Editorial Overview

Theory and Application of Network Biology Toward Precision Medicine

Clinical research and medical treatments are poised to experience a dramatic change in the next decade, thanks to the advent of population-wide 'omics profiling, electronic medical records, and artificial intelligence. The interpretation of such massive amounts of data and its relationship to disease is a major challenge when trying to make actionable predictions that can lead to effective patient-specific therapeutics. Network biology provides a conceptual framework and toolkit to integrate and interpret large data sets and to generate hypotheses about gene function, gene–disease associations, drug efficacy, and disease prognosis. The promise of network biology for the rational design of novel precision therapeutics is well reflected in the 10 review and research articles in this Special Issue.

Cancer therapeutics is a field that can greatly benefit from network approaches, as each patient carries a unique set of genetic and epigenetic alterations that can uniquely affect biological functions. Ozturk et al. [1] review the applications of network analyses for studying cancer along with methods to perform *n*-of-1 tumor genome analysis. They also discuss how these approaches can be translated into clinical practice. Shen et al. [2] discuss how synthetic lethal or sick interactions—pairs of genes in which the simultaneous loss of function causes cell death or slowed growth—can be harnessed to attack cancer-specific weaknesses.

Yao et al. [3] summarize state-of-the-art approaches to delineate context-specific integrative networks and their ability to predict tissue-specific molecular responses and identify candidate disease genes. Similarly, Pai et al. [4] discuss predictive methods based on patient similarity networks in which patients can be stratified based on their similarity in genomic, phenotypic, or functional features.

This Special Issue also presents original research articles presenting novel network-based approaches to stratify patients, identify disease genes, and predict drug responses. Wang et al. [5] describe an algorithm called Seed Connector algorithm that tackles one of the limitations of most network approaches: how to deal with incomplete data. The authors apply their algorithm to coronary artery disease where they uncover signaling pathways involved in the disease and identify novel drug targets. Non-synonymous mutations can rewire biomolecular interaction networks and ultimately lead to disease. Hutt et al. [6] present a method called ProVarA that integrates mass spectrometry with genomic tools to understand the differences in onset, progression, and therapeutic responses in patients carrying different disease-associated variants. When applied to patients with mutations in cystic fibrosis, this approach revealed protein interactions contributing to disease. The paper by Cui et al. [7] presents a multi-level characterization of mutations associated with human genetic disorders and illustrates how different types of mutations (single-nucleotide variants *versus* frameshift mutations) have different rewiring effects on the human interactome.

One of the major challenges for current therapeutic approaches is that drug efficacy greatly depends on genetic, epigenetic, and environmental factors, which can differ greatly between patients. The paper by Le et al. [8] describes a network-based method called GloNetDRP to predict patient-specific drug responses. This method connects drug and cell line similarity networks by known drug-cell line responses, and goes beyond the commonly used approach of using network neighbors for association predictions by exploiting other drugs and cell lines in the heterogeneous network. An alternative strategy proposed by Sidders et al. [9] couples a network pharmacology *in silico* approach with a functional phenotypic screen to identify small molecules that can selectively disrupt the structure of a chronic pain disease network, increasing the efficiency of drug discovery or repurposing. Finally, in the paper by Juan-Blanco et al. [10], the authors use a network-based strategy that clusters cell lines according to their molecular similarity to identify genes in each cluster and correlate their status to drug responses allowing them to identify a limited set of genes that might be involved in drug sensitivity or resistance.

This collection of articles tackles some of the key areas where network biology is making strides toward the rational design of patient-specific therapeutics. However, many challenges remain to be addressed, including increasing the completeness of different biological networks, developing computational frameworks that increase prediction accuracy,

and building clinician-friendly tools that can guide patient-specific therapies. We look forward to future research in these directions as we consider solving these challenges central for the advancement of precision medicine.

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