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REVIEW ARTICLE

The new biology: a bridge to clinical cardiology

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Abstract

The recent advances in the biological research have produced new biological disciplines with clinical applications in medicine and cardiology. The integration of multilevel biological data and the connection with the clinical practice reveal the potential of personalized medicine and nanotechnology with future implications for prognosis, diagnosis and management. In the post-genomic time period the new disciplines, systems biology, synthetic biology and translational medicine are emerging as significant research areas in biology and medicine with extension in the field of clinical medicine and cardiology. These disciplines, with their predictive, preventive and therapeutic potential, are formulating the concept of personalized management, with patient's energetic involvement and participation in the diagnosis and treatment. Personalized medicine and cardiology, using biomarkers as health and disease indicators, encourage drug development and direct towards a better molecular comprehension of disease processes. Hippokratia. 2012; 16 (2): 106-112

Key words: systems biology, synthetic biology, translational cardiology, personalized cardiology, review

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The term 'biology' includes the notion of function or purpose for the living systems which differentiates the science of biology from the other natural sciences of physics and chemistry[1]. The nonlinear interactions of the biological processes assign a restrictive role to classical biology and do not permit biology to explain the behavior of the components, or determine 'how' these components are interconnected, and therefore to interpret and understand the living world[2]. This led to the next step, to the molecular biology, which characterizes the structure of the biological material and delineates the mechanism of interconnections between molecular elements. Molecular biology was successful in identifying structure and pathways, but proved ineffective in the experimental prediction of biological events. Despite the progress of classical and molecular biology, there are objections to the belief that by studying separately the molecules, molecular biology can explain the complete biological phenomenon. The new biology should decode the functional interconnection of molecules, pathways and networks, and define biological concepts that are effective to explain physiological phenomena, diseased states and genetic and systems adaptation. Human diseases are complex states consisting of various inputs with positive and negative feedback mechanisms.

Systems biology

According to the classical reductionist strategy, only molecular or genetic diversions are responsible for abnormal biological conduct or genesis of pathological situations. In contrast, the philosophy of systems biology is based on the assumption that disturbances in complex biological systems and diseases are directed by the functional impact of integrated networks of molecules, genes or metabolites[3]. The new approach to understand the biological systems is to see them as a whole instead of explaining them with the reductionist point of view. The systems biology methodology decodes the way that the various biological components and networks are organized, combined and control each other. Also, it is important to recognize the emergent properties of the integrated biological network and their role in the diagnosis and therapy of different clinical situations[4]. Systems biology is a novel approach to decode the hidden information from genetic and molecular networks and to make significant steps towards drug development process, clinical medicine and personalized therapeutic interventions[5-8].

Physiologists regard the term 'systems biology' as redundant because biology is basically integrative and physiology has been interested in systems description for a long time[9]. This position is supported by integrative physiologists who employ the new techniques and modalities used by systems biologists to study complex biological processes, like cardiac remodeling and heart failure[10]. These physiologists go a step further and advocate that systems biology should be integrated into physiology to create "Integrative Physiology 2.0". The above opinion is not supported by the recent advances in the

fields of cellular molecular networks and disease modeling, from the holistic understanding of the biological functions to personalized medicine.

In the field of complex cardiac system, systems biology integrates the information taken from the available multiple databases and produces experimental or computational models[11]. The top-down approach for multilevel biological analysis is the classical physiological approach[12], while in systems biology three ways of analysis are described: bottom-up, middle-out and top-down[13]. As an example, according to systems biology approach the biological and clinical analysis of heart failure could be based in two biological systems of interaction: the functional composition (bottom-up direction) and functional decomposition (top-down direction)[4].

In the existing and ever-growing number of public databases for systems biology, there are some inconsistencies in nomenclature and differences in conceptual understanding and terminology advanced by various research groups[14,15].

Synthetic biology

The term 'synthetic' biology was originally invented as a scientific approach to overcome the limits of natural evolution and as a link between functional and evolutionary biology[16]. The main purpose of synthetic biology is to produce new functional modules from the combined action of different components. Synthetic biology studies cellular behavior, and constructs biological systems and cellular circuits with cells being build module by module in the bottom-up direction[17, 18]. This way, the role of synthetic biology is expanded and related to systems biology. Systems biology approach constructs modules and networks and gives an explanation for their building and for their emergent properties. Synthetic biology uses the same building blocks, modules and networks, to construct stable and robust biological circuits and networks[19], and enables systems biology to break up the complex assembly and composition of cellular systems[20]. Synthetic biology creates biological networks in order to understand or redesign living complex systems, and to assist biotechnology industry in fundamental research for the improvement of human health, welfare and environment[21]. A recent article gives a new framework for synthetic biology using a Bayesian model selection and emphasizes the difference between inference (reconstruct the system with the observed data) and design (construct the system with the desired data)[22].

Synthetic biology, after the first successes of constructing synthetic gene networks, is producing increasingly complex biological circuits and therapies for a variety of diseases[23]. Biotechnology companies are using its potential to reduce research time and cost for the production of chemicals, pharmaceutical substances, food ingredients and health care products[24].

Translational cardiology

The term 'evidence based' medicine and/or 'evidence based' cardiology was established as a central concept in medical treatment during the last two decades of the 20th century. This concept meant to ask a proof for a specific treatment after statistical confirmation of its efficiency during execution of prospective experimental protocols. The emerging field of 'translational' medicine is related to 'evidence based' medicine, and as a concept refers to the translation of the experimental findings obtained in the bench of the research laboratory to terms of clinical practice[25]. There is a close relationship between medicine, medical technology and society at large, with nanotechnology as an example of emerging and innovative technology with social implications.

Translational cardiology transfers knowledge, from basic research and pre-clinical studies, to the clinical cardiology through well executed clinical trials. Thus, translational cardiology transfers the pre-clinical research from the field of cell-based cardiac tissue repair into early-phase clinical trials in patients with acute myocardial infarction or refractory myocardial ischemia. At the present time, cell priming, bio-nanotechnology and tissue engineering are coming up as valuable techniques for ischemic tissue repair and cell-based therapy application in clinical cardiology[26].

As an example, is the translation of S100A1-based research from initial clinical observations in heart failure syndrome, over basic research experiments, back to the clinical setting on the verge of clinical trials[27]. The loss of cardiomyocyte Ca (2^+) cycling integrity is significant for the development and progression of heart failure syndrome. The cardiomyocyte EF-hand Ca (2^+) sensor protein S100A1 is a regulator both of sarcoplasmic reticulum, sarcomere and mitochondrial function, and probably the S100A1 gene therapy has a therapeutic potential for heart failure patients[25]. Another important translational study demonstrates the preclinical feasibility of long-term therapeutic effectiveness of cardiac AAV9-S100A1 gene therapy in a preclinical model of heart failure and opens the possibility for a clinical trial of S100A1 gene therapy for human heart failure[28].

A. Personalized cardiology

Personalized cardiology is an ambitious target of systems biology, synthetic biology and translational cardiology, and intends to modify the practice of medicine producing a more predictive, preventive and individualized cardiology. The current approach to human disease is founded on reductionist principles of experimentation and analysis but holistic systems biology proposes a new method for diagnosis and therapy[29]. The individualized or personalized treatment is an application of the holistic systems biology that is based on modern molecular medicine and use of the large data stores for complex diseases (Figure 1).

Genetic and epigenetic abnormalities or different environmental circumstances modify the human cardiovascular disease and produce various phenotypes. Therefore, the term of personalized cardiology refers to the preven-

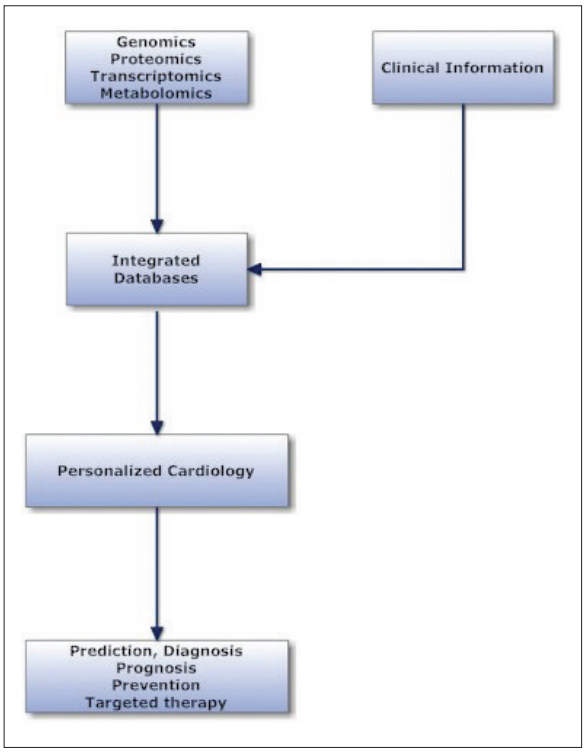

Figure1: Integration of clinical and 'omics' information, necessary for personalized cardiology.

tion, diagnosis and therapy of cardiovascular diseases based on individual genomic, proteomic and metabolomic data[30]. The clinical practice is individualized especially in complicated cardiac states with multi-organ involvement and in acute heart failure syndromes, with neurohormonal adaptations, abnormal haemodynamics, and variant clinical picture including acute or chronic renal dysfunction[31].

Also, the various diagnostic techniques in clinical practice should be expanded and adapted to a more individualized cardiology. A more personalized echocardiography should be advanced to real-time data acquisition from tissue and fluid motion, with improvements in 3D echocardiography, tissue Doppler and exercise stress echocardiography[32].

The screening for changes in proteome and metabolome is a useful technique to detect specific biomarkers in coronary heart disease and heart failure. New cardiovascular biomarkers are under investigation for their diagnostic, prognostic and therapeutic value in patients with acute coronary syndrome (ACS) or after percutaneous coronary intervention (PCI). Thus, promising biomarkers like cardiac troponin (cTN), high sensitive cardiac troponin (hscTn), natriuretic peptides (NPs) and some future biomarkers like copeptin, choline and lipoprotein-associated phospholipase A2 (LP-PLA2), will improve the diagnostic and risk stratification processes and soon will be introduced into routine clinical practice[33].The identification of all responsible genes for coronary artery disease remains elusive while the identification of variants to disease process is considered as a challenge[34,35].

Genomics and Proteomics

Genomic and proteomic advances in the recent years have increased our understanding of cardiovascular diseases. A Mendelian mode of monogenic transmission to an offspring has been demonstrated in a variety of cardiovascular diseases, like hypertrophic cardiomyopathy[36], Marfan syndrome[37], long QT syndrome[38] and arrhythmogenic right ventricular cardiomyopathy[39]. It appears that there is a genetic ground to more complex cardiovascular diseases like atherosclerosis and heart failure. These complex diseases without monogenic transmission, demonstrate a genotype with interdependency and interactions between various genes, and reciprocal activity between genes and environment.

In the majority of the patients with coronary artery disease there is genotypic heterogeneity, and therefore the clinical appearance has a multifactorial origin as the result of many genes action with minimal individual effects. Recently, many genome-associated studies have replicated a novel gene marker on chromosome locus 9p21 which is related to non-coding RNA gene and needs further research. Genetic information acquired from single nucleotide polymorphisms (SNP_s) or haplotypes of genes related to atherothrombotic cardiovascular process, is expected to improve prediction and management of coronary artery disease. In the near future, a more personalized approach, that integrates clinical data with environmental and genomic risks, is anticipated to clarify risk stratification and early clinical intervention in high-risk persons[40].

Proteome includes all existent proteins in a cell or tissue, and proteomics is the study of the proteome encoded by the genome. In contrast to the genome, proteome is not static and adapts to cellular circumstances and environmental conditions. The existing 30000 human genes are responsible for the construction of one million proteins[41], but there is a protein diversity due to alternative splicing, multiple transcription start sites, changes in pre-messenger RNA, polyadenylation and post-translational modification of proteins[42]. The liquid chromatography-mass spectroscopy technique is a sophisticated invention that could evaluate complex biological material, fluid and tissue proteomes, enclosing many biological molecules like proteins or lipids[43-45].

The proteomic cardiac studies receive significant assistance from online databases of human cardiac proteins and from international organizations that provide standards of data being discovered in proteomic studies[30]. In the online databases are included the HSC-2DPAGE[46], HEART-2DPAGE[47] and HP-2DPAGE[48], which are displaying more than 6000 myocardial proteins. Two known international organizations are publishing standards of proteomic data for diagnosis, therapy, prevention and research: the Human Proteome Organization[49] that provides guidelines for proteomic research and the Proteomics Division at the National Heart, Lung and Blood Institute[50].

Proteomic studies have recognized changes in many protein groups that are related to cytoskeletal, sarcomeric and extracellular matrix construction and function of the myocardium, to mitochondrial metabolism pathways in preconditioning, to calcium control mechanisms and to redox regulation[51,52].

Pharmacological targeted therapy is the main field of clinical implementation of genomic and proteomic technological advances after the identification of specific molecular targets in disordered biochemical pathways. The use of anticoagulant drugs is an example of personalized medicine in the practice of modern cardiology[53].Warfarin is used extensively in clinical medicine and cardiology, but it has a small therapeutic window with an uncertainty in dosing and inconsistency in patient's reaction. The responsiveness to the warfarin depends on polymorphisms in genes with an impact to metabolism (CYP2C9) and to pharmacodynamic response (VKORC1). Two allelic variants, CYP2C9*2 and CYP2C9*3, are associated with impaired hydroxylation of S-warfarin and inefficient warfarin metabolism[54]. Individuals having one or more CYP2C9 variant alleles require a low warfarin dose and have an increased risk of bleeding. Also, variants in the gene VKORC1, that encodes vitamin K epoxide reductase complex 1, are associated with reduced expression of VKORC1 and lower response to warfarin. The VKORC1 haplotypes can explain differences in dose requirements while the molecular mechanism of this response is regulated at the transcriptional level[55].

In interventional cardiology and in patients with ACS, it is essential to individualize the antiplatelet therapy. Particularly in patients with ACS, who are submitted to PCI and stent implantation, the use of dual antiplatelet therapy with aspirin and clopidogrel, a P2Y12 receptor antagonist, is considered as the mainstay of the management for preventing future cardiovascular events. The object of many recent trials is the assessment of the relationship between the genetic variation in cytochrome P450 (CYP) isoenzymes and the pharmacokinetic response of the clopidogrel. There is significant variability in the antiplatelet effect between patients due to drug interactions, clinical factors, and the presence of CYP2C19 loss of function alleles that obstruct the metabolism of clopidogrel to its active form[56]. There is 3-fold increase in .stent thrombosis among patients with the CYP2C19*2 genotype who were treated with clopidogrel[57]. Therefore, in patients with acute coronary syndromes, genotyping for a CYP2C19 loss of function variant could be considered[58].

Also, the pharmacodynamic response to clopidogrel is variable due to impaired activity of CYP3A4 enzyme. Clopidogrel therapy is ineffective in 10-30% of the treated patients while the resistance and suboptimal response to aspirin is about 5.5-9.5% and 23.8% accordingly[59,60]. Probably, platelet function tests measuring the effect of clopidogrel on the P2Y12 receptor and upcoming clinical trials would change our approach to antiplatelet therapy and lead to a more personalized cardiology[61].

Three hundred patients were evaluated after PCI for changes of the clopidogrel platelet reactivity (PR) and its relationship with genotype and clinical outcomes. In these patients, the PR decreased from baseline to one month while the genotype (gene polymorphisms, CYP2C19*2, *17, CYP3A5*3, and ABCB1) influenced approximately 18% of this trend[62,63].

The beta-blockers are an important group of drugs for heart failure patients. Genetic variants of the $beta_1$-adrenergic receptor are considered therapeutic beta-blocker targets. In humans, polymorphisms at amino acid residue 389 (Arg/Gly) of the $beta_1$-adrenergic receptors, predisposes to heart failure due to hyperactive signaling programs guiding to ventricular dysfunction[64]. The homozygosity for Arg389 was characterized by left ventricular functional improvement when these patients with heart failure were treated with carvedilol[64]. Homozygotes with Arg389 treated with bucindolol, had a 38% reduction in mortality, and 34% reduction in mortality or hospitalization compared with placebo[65].

The angiotensin-converting enzyme (ACE) deletion allele (ACE-D) is associated with increased renin-angiotensin-aldosterone system (RAAS) activation and in patients with systolic dysfunction was associated with a significantly poorer transplant-free survival[66]. The use of higher doses of ACE inhibitors reduced the impact of the ACE-D allele in patients with systolic dysfunction, while the advantages of using beta-blockers and high-dose ACE inhibitors seem to be the greatest for DD patients[67].

Genetically based individual differences, are considered as major determinants of left ventricular remodeling. The application of molecular imaging techniques, to decipher the cellular and molecular mechanisms of the left ventricular remodeling, contributes to a personalized assessment and follow-up in patients with heart failure[68].

'Theranostics' is the scientific field that combines diagnostic methodology and therapy and incorporates the entities of personalized medicine, pharmacodiagnostics, integrated medicine and nanotechnology. The development of molecular-imaging techniques, like MRI and optical imaging, is based on nanoparticles, while drug-delivery approaches are important in order to understand the biomedical processes and therapies at a molecular level[69]. The molecular imaging technique is targeting molecular and cellular sites designed to visualize disease-associated molecules and cells, to assess disease progression and to evaluate the in vivo molecular effects of drugs[70]. The single nucleotide polymorphism (SNP) mapping technique is effective to detect genes important for coronary artery disease genesis and progression, and advances the concept of personalized medicine [71,72].

Trancriptomics

Transcriptomics is the study of the transcriptome, which includes the complete set of mRNA transcripts in the cell generated by the genome, and reflects the genes that are expressed at any given time. In contrast to the genome, which is fixed for a given cell line, the transcrip-

tome can change with external environmental conditions. The microarray analysis is a technology that enables the quantification of many thousands of mRNA transcripts, detects new molecular abnormalities, produces new clinical biomarkers, and explores drug efficacy[73]. In human heart failure, transcriptional regulation and transcriptome variability was studied with microarray analysis[74,75]. Gene expression and transcription analysis in human heart failure was portrayed in ischemic and nonischemic cardiomyopathy[76], and in patients supported with left ventricular assist devices[77]. The integration of clinical assessment (NYHA class) with T cell receptor signaling gene expression was proposed as a model to predict survival of heart failure patients[78].

MicroRNAs (miRNAs, miRs) are a class of small (22-nucleotide) noncoding RNAs, post-transcriptional regulators of gene expression, which can link to messenger RNA transcripts[79]. The microRNAs are an endogenous class of small RNA molecules that negatively regulate gene expression and mediate post-transcriptional repression (inhibit translation) or mRNA degradation[80]. The miR-133 and miR-1 are expressed in cardiac and skeletal muscle, and regulate myogenesis, cardiac development, cardiac performance and cardiomyocyte hypertrophy, while other microRNAs participate on the myocardial growth, electrical balance and angiogenesis[78]. Probably, future experimental and clinical research on microRNAs will contribute to sudden cardiac death prevention and heart failure treatment targeting cardiac fibrosis, hypertrophy, stem cell differentiation, cardiomyocyte survival, apoptosis and myocardial failure through modulation of cardiac microRNAs[81,82].

Genes were identified indicating the important role of chemokines, cell-extracellular matrix and lipoprotein alterations in the pathophysiology of acute myocardial infarction[83]. Also, were identified genes preferably expressed in atrial cardiomyocytes and proposed to be tested as potential biomarkers for atrial stress[84].

Metabolomics

A number of small molecules named metabolites reside in the human cells or tissues with a significant biological effect on health and disease. There is speculation about the exact number of metabolites normally existing in human cells, but it is calculated to be a few thousands. The discipline of metabolomics studies the biological impact of metabolites under normal circumstances and during the state of a disease, and identifies novel biomarkers and new drugs[85]. In transgenic mouse model, are described experimental methods able to determine genes, proteins and metabolites involved in the three processes of atherosclerosis: lipid metabolism, inflammation, and tissue changes[86].

Three complementary approaches are used for metabolic research: metabolomic fingerprinting (metabolites altered in a disease), metabolomic profiling (metabolites that participate in a targeted pathway), and metabolomic footprinting (monitoring metabolites that are secreted or fail to be taken up by a cell or tissue)[87].

The main objective of metabolomics studies is to identify and intervene in specific locations of metabolic pathways with advantageous effect in early detection, metabolic individuality, exact diagnoses and ultimate halt of disease processes. In patients with primary dilated cardiomyopathy, 61 metabolites were found to be significantly different between people with primary dilated cardiomyopathy and control individuals[88]. This metabolomic profiling identifies biomarkers of primary dilated cardiomyopathy that probably have protective or harmful effects on cardiac structure and function.

Conclusions

In this paper an overview is presented of the new disciplines of systems biology, synthetic biology and translational medicine with a focus on cardiology. These new fields of knowledge integrate data from physiological measurements, genetic and molecular networks, and clinical findings. The recent advances in these disciplines improve the status of current practice of medicine and cardiology, and guide to a more personalized cardiology with personal participation in diagnostic, preventive and therapeutic decisions.

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