Multi-author Review
Genetic studies of diseases

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Cellular and Molecular Life Sciences

Applications of systems biology

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Recent advances in human science, especially the vast amount of data from the human genome and high-throughput technologies in molecular and diagnostic applications, have driven medicine onto a more comprehensive path. There now exists a unique opportunity for understanding human health and exploring disease mechanisms in the new century. On the other hand, this also represents a great challenge in developing efficient, personalized disease prevention and treatment using more precise knowledge of medical science.

Complex human diseases affect the health status of populations to a greater extent. Understanding biological systems and exploring etiopathogenesis are fundamental in the search for a cure for human diseases. Most complex diseases, including cancer, obesity, diabetes, cardiovascular disease, hypertension, asthma, inflammation and psychiatric illness, develop from integrated actions of multiple genetic and environmental factors, through dynamic, epigenetic and molecular regulatory mechanisms. Recently, systems biological research has been providing a framework for such integration.

Systems biology takes a living organism as a complex system and attempts to understand it in a systemically coordinated manner [1–3]. Living organisms are not just the sum of their components. Systems biology takes into account the interaction and coordination between each element of an organism, for example the various DNA, protein and metabolites in its body, and the elements of its environment. These components are hierarchically organized into large networks, in which the system's global behavior arises from the joint actions of many simple components. The general approach of systems biological studies in the etiopathogenesis of diseases are to combine information from molecular biology, genetics and epidemiology with comprehensive mathematical models to study how gene-gene interactions, gene-environment interactions and protein-protein interactions act together to cause disease [2].

In the last century studies in molecular biology, genetics and epidemiology were mainly focused on dissecting individual components, such as DNA structure, genes, proteins, environments and their limited interactions. But this alone is not sufficient for interpreting biological systems, and developing efficient and personalized strategies for prevention and treatment of disease. In addition, the major tools of molecular biology in studying individual components of biological systems are biological experiments. There is a lack of adequate mathematical models to describe and predict the behavior of biosystems. Although genes and proteins are of primary importance, they do not function in isolation. Rather, they act through complex networks consisting of many interrelated genetic and environmental components. It is increasingly recognized that complex interactions among genes, protein/metabolites and environments underlie most phenotypes of diseases [4–6].

Acquiring comprehensive knowledge of a living individual requires modeling biological systems and understanding their behaviors. Althought 'network' is not a new concept, biological networks have many unique features and poses a significant challenge because of their scale and unprecedented complexity. Systems biology provides a common language and

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powerful tools for describing and modeling the integrated action of genes, proteins/metabolites and environments as well as developing personalized treatment and prevention [7–9].

An important discipline of systems biology is its application in medicine. Tumor researchers have been applying this approach in broad aspects. For instance, [Wang, this issue] describes how to identify accurate biomarkers for diagnosis and treatment of tumors. researchers can construct gene-gene networks using gene expression profiles of cancer cells, and then reconstruct cancer gene regulatory networks by developing reverse engineering algorithms. In studies of pancreatitis, [Whitcomb this issue] proposed functional modeling from specific cellular molecules to physical cell compartments of the pancreas along with their bioenvironment to systemically explain mechanisms of disease. This may be superior to current approaches with individually detecting disease markers, or using surgical biopsies and autopsy studies. In neurodegenerative disorders, to discover effective treatments that increase neural activity in brain regions, Sestini applied a systemic approach in understanding cellular and molecular impairments underlying diverse signaling processes between neurons, astrocytes and blood perfusion [Sestini, this issue]. Recently, RNA interference (RNAi) technology has facilitated a broad spectrum of studies in medicine, especially in molecular function and potential drug development. From the viewpoint of systems biology, RNAi allows researchers to test a bionetwork system with controllable gene expression. It is an extremely important regulatory tool in bio-network modeling, since the regulatory function of each gene in proposed networks can be verified through specific RNAi. In addition, RNAi-based high-throughput screening methods for genetic interactions may provide a way to predict crucial genes contributing to human complex diseases [Li, this issue].

This special issue includes five papers that review applications of systems biology to genetic studies of complex diseases. These multidimensional reviews provide some examples of systemic approaches in understanding complex biological systems underlying initiation and development of diseases, as well as in their treatment. They view the biological system as a complex physiochemical system that involves many dynamic networks of biochemical reactions and signal interactions [Kwoh and NG, Whitcomb and Barmada, Sestini, this issue]. They suggest using biological networks as a platform for (1) integrating information from molecular biology to genetics, and various types of data such as multiple phenotypes, DNA variations, gene expression, protein expression, protein-protein interactions and metabolites, and (2) analyzing their interactions and emergent complex behavior [10,11]. Network analysis is an essential tool for dissecting the complex genetic structures of diseases and unraveling their mechanisms. A central challenge for application of the systems biology approach to human diseases is to develop a unified framework for combining the multiple sources of genomics and genetic information, biomedical data and analytic tools for analyzing systems properties of biological processes. Therefore, researchers require using tools from a variety of disciplines, including systems science and nonlinear dynamics, information theory, statistic inference and stochastic modeling, complex theory, molecular biology and genetics [12–14].

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