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Review

Systems Approaches to Biology and Disease Enable Translational Systems Medicine

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Abstract

The development and application of systems strategies to biology and disease are transforming medical research and clinical practice in an unprecedented rate. In the foreseeable future, clinicians, medical researchers, and ultimately the consumers and patients will be increasingly equipped with a deluge of personal health information, *e.g.*, whole genome sequences, molecular profiling of diseased tissues, and periodic multi-analyte blood testing of biomarker panels for disease and wellness. The convergence of these practices will enable accurate prediction of disease susceptibility and early diagnosis for actionable preventive schema and personalized treatment regimes tailored to each individual. It will also entail proactive participation from all major stakeholders in the health care system. We are at the dawn of predictive, preventive, personalized, and participatory (P4) medicine, the fully implementation of which requires marrying basic and clinical researches through advanced systems thinking and the employment of high-throughput technologies in genomics, proteomics, nanofluidics, single-cell analysis, and computation strategies in a highly-orchestrated discipline we termed translational systems medicine.

Keywords: Systems biology; P4 medicine; Family genome sequencing; Targeted proteomics; Single-cell analysis

Introduction

Systems biology strives to unravel the enormous complexity of biological systems through a holistic approach in the context of a cross-disciplinary environment. Since its founding in early 2000, the Institute for Systems Biology (ISB) has been pioneering systems strategies to biology and disease through the development of systems strategies and the application and/or development of cutting-edge high-throughput technologies to the investigation of model organisms and humans with varying degrees of complexity: from single-cell organisms (bacteria and yeast) [1–3] to experimental animal models (mouse) [4–7] and to human disorders [8–10]. Over the last decade, rapid advancements in genomic and proteomic technologies, computational strategies and their applications in human diseases have demonstrated promising early success in genomic medicine. We discuss here our view of how systems approaches to biology and disease and emerging technologies are going to transform the medical practices by shaping up translational systems medicine for early diagnosis, disease progression, patient stratification, predicting recurrence, and therapeutic guidance.

Dealing with disease complexity—systems medicine and its 5 pillars

Human phenotypes are specified by two types of biological information: the digital information of the genome, and the environmental information that impinges upon and modifies the digital information. Two general biological structures connect the genotype and environment to phenotype: (1) biological networks capture, transmit, process and pass on information; these networks organize,

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integrate and model data to enormously increase the signal to noise; (2) simple and complex molecular machines execute biological functions. A systems view of disease postulates that disease arises from disease-perturbed networks. A ramification of this premise entails studies of disease pathogenesis at the network level through a systems approach so that better strategies for early diagnosis and therapeutics targeting these perturbed networks can be devised. We stipulate five pillars to address disease complexity upholding systems approach as follows.

(1) Viewing biology and consequentially medicine as an informational science is one key to deciphering complexity.
(2) Systems biology infrastructure and strategy—holy trinity of biology (*i.e.*, use biology to drive technology and computation development)—endorse cross-disciplinary culture and democratization of data-generation and data-analysis tools.
(3) Holistic, systems experimental approaches enable deep insights into disease mechanisms and new approaches to diagnosis and therapy through analyzing the dynamics of disease processes.
(4) Emerging technologies provide large-scale data acquisition and permit exploration of new dimensions of patient data space.
(5) Transforming analytic tools will allow deciphering the billions of data points for each individual—sculpting in exquisite detail the wellness and disease landscapes.

These five fundamental principles will allow in-depth interrogation of diseased networks at unprecedented molecular resolution. Some disease events will occur well before the disease manifestation for early detection, whereas key nodal points amongst perturbed networks can be identified for diagnostic detection or therapeutic interventions. Both diseased organs/tissues and patient blood constitute excellent specimen reservoirs for systemic assessment of diseased conditions in multiple spatial and temporal measurements. Whole genome and whole transcriptome sequencing, targeted proteomics via mass spectrometry and protein chips, single-cell analysis and a variety of targeted nucleic acid detection systems (*e.g.*, next-generation sequencing (NGS), DNA arrays, NanoString *n*-Counter [11], Fluidigm BioMark, *etc.*) will be the workhorse churning out enormous amount of data. We anticipate that in 10 years each individual will be surrounded by a virtual cloud of billions of data points. A key challenge is to fully integrate these diverse data type, correlate with distinct clinical phenotypes, extract meaningful biomarker panels for guiding clinical practice. We enumerate here some of the individual patient information-based assays of the present and future (**Table 1**).

Family genome sequencing: integrating genetic and genomics

Complete human genome sequence is becoming increasingly affordable and will be a fundamental part of one's medical record in 10 years. While a great deal can be learned regarding one's predisposition to certain diseases from individual genome, sequencing of a family permit one to use the principles of Mendelian genetics to eliminate 70% sequencing error. This will greatly facilitate better identification of rare variants, determining chromosomal haplotypes and intergenerational mutation rate, and identification of candidate genes for simple Mendelian diseases. Moreover, knowledge of *cis* and *trans* linkage relationships of genes and control elements will be key for understanding biology and disease, and reducing the chromosomal search space for disease genes [9,12]. Recent developments by Complete Genomics Inc (CGI) employing long fragment reads (LFR) have demonstrated whole-genome sequencing from as few as 10–20 cells with three striking advances over typical NGS approach. These advances include (1) high accuracy with a genome error rate of 1 in 10 megabases; (2) assembly of diploid haplotypes from individual genome sequences; and (3) *de novo* assembly of individual genomes, which enables discovery of structural variations [13]. With this technology, comprehensive genetic studies and diverse clinical applications are within reach.

Table 1 Clinical assays and emerging technologies for exploring new dimensions of patient data space

Genomics
Complete individual genome sequences will be done by sequencing families—predictive health history
Complete individual cell genome sequences—cancer
Complete MHC chromosomal haplotypes in families—autoimmune disease and allergies
300 Actionable gene variants—pharmacogenetics-related and disease-related genes
Sequence 1000 transcriptomes—tissues and single cells—stratification disease
Analyze aging transcriptome profiles—tissues and single cells—wellness
Analyze miRNA profiles—tissues, single cells and blood—disease diagnosis
Proteomics
Organ-specific blood SRM protein assays
2500 Blood organ-specific blood proteins from 300 nanoliters of blood in 5 min—twice per year (50 proteins from 50 organs)—wellness assessment
New protein capture agents—D-amino acid peptides joined to create dimer or trimer capture agents
Array of 12,000 human proteins—against autoimmune or allergic sera—stratify—diseases that kill cells (neurodegenerative)
Single molecule protein analyses—blood organ-specific proteins and single cell analyses
SWATH™ analyses—global, dynamical analyses