNA-212/ 83 132 with cardiac fibrosis and hypertrophy respectively (extensively 84 85 reviewed in [15,24,78,80]). Importantly, some miRNAs are transcribed as part of a cistron and regulated by cardiac transcription factors 86 (TFs), e.g. miR-1/miR-133 by myogenic transcription factor (MyoD) 87 and serum response factor (SRF) or miR-143/145 by cardiac NK-2 88 transcription factor (Nkx2-5) and SRF [65,76]. On the other hand, 89 miRNAs can directly regulate cardiac associated TF and signaling 90 pathways, e.g. miR-212/132, the anti-hypertrophic TF forkhead box O3 08 92 and the CN–NFAT signaling pathway [80]. To understand the complex effects of cardiovascular miRNAs their genomic localization including 93 promoter analysis as well as interaction partners all have to be taken 94into account. It is thus of high interest to understand the complex role 9596 and function of cardiovascular miRNAs for a better understanding of 97 their regulatory effects as a basis for future therapeutic approaches. For this purpose, different bioinformatics methods and search programs 98 are useful. Owing to their small length as well as their specific cardio-99 100 vascular expression profiles (cell type and development dependent), experimental methods alone cannot fulfill the detection and analysis 101 102of these miRNAs, e.g. regarding cardiac miRNAs with low expression levels or detecting sequence-structure-conservation [3,31,49,63]. For 103this, the combined use of experimental and computational approaches 104 105 has revolutionized the identification and analysis of miRNAs, and in 106 particular, their selective function in the heart.

107 2. Biogenesis, structure and miRNA biology

108 MiRNAs are located either in intronic regions of coding-genes, in non-coding genes or in intragenic regions of the genome. They are 109 transcribed by RNA-Polymerase II (RNA-Pol II) as a primary-miRNA 110 transcript (pri-miRNA) [31,50,53,55,65]. The pre-miRNA contains a 111 characteristic hairpin structure, which is recognized by the RNase III 112 113 enzyme Drosha. By binding of the RNase III enzyme Drosha and its cofactor DiGeorge Syndrome Critical Region 8 (DGCR8), a dsRNA 114 binding protein, the ~70 nucleotide long hairpin precursor-miRNA 115(pre-miRNA) is processed and further transported into the cytoplasm 116 by the nucleocytoplasmic shuttle protein Exportin 5 [15,31,65]. In the 09 118 cytoplasm, another RNase III enzyme, Dicer, cleaves and unwinds the 119pre-miRNA to form the ~22 bp double stranded miRNA [31,65]. Finally, this miRNA duplex forms a single-stranded guiding RNA (mature 120miRNA), which associates with the RNA-induced silencing complex 121(RISC) to regulate its mRNA targets, whereas the second single-122123stranded passenger RNA strand is mostly degraded [15,31,32,56,65]. In general, miRNAs regulate the gene expression by binding to the 3'-UTR 124of mRNAs, whereas few studies also reported that they also bind to 125the coding region or 5'-UTR [31,54,65]. As a result of a complete or 126incomplete complementary binding, a single miRNA can target multiple 127mRNAs and a single mRNA may be regulated by multiple miRNAs 128[14,57,65,31]. This clarifies their complex regulatory effect and high 129targeting potential (about 30% to 60%) of mammalian genes [30,65], at 130the same time pointing out their potentially important therapeutic 131 132 role. However, the experimental identification of miRNA targets is very complex and elaborate, indicating the necessity of computational 133 prediction tools. As a result, several computational tools were devel- 134 oped, mainly using miRNA length, sequence and structural information 135 (e.g. hairpin structure and minimal folding free energy; [31,58]), which 136 are very efficient in the identification and analysis of miRNAs. Algo- 137 rithms such as RNAfold and Mfold quickly and accurately predict the 138 putative secondary structure of an miRNA based on the principle of 139 minimum free energy and are used in different computational tools 140 [31,37,90]. MiRNA detection tools can be divided into comparative 141 and non-comparative methods [10,31,36]. Comparative algorithms 142 use the sequence conservation for the miRNA prediction and help to 143 identify miRNAs among species, whereas non-comparative algorithms 144 only use the intrinsic miRNA structure without any sequence conserva- 145 tion and are therefore able to identify evolutionarily distant species or 146 species-specific miRNAs (reviewed in [31]) (Fig. 1). **Q10**

3. Novel miRNA discovery through NGS platforms and experimental 148 identification of miRNA targets 149

3.1. Novel miRNA discovery

Microarrays have been widely and extensively used as an efficient 151 method for miRNA expression profiling on a genome-wide level. How-152 ever, the discovery of novel miRNAs is still an inherent weakness of this 153 hybridization-based technology. The short length of miRNA and the high similarity between miRNA family members make specific probe155 design for microarrays challenging.156

The development of next-generation sequencing technologies and 157 the drop of costs in recent years open an efficient route for the rapid dis- 158 covery of novel or low-expressed miRNAs. The miRDeep algorithm [29] 159 was first introduced in 2008 and is currently widely used to detect and 160 quantify miRNA from small RNA sequencing. This tool has been further 161 developed as an integrated program named miRDeep^{*} [4] which is free-162 ly available with a user-friendly interface. Sequence reads archived in 163 FastQ and alignment profiles in BAM/SAM format can be used directly 164 for further analysis such as miRNA detection and expression profiling. 165 A java-based sRNA analysis tool is the UEA sRNA workbench [74]. It 166 provides biologists with an easy solution, with a nice graphical user in- 167 terface, for handling their RNA-seq data, starting from quality filters for 168 the reads to target predictions. A major advantage of high throughput 169 RNA sequencing in cardiovascular disease is the unambiguous and 170 sensitive detection ability for novel miRNAs. On the other hand, deep 171 sequencing is a comparatively new approach and no standard data 172 analysis strategy has been suggested. Furthermore, substantial computa- 173 tional support is necessary for a more precise prediction and expression 174 quantification. 175

3.2. Experimental miRNA target identification

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The experimental identification of miRNA targets can be done by ex- 177 pression profiling (e.g. microarray analysis after miRNA overexpression 178 or knockdown, proteomics) or biochemical isolation of the miRISC 179 complex using immunoprecipitation (different experimental methods 180 extensively reviewed in [75,87]). Generally, miRNAs regulating the 181 mRNA level and miRNA and mRNA expression are often negatively cor- 182 related [28,31,33]. Therefore, miRNA profiling microarray experiments 183 to identify deregulated mRNAs after ectopic miRNA expression or 184 antagonism are useful for experimental identification of putative 185 miRNA targets and can be further combined with bioinformatics [75]. 186 However, results from Matkovich et al. show for cardiovascular research 187 that compared to mRNAs, cardiac miRNAs are more sensitive to the 188 acute functional status of end-stage heart failure [61], exemplifying 189 that changes in mRNA level are not always a reliable method for 190 miRNA target prediction [87]. Therefore, different additional techniques 191 for miRNA target identification in cardiac tissues are available, such as 192 RISC-IP and proteomics. The RISC-IP is a new biochemical method for 193 Download English Version:

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