Biology and Pathology

Biology and Pathology – Systems Biology and its Link to Molecular Imaging

An Integrated-omics View of Cellular Regulation

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Learning Objectives:

- Understand how to describe the genotype/phenotype relationship
- Recognize how cellular regulation is a multi-level process and how protein levels and transcript levels are related to each other
- Understand the history of models of cellular regulation

In 1908, Archibald Garrod theorized that a gene is responsible for a particular protein and can be responsible for a disease. He suggested (correctly) that alkaptonuria results from one recessive gene, which causes a deficiency in the enzyme that normally breaks down alkapton. Beadle and Tatum subsequently demonstrated that single gene mutations could incapacitate specific enzymes and that such an incapacitation could cause a neurospora to have significantly altered physiology. Given these findings it is natural to conclude that innate diseases (e.g., alkaptonuria and cancer) result from single gene alterations. This led to the hypothesis that each gene is responsible for directing the construction of a single, specific enzyme and accordingly that disease occurs through the alteration of a gene. Decades later, this single-gene/single-enzyme view of how cells work (or break) has defined the major focus of much of biological investigation: identifying single genes whose mutation leads to pathology. In this world-view, the phenotype (disease outcome) is a sum of its parts (genotype). In much the same way that Newtonian physics explains a lot, but not all of the behavior of objects in motion, the early and ongoing views of biological regulation fail to fully explain or predict the biology. The flood of data generated by -omics technologies has given us a detailed view of the world of genes, biomolecules, and cells that we are just barely beginning to understand. Unfortunately, there is a chasm separating our knowledge of how molecular components and cellular and organismic physiology function together to enable cells to sense and respond to their environment, and to determine actions like proliferation, migration, and apoptosis. For example, the simple models of cellular regulation, driven solely by enzymatic cascades and modeled as first-order chemical processes, fail to describe the role of structural proteins (e.g., cellular cytoskeleton). Also, the emergent properties and self-organization evident in the interplay between transcription factors, DNA folding and unfolding, transcriptional machinery, and factors involved in translation and protein degradation collectively require sophisticated regulatory models to rigorously describe the diverse intermolecular interactions occurring within cells.

Relevant Publications:

1. Integrated inference and analysis of regulatory networks from multi-level measurements. Poultney CS, Greenfield A, Bonneau R. Methods Cell Biol. 2012;110:19-56.
2. Global quantification of mammalian gene expression control. Schwanhäusser B, Busse D, Li N, Dittmar G, Schuchhardt J, Wolf J, Chen W, Selbach M. Nature. 2011 May 19;473(7347):337-42.

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