Heart failure: a complex clinical process interpreted by systems biology approach and network medicine

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ABSTRACT

Systems biology is founded on the principles of integrative computational analysis and on the data from genetic and molecular components. The integration of biological components produces interacting networks, modules and phenotypes with remarkable applications in the field of clinical medicine. The evolving concept of network medicine gives a more precise picture of the intrinsic complexity of failing myocardium and its clinical consequences. The present review is focused on the impact of network cardiology in explaining the progressive nature of the clinical syndrome of heart failure. The failing myocardium and the subsequent clinical syndrome of heart failure disclose a dynamical and nonlinear system with a progressive picture of clinical deterioration. The classical description of heart failure is based on tissue pathology and clinical presentation, and lately on specific genetic and molecular modifications. This characterization of heart failure has significant limitations to recognize preclinical disease features and to explain the progressive nature of the syndrome. Systems biology detects and evaluates specific networks from molecular, cellular and tissue elements, and assesses their influence on the appearance of clinical phenotypes. The classical reductive concept of heart failure is inadequate to provide data for molecular dysfunctions or defective coordination of the interconnected network components that are central to the genesis and clinical deterioration of heart failure. In heart failure, the recognition of molecular targets within the complex networks will increase the conceptual basis of pharmacology and the identification of novel biomarkers and at the same time will accelerate the discovery of new drugs. *(Anadolu Kardiyol Derg 2014; 14: 178-85)*

Key words: systems biology, network cardiology, heart failure, modules of failing myocardium, models of heart failure

Introduction

Systems biology defines the function and describes the behavior of complex biological networks and systems. It is rather a scientific approach to the structure and function of cells and organisms than a method of explaining the function of cellular elements or parts of an organism (1). To understand molecular biology and complex biological systems requires the integration of mathematical biology with experimental biology. Two significant projects have emerged to deal with the biological complexities in data analysis, modeling, network research and experimental design: the European Network of Excellence (ENFIN) and the Dialogue for Reverse Engineering Assessments and Methods (DREAM) projects (2). The ENFIN projects put together computational predictions and experimental proofs while being particularly focused on the function prediction of specific molecular elements, network reconstruction and modeling. The DREAM project tries to reconcile computational systems biology algorithms with biological understanding. The communication between the theoreticians and experimentalists is important for analyzing the mechanisms underlying the behavior of complex biological systems (3). Systems biology accomplishes this objective by deciphering the biological data and explaining the interaction between the biological components with the help of various genomic, proteomic, transcriptomic and metabolomic technologies. Biological dynamical systems include models of networks on different levels, like those of genes, proteins, metabolites, neural networks and many self-organizing systems (4). The term biological network is referred to a group of dynamically interacting biological elements or functions that underlie the biological processes. Human diseases represent self-organizing highly clustered dynamical systems that implicate many models of interrelated networks. The molecular events taking place at a lower level of the biological scale do have causal influence at the higher level of the scale, but the emergent biological properties in a higher level are novel with a

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higher degree of causal influence. The emergent properties are not expected from the individual biological units of the network but represent new collective behaviors that increase our knowledge for the functional whole behavior of the system. Thus, in systems biology, 'emergence' is a term addressed to the appearance of new (holistic) properties in higher biological systems from simpler interacting subsystems. The functioning of regulatory cellular biological networks, the communication between biochemical pathways and the interaction of various networks in the complex environment of supra-cellular space, are all involved in explaining human diseases. The interaction between components of these networks control human disease pathogenesis and express disease phenotype. The clinical applications of biological networks to understand human disease is rather premature but there are some promises in this field.

The heart is an effective pump forcing blood to the whole body and delivering oxygen and nutrients to a variety of tissues and organs. The heart is behaving like a multifunctional organ with significant role in the homeostatic regulation of the body. Heart failure (HF) is an entity that occupies an imaginable multivariate space of various metabolic and hormonal changes under the constant intervention of many biological components and environmental factors with a continuous change of values. In the field of HF syndrome, it is challenging to integrate genetic and molecular data with higher-scale biological networks, and to analyze the dynamics of the new clinical behaviors with the construction of conceptual intermediate modules (compensatory regulatory mechanisms) and clinical models (Fig. 1).

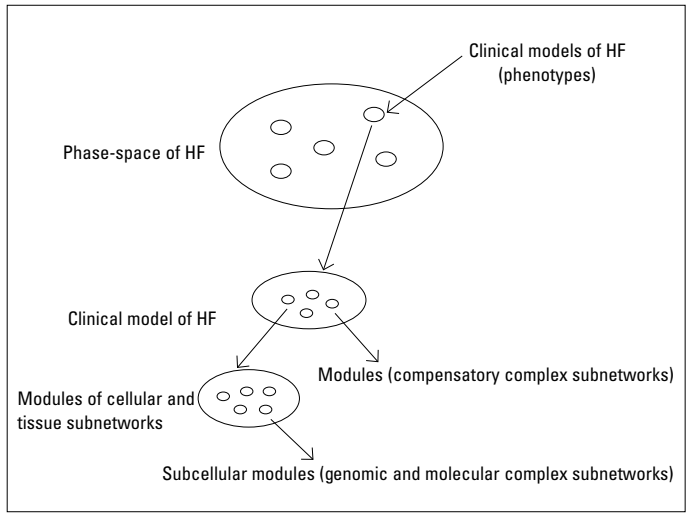

Figure 1. The multivariate phase-space of heart failure and biological structures (networks, modules, models)

Classical concept of heart failure

The Oslerian conventional definition of human disease connects the tissue pathology with the clinical presentation, and currently incorporates genetic and molecular changes to the pathology of the disease (5). Loscalzo et al. (6) suggested that this traditional classification of human disease has significant limitations that reflect the deficient sensitivity in recognizing preclinical disease and the absence of specificity in defining a disease without doubt. Furthermore, Loscalzo et al. (7) have described the potential limitations of classical disease definition and the differences from systems biology approach, and proposed a redefinition of human disease. They argued that the conventional definition of a disease concentrates "on the late-appearing, intermediate pathophenotypes within a given organ system" and overlooks "the specific genetic or environmental susceptibility determinants of the disease phenotype". Also, they suggested that the traditional definition of a disease is based on pathological and physiological characteristics of the pro-molecular era, while with systems biology methodology the disease phenotype is an emergent property of various interactions in a complex biological network.

The classical concept of HF like other human disease is established on the grounds of correlation between clinical signs or symptoms and pathological findings. The traditional reference to HF in medical texts is based on the description of clinical and experimental facts that are related to the epidemiology, diagnosis, prognosis and therapy. The clinical phenotype of HF includes specific characteristics in clinical presentation, biochemical and functional abnormalities, and pathological findings. In conventional clinical classification, there is a tendency for generalization of HF phenotype term without clear distinction between the specific HF models representing a variety of clinical phenotypes. Diverse myocardial stresses share a common pathological track of adaptive myocyte hypertrophy with further progression to systolic myocardial dysfunction and ventricular dilation. In a patient with HF, the conventional characterization of the clinical picture is insufficient to define the true nature of the syndrome if only the pathophysiological mechanisms of systolic or diastolic failure are considered, and if the point of interest is restricted on the end-stage of cardiac pathology. Only under systems biology holistic view is determined the complexity of HF that involves the variety of metabolic or hormonal changes in each model, and is emphasized the importance of the molecular and environmental intervening agents. This approach explains better the progressive deterioration of HF or the successful aspects of the new therapeutic agents.

Systems biology concept of human disease

The classic concept of genetics connects genetic variability straightforwardly with disease clinical phenotypes. Instead, systems biology evaluates genetic and environmental impact on molecular, cellular and tissue phenotypes, specifies the manner of interaction between these elements and detects specific networks on them that exert considerable influence on the appearance of clinical phenotypes. Biological networks are responding to the intrinsic network dynamics and to external adaptive pressures, and create models and phenotypes. The classical reductive concept of a disease is insufficient to provide information about simple molecular dysfunctions or faulty coordination of the interconnected components of complex biological networks that are underlying the genesis and progres-

sion of the disease. In human diseases, instead of the reductive method, it is now more scientifically appropriate to apply the holistic systems biology approach and develop individualized (personalized) treatment strategies exploiting the knowledge from modern molecular biology and data sets (7). Also, systems biology approach allows individuals and medical practitioners to have access to the most current information for disease prevention, diagnosis and therapy. To accept systems biology as a concept has significant repercussions to 'understand' the causes of the disease, to approach rationally the diagnosis of an established disease, and to develop personalized therapy according to contemporary molecular pathology. The existing sequencing technologies are critical tools to characterize the genetic mechanisms of a disease and to disclose novel pathways that determine clinical modules and phenotypes. The sequencing technologies possess a clinical potential for diagnosis and treatment, and promote the concept of a personalized medicine together with the individualization of therapy.

The limitations of the classical disease definition explain the shortcomings of pharmaceutical research and development, with new-drug output from pharmaceutical companies remaining constant since 1950 and the number of new drugs approved by the US Food and Drug Administration (FDA) continues to be at low levels (8). Recently, changes in legislation made more efficient the approval process of new drugs. Some critics claim that these changes in the legislation have compromised public safety and have increased the number of products recalled from the market, but others argue that these changes help patients with debilitating diseases to get critical medication (9). In systems biology approach, the pharmacologic drug design targets specific proteins associated with disease related networks. Recently, cell biologists are involved in pharmacology and drug discovery after recognition of the important role that networks have in cellular and tissue function. The networks that operate within and between cells are liable to changes induced by therapeutic agents (10). Cell biologists are rethinking the conceptual basis of pharmacology and drug discovery and are appreciating the quantitative behaviors of networks in cells, tissues and organisms (11). Furthermore, the identification of new biomarkers requires the understanding of molecular targets in the setting of biological networks, homeostatic processes and pathophysiological mechanisms (12).

Systems biology view of human heart failure

Through a systems outlook, the contemporary approach to human HF integrates genomic, metabolomic, cellular, pathological, physiological and clinical data, defines compensatory regulatory networks (modules) and describes emergent clinical phenotypes (models) (Fig. 2). The HF syndrome involves multiple cellular mechanisms leading to different phenotypes (models) resulting in reduced ventricular contractility and dilation. Thus, human HF is a syndrome displaying multiple clinical phenotypes with the involvement of a number of molecular, biochemical and pathophysiological mechanisms. These clinical phenotypes are characterized by multiorgan dysfunction because of upregulation or downregulation of the above mechanisms. It is essential from a clinical perspective to specify these phenotypes and to outline a therapeutic strategy for the diversity of clinical appearances targeting to a more individualized therapy. Human HF is apparently complex in its expression with various phenotypes to describe different clinical syndromes having a variety of clinical characteristics and outcomes. In clinical practice a variety of HF phenotypes (models) is described, like the cardiorenal model, the cardiocirculatory model, the neurohormonal model and the biomechanical model (13). The original molecular or cellular concept of module is extended to higher level of organismal organization like the homeostatic cardiac regulation systems. The homeostatic cardiac regulation mechanisms (modules) include the compensatory neurohumoral systems of RAAS and natriuretic peptide axis system, and the cardiac remodeling systems (14). The neurohumoral system promotes or suppresses the cardiac remodeling system in an attempt to assist failing myocardium and preserve cardiac output. These regulatory mechanisms are not able to stop the decline of myocardial function and the relentless nature of HF worsening.

Systems biology directions in heart failure

The classical two directions of systems biology are important for defining the integrated processes of various biological networks in cells, tissues and organs, and are used in explaining the genesis and progression of a disease. In clinical medicine, the rationality of both directions is based on the integrated biological networks that are considered significant for the genesis and progression of a specific disease. The logical outcome of the above is that the understanding of a disease is equivalent with the knowledge of the underlying integration of specific biological networks. In explaining HF, the 'bottom-up' direction (functional composition) examines the mechanisms of construction of complex biological networks and models, investigates the nonlinear reactions of the self-organized networks and explores the rise of functional and emergent properties in each step of the diseased biological ladder, up to the level of HF phenotype. Thus, the study of the causes, effects and progression of HF is related to the interpretation of the behavior and hierarchical construction of the self-organized networks from molecules to phenotypes. This way, the novel biological networks merge the classical regulatory biochemical pathways involved in the progression of HF with the more informal molecular data.

In a 'top-down' direction, the systems biology decomposition of a biological network into modules (subnetworks) is succeeded with initial recognition and isolation of the specific modules. Then, systems biology approach takes a further step reassembling the different modules in a bottom-up manner towards a specific model (phenotype) but still is required the 'top-down modeling that embeds the modules into the cellular processes' and 'genetic-regulatory and signaling networks' (15). Therefore, in the HF syndrome, the 'top-down' direction (functional decomposition) is based on 'omics' data (genomics, proteomics, tran-

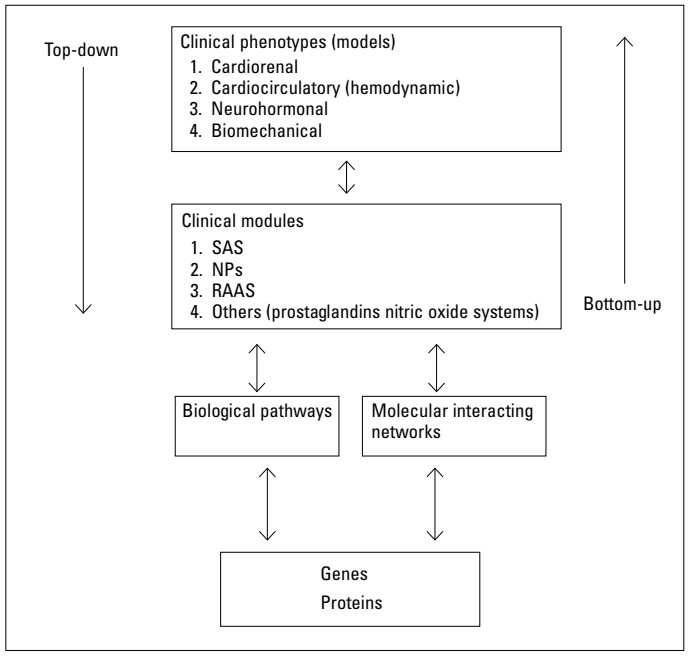

Figure 2. The human heart failure and systems biology approach. Heart failure modules and clinical phenotypes
LVR - left ventricular remodeling; NPs - natriuretic peptides; RAAS - renin-angiotensin-aldosterone system; SAS - sympatho-adrenal system

scriptomics, metabolomics) and intends to explain the compensatory regulatory mechanisms (modules) and the genesis of clinical HF phenotypes (16, 17). Important strategy in the evaluation of 'omics' data by systems biology approach is to identify within the network of clinical phenotype some viable and physiologically relevant subnetworks or modules capable to give a robust explanation for HF genesis and progression. Such physiological modules are the regulatory mechanisms of neurohumoral and cardiac remodeling systems. These regulatory mechanisms of neurohumoral and cardiac remodeling systems are important as efficient biological factors for the homeostatic regulation of the body and as effective compensatory mechanisms for the failing myocardium. The functional decomposition from phenotypes to critical functional regulatory modules gives a comprehensive and integrated approach of the HF syndrome. This is possible only through the accumulated knowledge of-omics data and functional integrated networks that are participating in the construction of modules and phenotypes that characterize HF.

Biological networks

Biological networks are present in all levels of biological processes from genes, proteins, transcripts to cells, tissues and organisms. The intracellular biological networks are responsible for sustaining cellular functions while their organization is identical for all living organisms. The biological networks, rather than linear biological pathways, are the functional effective components of metabolic organization. The design of this metabolic organization is robust, error-tolerant and represents a common pattern for the large-scale organization of interactions with which all living cells should comply (18).

Nadeau et al. (19) used a multigenic variation of cardiovascular properties in genetically randomized mice to perturb cardiovascular functions in the normal range of variation. In the described cardiovascular functions were included cardiac output, end-systolic left ventricular dimensions, septal wall thickness, and heartbeats per minute. In those genetically controlled differences, computational analysis of the findings correctly identified the known relations between cardiovascular properties and emerged functionality at higher levels of the cardiovascular system.

Weiss et al. (20) in a review, approached the cardiovascular metabolism from three points of view: a metabolite network composed of nodes and links, a modular spatially compartmentalized network, and a network of dynamically interactive metabolic modules. The functional modular compartmentalization of the energy-generating systems of the cardiovascular metabolism includes oxidative phosphorylation, glycolysis, and glycogenolysis which are channeling ATP in different cellular compartments (20). Glycolysis is channeling energy to the sarcolemma, glycogenolysis to the sarcoplasmic reticulum and oxidative phosphorylation (mitochondria) to the myofilaments and the cytoplasm (21).

As a scientific application, the holistic approach of systems biology probably is the most relevant method to describe a human disease, to recognize complexities and to detect the appropriate therapy. The purpose of systems biology is the transfer of knowledge about the structure and function of biological networks from model organisms (yeast and tissue culture cells) to higher-level networks and clinical modules that are underlying emergent potentialities and behaviors of human diseases (22). Furthermore, the classic linear metabolic pathways are depicted as graphs where the biological elements or entities (genes, proteins, metabolites, modules, phenotypes) are called 'nodes' and their interactions are named 'links' or 'edges' (21). The new emerging concept of 'network medicine' uses network topology (static position of molecules) and network dynamics (flux of information) to explain the abnormal behavior of complex molecular interconnections (23). An important goal in systems biology is to focus on biological highly interconnected networks centralities ('hubs') and also to define networks with a high between-ness centrality ('bottlenecks') (24). The networks centralities characterized as 'hubs' are essential for the integrity of the entire network while the 'bottlenecks' represent essential functions necessary for cell survival (25). However, in molecular networks of most adult complex diseases, there is an unexpected gene peripheral location that can be explained only by an evolutionary argument. The vast majority of nonessential and compatible with survival disease genes is located in functionally peripheral and topologically neutral positions in the cellular network. That in contrast with essential genes (hubs) that are functionally and topologically central in the cellular network, whose mutations result in severe functional impairment leading to embryonic lethality (26). Therefore, disease genes are represented more often with non-hub nodes because dysfunction of

these nodes ordinarily is not associated with mortality. Goh et al. (26) observed in a disease molecular network that the associated genes and products are assembled in the same network locality ('local hypothesis') with an increased trend for them to interact with each other. These findings support the position that the disease-linked genes and proteins compose subunits (or modules) inside of the global molecular network, and are expressed as groups in specific tissues or organs. Frequently, cellular networks are assembled and produce local modules with high regional interconnection that have an impact on disease manifestation. Biological and metabolic networks are characterized by overlap and hierarchical organization between fundamental network groups. Groups of related nodes correspond to functional subunits, possess hierarchical organization or have widespread overlap of nodes consequently resulting in the existence of a close relationship between overlapping groups (27).

The identification of disease modules arises after the construction of the 'human interactome', a network that represents the totality of the interactions of cellular components in human cells or tissues (28). Specific molecular interaction data assist us to identify some of the interlocking subnetworks (modules) incorporated in the global 'human interactome' and involved in human disease progression leading to distinct clinical phenotypes. The systems biology methodology, in order to recognize biological networks specific for a disease, links different components of the complex and interconnected disease system, and determines the biological switch from a healthy to a diseased situation. The concept of network medicine improves the understanding of intracellular molecular networks, and proposes a new insight in the functional interconnection between specific disease modules and phenotypes. Thus, this network proposition gives a more holistic view to the nature of human disease, interprets the multiscale network connection between cells, tissues and organs, and identifies the complex network interplay processes responsible for the genesis and progression of a specific disease.

In a recent review were suggested some 'fundamental concepts of network medicine' on predicting and improving 'individual manifestations of human cardiovascular disease' (25). Network approaches have been evolved in order to comprehend interconnections between multiple pathological biological pathways, understand human cardiovascular pathogenesis and determine mechanisms for appropriate drug development. To understand the pathogenesis of atherosclerosis which is a multifactorial chronic disease with complex etiology, we need to specify appropriate biological networks or disease modules involved in the progression of the atheromatous disease. Thus, biological networks and modules have been described in atherosclerosis, like the transcriptomic modules derived from transcriptomic data of the Karolinska University Hospital, and constructed a gene association and correlation network of atherosclerosis (29). The coronary artery endothelial transcriptome was addressed in an experimental study and the transcript profiles were analyzed to identify the in vivo endothelial phenotypes (30). In a gene connectivity network analysis, specific coronary endothelial phenotypes expressed in gene modules were related to increased endoplasmic reticulum and oxidative stress in coronary arteries prone to atherosclerosis (30).

Systems biology and 'network cardiology' are equally important for the study of protein networks and compensatory regulatory networks (modules) involved in the genesis and progression of HF. Gao et al. (31) in a canine model of HF induced by tachycardia, investigated the gene networks and molecular systems that corresponded to hemodynamic and electrical remodeling processes. The advance of left ventricular dysfunction was associated with transcriptional changes early after the initiation of rapid ventricular pacing and with some additional posttranscriptional modifications responsible for myocardial structure and function regulation in later stages of HF. Asakura et al. (32) described 107 HF-related genes that are listed in previously reported microarray data sets which are probably linked to the pathophysiology of HF. Many of these genes are involved in mitochondrial dysfunction and oxidative phosphorylation, and in three extracellular molecules, periostin, pleiotrophin and SERPINA3. Zhu et al. (33) developed a systems approach linking gene expression data with data from a layered protein-protein interaction (PPI) network in order to clarify the underlying mechanisms of the ischemic cardiomyopathy. In this study the layered PPI network was subdivided into four layers, extracellular, plasma membrane, cytoplasm and nucleus, and the gene expression system of the four layers was compared, aiming to give a new perceptive to the mechanisms of ischemic cardiomyopathy.

A distinctive feature of prenatal cardiac metabolism is the prevalence of carbohydrate utilization for energy requirements in a rather hypoxic fetal environment which in the postnatal oxygen rich environment is changed to oxidation of fatty acids (34). In a miscellany of pathophysiologic conditions, like hypoxia, ischemia, hypertrophy, and failing heart muscle, the postnatal heart myocardium keeps the ability to return to the fetal gene program. It seems that common biological process pathways exist between fetal and failing myocardium. This metabolic remodeling under stress conditions is an adaptive mechanism that has the potential to protect the stressed myocardium from irreversible functional impairment and programmed cell death (35). In rats with experimental ascending aortic banding the induced left ventricular hypertrophic phenotype is linked with re-initiation of the fetal program of gene expression, which program continues after the development of left ventricular failure (36). Experimental murine findings demonstrate that expression of genes associated with a fetal transcription program is implicated with the post ischemic remodeling process of the ventricular myocardium (37). Also, in rats with post-myocardial infarction HF, was observed a prompt induction of the fetal transcriptional gene program prior to myocardium hypertrophy (38). Dewey et al. (39) used gene co-expression network analysis and determinated the gene expression network topology of cardiac hypertrophy and failure, as well as the degree of re-

emergence of fetal gene expression programs in the hypertrophic and failing adult myocardium. This network analysis based on myocardial transcript data from the Gene Expression Omnibus, a publicly available repository of all microarray data, and focused on the most complete murine dataset, has disclosed specific gene expression modules triggered during both development and disease. In developing myocardium, were discovered 50 fetal gene co-expression modules (between 25 and 914 genes) that were not present in normal adult myocardium, and of those three were re-emerged in the hypertrophic and seven in the failing adult myocardium. At present, we are at the start of knowledge accumulation in creating complex patterns of biological and hierarchically ordered networks in the area of cardiovascular diseases. It is fundamental to advance from animal experimentation to human conceptualization of interconnected networks and their application to the clinical perception of human HF.

Cellular and clinical modules of heart failure

The cardiovascular diseases usually are caused by multiple genetic and environmental factors that increase the disease risk. The classical reductionist approach to human diseases gave the impression that permanent aberrations in genes or proteins could lead directly to a disease phenotype. This notion is not correct, as a disease rarely is the result of an abnormality of a single effector gene product (28). The McKusick's Online Mendelian Inheritance in Man (OMIM), a large database scanning every day from the peer-reviewed biomedical literature, currently contains 18961 full-text entries describing phenotypes and genes, but of those only 2239 genes have mutations with direct disease relationship (40). The insufficient collected data from human samples directed to the exploration on murine experimental module systems to answer fundamental biological questions for the failing heart. Often, the intramodular connectivity is calculated, in order to identify gene coexpression modules and estimate reproducibility of gene modularity between networks. Dewey et al. (39) analyzed gene coexpression modules for over-representation of known transcription factor targets. In hypertrophied and failing myocardium, the transcriptional targets are assembled in nodes in a meta-network higher order topology of the transcriptome. This way, gene expression analysis promotes assessment of higher-order topology of the transcriptome and related transcriptional regulators in HF and developing myocardium. Some of those transcription factors play a significant role in modulation of the gene programs involved in developing myocardium and myocardial adaptation. In vertebrate development, in the group of regulatory genes, that control spatial and temporal patterning, structural identity and cell longevity, are included the HOM-C/Hox homeobox genes. These regulatory genes can function as transcription factors of downstream target genes in normal and mutant hearts. The Hoxa-5 with a potentially significant role in fetal mouse lung development and in apoptotic heart morphogenesis in amphibians is also highly expressed in modules of developing or failing myocardium (41, 42). Members of the transcription factor of FOX family are targeting various areas of the immune regulation, from lymphocyte survival to thymic development. Also, the transcription factor of FOXN1 has a critical role to play in modules allocated in developing and hypertrophied myocardium (43).

The present clinical reality forces us to study a complex human disease with a more refined methodology involving clinical modules (subnetworks) and phenotypes. The perturbed collective gene expression and transcriptome data are conveying information to higher order networks with an undefined mode. The concept of modularity is crucial to systems biology in the endeavor to comprehend human biological organization and to understand the genesis and progression of a human disease. In the present article, the term 'clinical module' is given to the functional regulatory network systems that are responsible for maintenance and progression of HF syndrome. This trend to modularity is what makes possible the construction of a complex multileveled biological scale with interaction between different modules as an essential part for the genesis of a clinical phenotype (model). Therefore, the term 'disease' represents a pathological phenotype caused by malfunction or disintegration of specific clinical modules that are related to dysfunctional network components and faulty interacting biological pathways.

Human HF is a syndrome having different causes and clinical appearances (phenotypes), and implicates many physiological regulatory systems (modules) (44). The compensatory regulatory systems or clinical modules are interdependent and include the vasodilatory systems, the vasoconstrictive systems and the cardiac remodeling system. In the vasodilatory systems, are incorporated the early motivated natriuretic peptides (NPs), the prostaglandins (PGE_2 and $PGEI_2$) and the nitric oxide systems, while in the later activated vasoconstrictive systems, are included the sympatho-adrenal system (SAS) and the renin-angiotensin-aldosterone system (RAAS) (16). The above neurohumoral regulatory systems are linked with the cardiac remodeling system, another important regulatory module that participates in HF progression. The neurohumoral regulatory systems are related positively or negatively to cardiac remodeling system, as they upgrade or inhibit the left ventricular remodeling process during HF progression. In advanced stages of HF, the initial beneficial impact of the neurohumoral systems on the cardiac hemodynamic compensation is replaced by their destructive effect on the HF progression due to the reduction of myocardial contractility and the increase of the deleterious processes of cardiac remodeling. Therefore, the compensatory regulatory responses represent maladaptive cardiac stress reactions with significant harmful end-stage consequences. In the later stages of the left ventricular dysfunction the progressive mechanical remodeling changes are deleterious and not counterbalanced by any other compensatory mechanisms.

Clinical phenotypes or models in heart failure

Phenotype is a term that is used in biology or clinical medicine to designate the physical (or clinical for a disease) appearance or biochemical characteristics of an organism as the out-

come of the interaction of the individual's genetic make-up and the environment. Phenotypic data are presented as network functional states that convey information about the actual flux distribution in a network (45). In HF syndrome, the complex processes of the network functional states, lead from genetic make-up to modular functional units (compensatory or regulatory mechanisms) and to clinical disease phenotypes (clinical modules). It is questionable if it is possible to predict HF phenotype or what significance or value this will have in clinical practice. Network cardiology when applied to clinical level describes features of the diagnostic and therapeutic conundrum of HF which otherwise would be lost under the classical description of HF. Network cardiology correlates and links known biological networks in all levels of 'omics' and assembles clinical networks up to the level of modules and models. This way, is constructed a meaningful argument and is formulated a 'whole' concept for human HF progressive nature and additionally are devised therapeutic options. The variety of the heterogeneous compensatory regulatory systems (clinical modules) and the diversity of the clinical phenotypes (clinical models) encapsulate the clinical appearances of HF syndrome. In clinical practice are presented patients with different clinical characteristics of myocardial impairment having diverse etiology and varying activation of the same regulatory mechanisms. The main clinical phenotypes that have been described are the cardiorenal model, the cardiocirculatory or hemodynamic model, the neurohormonal model and the biomechanical model (13, 16). The importance of the biomechanical model is emphasized since foresees more accurately HF progression. In fact, in the real world, there is a host of other HF models with comparable but not-equivalent molecular and end-organ derangements with dissimilar clinical picture. Probably, in the near future, this multitude of clinical phenotypes would be explained by the increased molecular knowledge in all levels of the biological ladder and by construction of more meaningful clinical prototypes leading to a more personalized therapy.

Conclusion

Systems biology approaches are able to explain and solve complex disease processes, like HF syndrome. The initial stages of myocardial dysfunction and the clinical worsening of the established HF syndrome are triggered and maintained by the interaction and integration of underlying specific biological networks and modules. It is suggested that a network based biological conceptual structure can determine the progressive nature of failing myocardium.

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