CARDIOVASCULAR DISEASE

# The regulatory network architecture of cardiometabolic diseases

Complex disease definitions often represent descriptive umbrella terms of symptoms rather than mechanistic entities. A new study shows how network-based approaches can help identify the mechanisms that link genes, cells, tissues and organs in cardiovascular diseases.

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Cardiovascular diseases are one of the leading causes of morbidity and mortality worldwide. Our limited understanding of these diseases is not least shown by their rather descriptive definition as an umbrella term that lacks mechanistic insight. Consequently, pharmacotherapeutic interventions cannot target causal mechanisms, but rather modulate symptoms and risk factors leading to a high number needed to treat[1]. Our efforts to elucidate causal mechanisms, including large-scale sequencing studies, have resulted in thousands of genes being associated with cardiovascular and cardiometabolic diseases with varying degrees of evidence. Irrespective of the reliability of individual findings, it has become clear that the traditional reductionist paradigm, that is, one disease–one target–one drug, or, if need be, a combination thereof, is insufficient to provide mechanistic explanations and enable actionable subtyping or endotyping of diseases for precision medicine[2]. The low heritability ($h^2$) attributable to individual genes suggests that mechanisms of complex diseases instead involve larger groups or networks of genes (or proteins when defining drug targets). A study by Koplev et al.[3] now embarks on a holistic approach guided by this hypothesis. Instead of focusing on individual genes, they consider gene network modules to identify causal molecular mechanisms or endotypes that drive the often multiorgan nature of cardiovascular and cardiometabolic disease phenotypes (Fig. 1).

The work is based on the Stockholm-Tartu Atherosclerosis Reverse Networks Engineering Task (STARNET) study[4], a large resource of transcriptomic data for cardiovascular diseases available to date, containing samples of various tissues and organs from more than 500 patients. This dataset allowed the authors to identify more than 200 gene modules with highly coordinated expression patterns. Machine-learning techniques were then used to extract potential regulatory interactions and key drivers. Taken together, the regulatory interactions comprise more than 40,000 independent expression-regulatory single-nucleotide polymorphisms (eSNPs), the collective contribution of which to heritability of coronary artery diseases was found to be up to 60%.

While the importance of regulatory networks for understanding the heritability and causality of complex diseases and traits is increasingly recognized[5,6], many details of their functional roles remain elusive. For example, Koplev et al.[3] observed more noncoding than coding genes to be differentially expressed. With few exceptions, such as long noncoding RNAs, the involvement of noncoding genes in gene regulation is still largely unclear. A critical next step toward a deeper understanding of these processes, and ultimately toward translation into clinical diagnosis and pharmacotherapy, is to identify the molecular basis of observed statistical associations. Functional modules, as presented by Koplev et al., do not necessarily represent direct physical relationships, such as a transcription factor binding to a

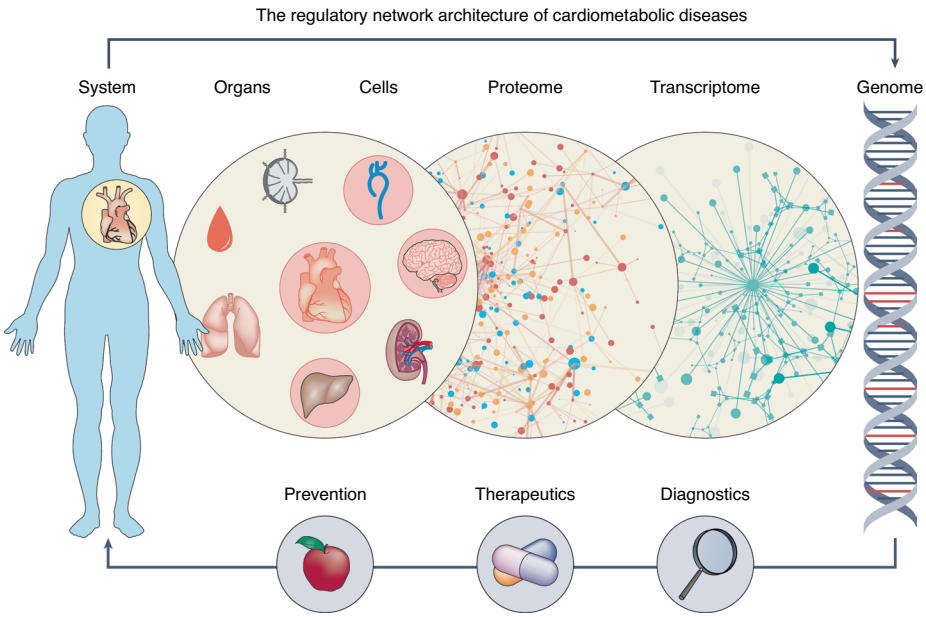


**Fig. 1 | A mechanistic understanding of complex diseases requires a detailed mapping of the underlying perturbations across biological networks.** This includes identification of the underlying mechanisms across organs, cells, proteins and, ultimately, the genome. A translation of this molecular understanding into medical applications will enable the design of therapeutic interventions and precise diagnostics on top of lifestyle recommendations. Credit: FrankRamspott / DigitalVision Vectors / Getty (proteome graphic); sumkinn / iStock / Getty Images Plus/Getty (transcriptome graphic)

promoter region of a target gene, but often also contain indirect associations. The study of strictly physical gene regulatory networks has a long history in model organisms and developmental processes[7]. More recently, single-cell sequencing technology has enabled large-scale mapping efforts of transcriptomes across a wide range of cell and tissue types under various conditions[8]. A combination of these datasets and the rigorous mathematical frameworks developed in model systems could help reveal the fundamental principles governing the relationship between genome sequence, the structure of gene regulatory networks, and their dynamic output. Such a principled understanding will help uncover the molecular mechanisms by which disease-associated genetic variations perturb regulatory homeostasis.

Furthermore, gene regulatory networks are embedded into a larger hierarchy of biological organization between genotype and phenotype, including translational efficacy and protein modifications, all contributing to the final functional state of a regulatory module. Networks can serve as a unifying framework for describing and characterizing the diverse types of relevant interactions within and between these different levels of organization[9]. Protein–protein interaction networks have proven to be particularly useful for investigating human diseases[10], also because most drug targets are still proteins. In the context of cardiovascular diseases, protein interaction modules for stroke[11] and hypertension[12] were identified and are in clinical validation.

Moving beyond genes and proteins, relevant interactions also extend to cells, tissues, organs and ultimately the whole body (Fig. 1). Most somatic modules will therefore cause symptoms in more than one organ, explaining the frequent co-occurrence of many non-cardiovascular phenotypes and comorbidities. Formally, different interaction types can be incorporated using so-called multiplex network approaches. In the context of rare diseases, multiplex networks have recently been used to pinpoint the cell types or tissues most strongly affected by specific genetic mutations[13]. Such approaches may eventually lead to a mechanistic redefinition of most, if not all, complex diseases, yet with network modules rather than single genes as causal base units.

It is worth keeping in mind, however, that ultimately we treat humans, not organs or tissues. To understand diseases at the systemic level, we must therefore consider also the coordination and communication between cell types, tissues and organs[14], as well as comorbidities[15]. Koplev et al. show how the connectivity between gene regulatory modules that are specific for a particular tissue and modules that occur across different tissues reveals communication patterns between organs. In addition, tissues and comorbidities that would not be considered cardiovascular prima vista may also contain common mechanistic traits. Signaling from fat to liver was found to be driven by endocrine factors. These results were validated in mice by injecting four adipose endocrine factors that indeed altered blood lipids and glucose, two cornerstones of cardiometabolic disease.

Although the road from here to diagnosis or intervention is still long, the study by Koplev at al. represents an important contribution to innovative cardiovascular research. It shows that network-based analyses can identify therapeutic targets to drive disease-relevant molecular and physiological parameters toward a healthier state. The quantification of transcriptional changes across multiple tissues opens up new avenues for understanding the full complexity of these disorders beyond cardiovascular and metabolic limits, and for replacing the current, largely descriptive disease ontologies with mechanistic ones.

In summary, network medicine, applied to intensely genotyped cardiovascular and cardiometabolic disease phenotypes, represents an ideal case, next to the progress in cancer, to accelerate the development of early and individualized diagnostics and therapeutics in the coming era of precision medicine. ❐

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## Competing interests

The authors declare no competing interests.