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EDITORIAL

From data gathering to systems medicine

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While molecular interactions have been a research focus for many years, the advent of updated molecular profiling methods has shifted the attention towards a more integrative approach. The '-omics' technologies—genomics, transcriptomics, proteomics, and metabolomics—allow us to gather a vast amount of information at the level of the genome, transcriptome, proteome, and metabolome. However, these updated technologies have also brought about the challenge to understand the complex interplay of molecular changes related to cardiovascular disease. This will be the formidable task of systems biology.[1,2] In this thematic Mini-Spotlight issue, four reviews summarize strategies how to advance this field.

Classic genomics aims to link variations in the DNA sequence directly to distinct phenotypes. As pointed out by Ware *et al.*,[3] the subsequent identification of the causative gene remains a substantial challenge. Currently, a wealth of susceptibility loci have been identified, i.e. the latest association analysis took the number of susceptibility loci for coronary artery disease to 46.[4] With the exception of loci related to lipid metabolism, for which an involvement of hepatocytes is a reasonable assumption,[5] it is largely unclear what cell types are affected. Moreover, most mutations for complex, non-Mendelian diseases such as cardiovascular disease are in regions within the genome that do NOT encode for proteins, and the complexity of the non-coding genome has only recently attracted attention. Besides epigenetic mechanisms, such as DNA methylation and histone modifications, non-coding RNAs such as microRNAs regulate the expression of protein-encoding genes. Integrative genomics may offer a way forward by using additional layers of information to inform the search space,[6] and there are currently many efforts on combining information from epigenetic modifications and microRNA expression with transcriptomic and genomic data.

Langley *et al.*[7] explores the current challenges of proteomic technologies and analysis of proteomics data followed by a discussion about the potential of combining proteomics and metabolomics in studies on cardiovascular disease.[8] Protein and metabolite levels can complement the genetic information by shifting the focus from the specific gene to the actual effects of the gene itself.[9] Protein function is regulated by post-translational modifications as well as proteolysis, none of which is captured by transcriptomic technologies. To fulfil the promises of a systems biology approach, it will be key to assess protein function and its effect on metabolite levels to complement the quantification of transcript levels that do not necessarily correspond to protein abundance.[9]

While '-omics' technologies are widely utilized for data gathering, interpreting this overwhelming amount of data represents a major hurdle. Two reviews are dedicated to this topic: Quinn *et al.*[10] describes how combining the wet laboratory and the dry laboratory may alleviate the current bottleneck with single cell, tissue, and whole-heart studies of cardiac electrical and mechanical function and stresses that any computational model will depend on the input of high-quality data. Azuaje *et al.*[11] explores the use of computational methods to predict drug interactions. Just like pathogenetic mechanisms, drug effects are also looked at in a reductionist fashion, which relies on the notion of identifying single drug–single target interactions. Compared with the traditional reductionist approach that attempts to explain cardiovascular disease processes by studying individual pathways, systems biology is underpinned by the view that pathological processes are likely to arise as the result of dysregulation of multiple interconnected pathways. Properties of biological networks—such as modularity and dynamics—are important in understanding how cells function and how they change in disease. Conventional inference statistics attaches utmost importance to molecular entities with the 'biggest' fold changes and the 'lowest' *P*-values, while disregarding the concept of adaptive changes in flux or turn-over and the added value of integrating equivalently expressed focus objects in network analysis of differential expression experiments[12] (*Figure 1*).

Two original papers complement the reviews: one identified 700 genes in rats that played a role in hypertension, with conserved parallels in humans.[13] The other investigates lipidomic and metabolic profiles in a pre-clinical model of atherosclerosis.[14] Undoubtedly, the integration of genetic information and metabolite data will be a promising area of future research.

In combination, '-omics' technologies and bioinformatics/computational modelling[15] may allow us to address the complexity of cardiovascular diseases by integrating biological information in disease-specific networks that drive pathophysiological changes. As Sydney Brenner has provocatively pointed out there is the risk that high-throughput technologies generate factory science and 'low input, high-throughput, zero output biology'.[16] Undoubtedly, it is a long way from data gathering to actionable knowledge about the com-

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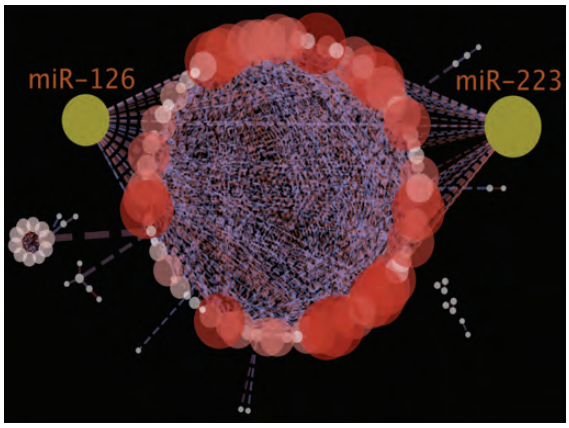

Figure 1 MicroRNA biomarker network. MicroRNAs can be studied in a context of relevance network as well as individual over- or under-expression. In a network, individual microRNAs are represented as nodes, while relationships between them can be shown as edges. MicroRNAs can therefore be analysed by the virtue of their topology. For example, support to the putative value of circulating microRNA biomarkers, i.e. miR-126 and miR-223, can be provided by the inference of microRNA relevance networks in cardiovascular disease.

plexity of human diseases and a translation of the information into benefits for cardiovascular patients, such as new biomarkers, mechanistic insights, or novel therapies. Nonetheless, the advent of new technologies offers unprecedented opportunities and to quote Winston Churchill: 'A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty.'

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