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Deciphering the Molecular Basis of Human Cardiovascular Disease through Network Biology

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Abstract

Purpose of review—This review introduces the fundamental concepts of network medicine and explores the feasibility and potential impact of network-based methods on predicting and ameliorating individual manifestations of human cardiovascular disease.

Recent findings—Complex cardiovascular diseases rarely result from an abnormality in a single molecular effector, but, rather, nearly always are the net result of multiple pathobiological pathways that interact through an interconnected network. In the post-genomic era, a framework has emerged of the potential complexity of the interacting pathways that govern molecular actions in the human cell. As a result, network approaches have been developed to understand more comprehensively those interconnections that influence human disease. “Network medicine” has already led to tangible discoveries of novel disease genes and pathways as well as improved mechanisms for rational drug development.

Summary—As methodologies evolve, network medicine may better capture the complexity of human pathogenesis and, thus, re-define personalized disease classification and therapies.

Keywords

network medicine; systems biology; cardiovascular disease

Introduction

The modern translation of scientific knowledge from initial discovery to effective therapeutic delivery in human disease is primarily driven by an Oslerian system of disease definition [1]. This “Oslerian principle” essentially defines a disease presentation by alterations in tissue pathology (clinicopathological correlation) and, now in the modern era, by molecular or genetic markers that correlate with or drive such pathology. Inherent to this principle are the concepts that certain key factors operate in simple regulatory molecular circuits to control disease pathology, and, that their therapeutic manipulation can ameliorate disease progression.

While Oslerian theory has been instrumental in initiating our appreciation of the molecular basis of disease, it oversimplifies the underlying basis of specific pathologies and, thus, ironically imposes limitations on a full understanding of complex human disease. It is becoming increasingly clear that although a single event or genotype *(e.g.*, gene mutation) can affect pathogenesis, individualized manifestations of disease rarely result from an

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abnormality in a single effector; rather, they are almost always the net result of multiple pathobiological pathways that interact through a complex network. Until recently, the richness of these interactions was theorized but not easily identified.

In the post-genomic era, we now have a framework of the potential complexity of the interacting network of molecules in the human cell. The current human "interactome" consists of ~ 25,000 protein-coding genes, ~1,000 metabolites, and a growing number of post-translationally modified proteins and functional RNA molecules, together exceeding 100,000 participants [2**]. The functional interactions among the components of these networks are exponentially greater in number. Driven by a growing appreciation of these complex relationships, it is widely suspected that these interdependencies drive human pathogenesis by working in concert and are hardly ever superceded by a single effector or simple regulatory circuit. Recently, application of the scientific study of network theory has greatly aided our understanding of how such cellular interconnectedness can be understood and potentially manipulated in order to control disease phenotype. These principles of disease network behavior and the methodologies for such study are increasingly referred to as "network medicine" [2**]; the application of network medicine to cardiovascular diseases is just emerging. In this review, we will describe the overarching principles of biological network theory, their application to cardiovascular medicine, and the implications for improving the discovery of novel disease genes and pathways, tailored drug therapy, and overall disease classification.

Construction of the Human Interactome

Network theory offers a functional framework for gaining insight from the vast set of cellular interconnections derived from contemporary profiling arrays of human tissue in health and disease. A network can be organized and visualized by mapping representative nodes arranged in topological order (Fig. 1). In biological terms, a "node" may be a biological factor (*e.g.* gene, protein, metabolite, etc.) or even a particular disease/phenotype that is connected to other factors by "links" through a variety of functionally important interactions. The construction of the human "interactome," or complete network of relevant functional interactions in human tissue, is a daunting and still incomplete process but has been aided by three primary mechanisms of data accumulation [3*]. These include network construction based on prior scientific investigation, physical interactions, and systematic experimental perturbations.

First, freely available databases catalog the known effectors of molecular pathways as curated from the scientific literature. These include compilations such as the Kyoto Encyclopedia of Genes and Genomes (KEGG) and the Biochemical Genetic and Genomics knowledgebase (BIGG), among other experimentally confirmed data sets. Predicted protein-DNA interactions have also been compiled into databases such as TRANSFAC and the B-cell interactome (BCI). Functional links of interest include protein-protein interactions; metabolic associations via kinase-substrate or enzyme-metabolite interactions; and regulatory interactions among transcription factors, downstream genes, and non-coding nucleic acid molecules. Notably, a systematic phenotyping project based on manifestations of cardiovascular disease in the rat has been initiated [3*], and specific databases for cardiovascular-specific interactions now exist [4*].

Second, as derived from a variety of high-throughput technologies, direct physical interactions among molecules have been catalogued. Mostly derived from yeast two-hybrid and more recently, three-hybrid screens, databases exist that list experimentally validated protein-protein interactions (as reviewed by [2**]). Regulatory interactions detailing the relationships among transcription factors and downstream genes have also been compiled from techniques such as chromatin immunoprecipitation followed by microarray analysis

(ChIP-ChIP) and ChIP followed by sequencing (ChIP-Seq). Relevant ChIP databases include the Universal Protein Binding Microarray Resource for Oligonucleotide Binding Evaluation (UniPROBE) and the open access database of transcription factor-binding profiles, JASPAR. Regulatory relationships that coordinate post-translational modifications (e.g., phosphorylation, acetylation, S-nitrosylation, redox modifications, etc.) or that coordinate enzyme-DNA interactions for epigenetic modifications (*e.g.*, acetylation) are described in databases such as PhosphoELM, PhosphoSite, phosphorylation site database (PHOSIDA), NetPhorest, and the CBS prediction database. Compilations of nucleic acid interactions, such as messenger RNA-microRNA (TargetScan, PicTar, miRBase, and others), RNA-RNA, and RNA-DNA, also exist.

Third, networks have begun to be identified by chemical or genetic perturbation followed by analysis of resulting cardiovascular consequences. Such an approach has successfully delineated a network of cholesterol-responsive genes mediating the development of atherosclerotic plaques in mice [5] and an endothelial inflammatory network associated with atherosclerosis [6]. Further systematic perturbations with libraries of small molecules are currently under investigation with relevance to additional pulmonary and cardiovascular illnesses. Thus, the current representation of the human interactome is quite expansive but still incomplete, and this fact should not be overlooked when studying human disease. Emerging databases specific for cardiovascular function and disease may offer a more comprehensive network view [7*]. As the coverage of human interactome maps continues to grow owing to systematic profiling efforts and two- or three-hybrid screens, we expect even greater improvements within the next few years.

Properties of the Human Interactome and Human Disease Modules

Similar to networks in natural, technological, or social systems, human disease networks display certain stereotypical properties that contrast with randomly linked networks (Fig. 1) (as reviewed by [2**,8*]). First, cellular networks show a high degree of clustering, forming pockets of topological modules that carry especially high local interconnectedness. Second, cellular networks are frequently “scale-free,” wherein the probability of gene interactions occurring by chance is very low and the degree distribution follows a power-law tail. The result is the existence of a few highly connected “hubs,” which are nodes that exhibit a high degree of interconnectivity among other nodes, and tend to be essential for maintaining the integrity of the entire network. Hub proteins tend to be encoded by conserved and evolutionarily ancient genes that function in essential cellular processes. Hubs can be further sub-classified based on their primary function -- some hubs serve to coordinate intrinsic cluster function, while others preserve the integrity of the interactome linking distinct clusters (so-called “weak links”). Third, each node in a cellular network is usually only separated from any other node by a few links (or interactions). Thus, perturbation of a single factor in a biological network has the potential to cause widespread effects that influence function of the system. Fourth, certain “motifs” in cellular networks are apparent -- groups of nodes that always link to each other, may appear more or less frequently than expected, and may be associated with some degree of regulatory optimization (i.e., positive or negative feedback loops, molecular oscillators or “switches,” etc.). Finally, cellular networks may carry “bottlenecks,” or nodes with a high between-ness centrality, a measure of the number of shortest paths traversing each node. Such bottlenecks tend to represent essential functions necessary for cell survival .

Disease-relevant genes exist within these cellular networks and also follow certain topological characteristics in the human interactome. To date, only 10% of human genes have been associated with known disease (www.omim.org). Since functional alterations (*e.g.* mutation, deletion) in hubs are commonly associated with a higher number of phenotypic abnormalities as compared with alterations in non-hub nodes [9], one may

predict that disease genes exist as hubs. Although this is true in some instances, genetic mutation of essential genes is more often correlated with embryonic lethality. In contrast, dysfunction in non-essential genes is much less commonly associated with mortality and, consequently, disease genes have been found to map more often to non-hub nodes [10]. Disease genes also tend to interact directly with other disease genes that induce a common pathophenotype (following the so-called "local hypothesis") [10], forming local clusters called "disease modules." Construction and identification of disease modules entail merging known disease genes with the human interactome, followed by the use of network-clustering algorithms to identify specific sub-networks that either carry a quorum of disease-associated factors or encompass identifiable functional pathways with one or more disease genes. Such disease modules are thought to carry significant overlap with related "topological modules" that are identified by unbiased network-clustering tools and with related "functional modules" defined as an aggregation of nodes of similar or related function [11]. Accordingly, as has been suggested in polygenic disorders, including cancer, and even the most predictable monogenic disorders, such as sickle cell anemia, a disease phenotype may arise from multiple insults on a single disease module that may carry many of the same components as related but independently mapped topological and functional modules. Thus, the relative position of a single disease gene in the topographical map of its disease module may yield a wealth of information regarding its function, connected partners, and connected modules that influence disease manifestation. Furthermore, as the strength and direction of these interactions become defined, the dynamic *flux* through these modules will be better understood and could eventually establish methodologies to specifically model how combinatorial perturbations of specific nodes drive complex pathophenotypes.

Application of Network Medicine to Human Disease and Cardiovascular Illness

Currently, chromosomal linkage mapping and genome-wide association studies (GWAS) are the most common contemporary methodologies employed for the identification of common and rare genetic variations associated with disease. Although useful, these methods can be costly and time-consuming in order to interpret correctly the data and validate those candidate genes that are most crucial to disease pathogenesis. The application of network medicine greatly complements these investigations by simultaneously analyzing related molecular alterations in the presence or absence of these genetic variations. Furthermore, its broad utility may far exceed merely identifying additional disease genes: it may offer unique insight into how such molecular networks physiologically connect cells, tissues, and organ systems and how diseases may be connected to one another.

In its simplest application, network theory can successfully predict novel disease genes based on their non-random topographical placement in the human interactome (Fig. 2A). First, the direct linkage of known disease-associated proteins with other disease genes has allowed for successful identification of novel factors that may be important in mammalian disease (linkage method), specifically in coronary artery disease [12*] and obesity [13]. Alternatively, disease modules have been constructed for numerous human diseases or pathobiologies (as reviewed by [2**]) including cancer, neurological disease, systemic inflammation, obesity, and type 2 diabetes mellitus, leading to the identification of the disease-modifying roles of a number of proteins interacting within these modules (disease module method). Such modules have also been found in a variety of cardiovascular diseases and in the process of cardiomyocyte maturation [14]. These have included an inflammatory module particular for myocardial infarction [15] and in-stent restenosis [16], adipose-specific modules related to atherogenesis [17], endothelial-specific modules representing endoplasmic reticulum and oxidative stress in atherosclerosis [18], and transcriptomic modules in carotid atherosclerosis [19], among others. More detailed characterization of modules such as those activated by oxidized phospholipids has led to the identification and

experimental validation of novel genes (i.e., *GPR39* and *OKL38/OSGN1*) that are important but not previously implicated in the endothelial response to atherogenic stimuli [20*]. A variation of this approach has also successfully identified specific microRNA such as miR-21 controlling pulmonary hypertension (PH) based on the predominance of their predicted targets in a PH-relevant module [21*]. Finally, analysis of pathways that closely neighbor but do not interact with a relevant disease module has led to successful detection of disease genes in diabetes mellitus, cancer, and Alzheimer's disease (diffusion method [22*]). Each of these methods utilizes the topological and functional information of the interactome to an increasing degree. Notably, a comparative study using the same data set demonstrates that linkage analyses offer the least predictive power while diffusion methods carry the best predictive performance [23*]. Thus, appreciation of network complexity offers tangible advantages to identifying *bona fide* disease genes and biomarkers of human disease.

As a result of multiple interconnections among disease modules, network medicine may also reveal the molecular underpinnings of the interdependence of distinct human diseases or individual disease traits. In the former case, a comprehensive map of disease modules in the human interactome has been constructed. This “diseasome” consists of nodes that represent diseases and links that represent key molecular relationships between disease-relevant factors in each module [10] or key phenotypic similarities among diseases [24] (Fig. 2B). Such links may explain why certain comorbid conditions segregate together, as previously investigated through shared protein-coding genes, metabolic pathways, microRNA, and phenotypic progression of disease (as reviewed by [2**]). A variation of this approach (gene coexpression network analysis) has also been successfully implemented in constructing a transcriptomic network of normal myocardial development, cardiac hypertrophy, and cardiac failure, leading to the identification of candidate genes that are shared among developing and diseased conditions [25]. By identifying therapeutic targets that are shared among functionally linked diseases or traits, such “diseasome”-based approaches may also guide novel therapeutic strategies designed to re-tool certain approved medications that can regulate those targets in alternative disease contexts.

Application of Network Medicine to Drug Development

In addition to aiding discovery of additional molecular aspects of human disease, network medicine may also optimize future drug discovery. Traditionally, rational drug design has centered on the identification and subsequent pharmacologic manipulation of a key molecular target that, when dysregulated, controls a measurable pathophenotype. However, in complex human diseases, the molecular pathobiology most relevant to clinical manifestation is not always easily discernible and typically not driven by one factor alone. Notably, a recent analysis revealed that a large proportion of established drugs do not target actual disease-associated proteins but merely proteins in their network neighborhood [26]. Thus, such drugs may have, at best, modest effects on pathophenotype. In contrast, “systems pharmacology” facilitates a more rational and rapid approach to identifying the most relevant “network-based” targets based on their presence in relevant disease modules [27**]. As a result, network analyses prioritize efforts to target candidates exerting the most powerful and direct effect on the disease module and, thus, on consequent disease phenotype.

Specifically, an appreciation of the disease module can guide pharmacologic drug design to target specific interactions with single or multiple binding partners in the disease module (Fig. 2C). Such tailoring may offer the most reliable method for ensuring drug efficacy *in vivo* and avoiding unwanted side effects that result from unanticipated interactions with other components of the interactome [26]. To date, the most striking examples of network pharmacology are derived from studies of metabolism. Owing to the fine detail of metabolic networks in the bacterial and human interactome, *in silico* predictions have been possible

regarding the effects on metabolite flux and consequent phenotypic alterations after manipulation of specific nodes in those pathways. As a result, potent new antimicrobial agents, for example, have been identified and validated *de novo*, based on their predicted system-based metabolic responses on bacterial survival [28**]. Alternatively, pharmacologic rescue of deficient metabolic function could also be envisioned in certain human genetic metabolic diseases as an intriguing alternative to gene therapy. Although these successes provide impetus for further exploration of network (or systems) pharmacology, the very nature of these expansive cellular connections suggests the severe limitations of single-target drugs in treating complex human disease. Thus, increasing efforts have been made to explore combinatorial drug therapy for complex disease phenotypes (i.e., cancer, HIV/AIDS, etc.). Recent advances in mathematical prediction of so-called "driver" nodes which can control the entire dynamics of a disease module may identify better the most robust, synergistic therapeutic targets [29**]. As a result, development of optimal regimens based on their *individualized* systems-wide effects is under further investigation [30*, 31*].

Conclusion

Although still in its infancy, network medicine offers a potentially powerful set of methodologies to improve our molecular understanding of the interconnected nature of human disease and to design therapies rationally based on the complexity of these biological links. It allows for prediction of disease genes, the roles of those genes within a disease module, the connections between distinct disease modules, and the functional consequences of those connections for disease phenotype. Notably, the fidelity of network medicine is currently limited by the incomplete nature of the interactome maps. Furthermore, while Bayesian modeling (as reviewed by [3*]) and more recent applications of control theory [29**] have been attempted to predict the *flux*, or flow, of information through biological networks, current mathematical and statistical tools have not yet been validated to predict accurately more than what the static topological features of a given network can describe regarding complex biological phenotypes. Yet, while a number of hypotheses and predictions made by network approaches remain to be verified, it is encouraging that some fundamental network principles have been well supported by experimental evidence in human disease. Consequently, as these methods are optimized, we expect a broad expansion in the use of network approaches in medicine in the years to come. Moreover, these approaches are likely to encompass not only an improved understanding of intracellular networks but also the poorly understood networks that connect cells, tissues, and organ systems and form the underpinnings of systems pathophysiology.

Importantly, by appreciating the complexity and interconnections among biological networks, we realize the shortcomings of current reductionist-based approaches used for disease definition and molecular discovery. Thus, a new network-based framework has been proposed to define human disease (Fig. 2D). Briefly, clinical disease manifestation results from a consequence of multiple overlapping and connected networks -- a primary disease gene connected to other components in a disease module and a disease module that is connected to other modules associated with distinct diseases or, perhaps, with intermediate pathophenotypes shared among various disease states (i.e., inflammation, thrombosis, *etc.*) [32]. In addition to genetic determinants, environmental and perhaps behavioral variables of disease can also be adequately represented within these networked modules. The resulting clinical pathophenotype emerges from the complex interplay among these components and is highly individual. As personalized medicine offers the first glimpse of individualized patient care based on patient genotype, we believe this type of disease classification will offer an even greater, integrated view of pathogenesis and provide an improved framework for future advances in medicine.

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Key Points

- Network medicine has the potential to capture the molecular complexity of human cardiovascular disease while offering computational methods to discern how such complexity controls disease manifestation.
- Network medicine has already led to tangible discoveries of novel disease genes and pathways as well as improved mechanisms for rational drug development.
- As methodologies evolve, network medicine may re-define personalized disease classification and therapies.

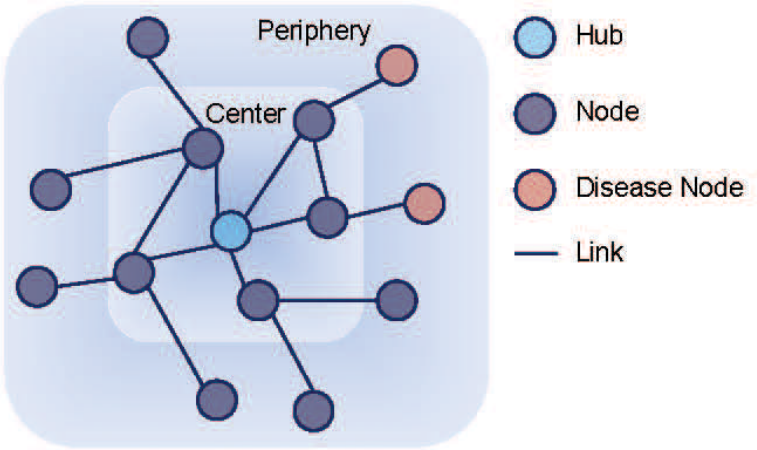

Figure 1. Overview of a biological network

Essential genes (hubs) exhibit a high degree of interconnectivity and are located centrally, while non-essential genes (nodes) are located in the periphery and have a small degree of connectivity. Genes that account for normal biological variability typically are non-essential (as reviewed by [2**]). Human disease genes tend to exist as peripheral nodes and have a propensity to interact with other disease genes (so-called “local hypothesis”).

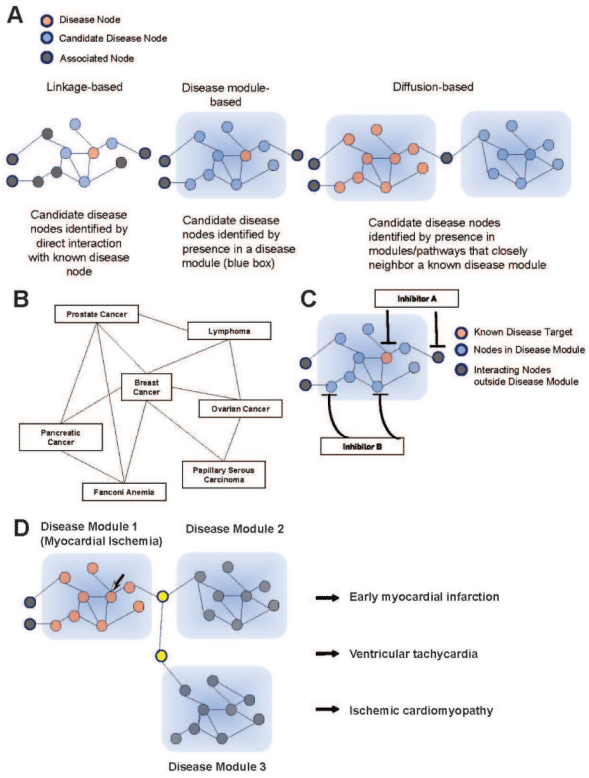

Figure 2. Application of network biology to scientific discovery in biomedical research

(A) Successful network-based methodologies for the discovery of novel disease genes. **(B)** A subset of the human diseasome reflects the functional interconnections among distinct manifestations of human disease. A link denotes the involvement of the same disease factor across different disorders. Adapted from [10]. **(C)** A network-based pharmacology approach to guide the rational identification and characterization of novel inhibitors of disease-relevant targets. Based on hypothetically available network-based analytic methods, Chemical A inhibits a known disease gene but may carry undesired side effects by influencing non-disease nodes outside the relevant disease module. Chemical B inhibits multiple nodes in a relevant disease module and, thus, may carry robust activity in inhibiting relevant pathogenic processes *in vivo*. **(D)** Human disease classification guided by network biology. In this hypothetical construct, a relevant disease module, affecting myocardial ischemia (1) and carrying a known disease gene (arrow), is connected to two other disease modules (2, 3) by common nodes and links (yellow). These common nodes may influence intermediate phenotypes important in numerous disease processes, such as inflammation or thrombosis. Depending upon a combination of environmental and genetic events that influence these disease networks, individualized manifestations of myocardial dysfunction result (early myocardial infarction, ventricular tachycardia, or ischemic cardiomyopathy). By improving our definition and understanding of network function in these biological circuits, these manifestations may be better predicted and ameliorated.