Bio-network medicine

Complex diseases such as cancer or diabetes generally not result from mutations or malfunctions of individual molecules but from dysfunction of relevant networks. Thus, it is of great importance to analyze molecular mechanisms of the diseases on a network basis. Although classical medicine based on molecular biology has made significant progress in general, current methodologies, which are still mainly based on studying individual genes and proteins, are not good enough to solve increasing problems of complex diseases. Therefore, innovative methodologies and techniques from the perspectives of systems biology are strongly demanded to be applied for designing and searching for new medical solutions for preventing, diagnosing, and curing the diseases. Bio-network medicine is such an area to study complex diseases by a network-based approach at the molecular level, and is considered as a powerful method to assist the effective diagnosis, prognosis, and treatment of complex diseases.

This special issue of *Journal of Molecular Cell Biology* is published to present the latest advances in the field of systems medicine based on biomolecular networks, in particular new approaches developed to decipher the complexity of disease progression, and their implications for therapeutic endeavors. Research papers in this special issue cover topics ranging from disease gene analysis, to biomarker detection, and to disease diagnosis by employing the molecular networks, and can be grouped into sequence data-based studies and expression data-based studies.

In the first article, Wang et al. computationally detected 9606 potential phosphorylation-related single nucleotide polymorphisms (phosSNPs) that could significantly affect population-specific kinase–substrate networks, by using a sequence-based predictor with known phosphorylation and protein–protein interaction information as filters. The authors further demonstrated that these networks involved in phosSNPs may influence cancer susceptibility.

Based on sequence data, Melamed et al. developed an information theoretic framework associated to the correlation network, i.e. Genomic Alteration Modules using Total Correlation (GAMToC) that integrates copy number and mutation data to identify gene modules with any non-random pattern of joint alteration. In addition, also based on the sequence information, Dr Jiang proposed a method named pgWalk to prioritize candidate disease genes by constructing a disease–gene network with the integration of multiple phenomic and genomic data.

Different from relatively static information of DNA sequences, the expression information of genes or proteins provides signals for the dynamic state of the diseases. By exploiting the association or network information of expression data, Zhang et al. developed a novel computational framework, EdgeBiomarker, which identified edge biomarkers based on network properties and enabled accurate diagnosis even with single sample. In particular, edge biomarkers from non-differentially expressed genes (which are generally disregarded by traditional methods) even achieved better cross-validation accuracy of diagnosis than node biomarkers from differentially expressed genes, suggesting that certain pathogenic information is only present at the level of network and thus underestimated by traditional methods.

To investigate cell migration controlled by Rho-family GTPases, Kim et al. constructed a dynamic network model for the Rho-family GTPases signaling network. They also developed a Boolean network model to analyze different states and emergent rewiring of the Rho-family GTPases signaling network at protrusions during extracellular matrix-dependent cell migration.

To study epithelial-mesenchymal transition (EMT) in cancer metastasis from a dynamical viewpoint, Tanaka et al. established a model in which cancer EMT was considered as an overall structural change in the gene regulatory network (GRN) and employed network biology approach to grasp essential features of cancer EMT. They elucidated that cancer EMT...
underwent three sequential stable stages, each of which formed a potential basin along the EMT trajectory.

As a unique work on network model of cancer, Zhang et al. performed a computational analysis of tissue transcriptomic data from precancerous diseases, primary cancers, and metastases, aiming to reveal the drivers maintaining a high-level production of lactates throughout the entire cancer development across different cancer types. The derived LDHA-centric co-expression networks for different cancer types suggested various stress types as potential drivers and elucidated the associated transcription regulatory systems. These results provide useful information for designing personalized treatments for different cancers at different stages.

All studies presented in this special issue demonstrate great potentials and power of biomolecular networks on solving the problems of medicine. With further development combining with big data, bio-network medicine is expected to play crucial roles in precision medicine or personalized medicine in the future.