Chapter XL
The Breadth and Depth of BioMedical Molecular Networks:
The Reactome Perspective

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ABSTRACT

From a genetic perspective, disease can be interpreted in terms of a variation in molecular sequence or expression (dose) that impairs normal physiological function. To understand thoroughly the knock-on effect such pathological changes may have, it is crucial to map out the physiological relationship affected genes maintain with their functional neighbors. The goal of the Reactome project is to build such a network knowledgebase for all human genes. Constructing a map of such extent and scope requires a considerable range of expertise, so this project collaborates with field experts to integrate their pathway knowledge into a single quality-checked human model. This resource dataset is systematically cross-referenced to major molecular and literature databases, and is accessible to the community in a number of well-established formats. As an evolving network systems resource, Reactome is also starting to provide increasingly powerful and robust tools to investigate tissue-specific biology and steer targeted drug design.

INTRODUCTION

A major theme emerging from biomedical research in recent years is the multifactorial origin of many diseases (for example, (Talmud 2004; Barnetche, Gourraud et al. 2005)). This feature is thought to reflect the concerted evolution of a number of genes responsible for our survival on the one hand, and rapidly changing environmental pressures on the other. Therefore, disease is seen as a reporter phenotype for evolutionary and environmental change.

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As the effort to establish the genetic basis of disease intensifies, single genes and their products are under close scrutiny to determine their biological role and their individual contribution to pathology and morbidity. The challenge today is to integrate this accumulated knowledge to provide the 'bigger picture' – a global functional context in which every human gene has a well-defined role. A matrix of this nature, that describes the function of all genes in relation to each other, requires an eloquent grammar for the step-wise depiction of biological processes in detail.

From a medical standpoint, the notion of disease is based on a deviation from normal function. In the course of studying a specific pathology, establishing how to identify and quantify this deviation depends on a proper definition of function under normal conditions. Establishing a standardized approach to describe all large scale biological processes therefore creates a common platform that connects and relates all known disease mechanisms at a molecular level. Furthermore, such an approach provides a unique opportunity to reclaim and integrate applicable knowledge generated from studies using model organisms that are of relevance to human disease. In this review I discuss the basic principles and limitations of the methods employed to depict human molecular physiology.

BACKGROUND: DEPICTING NORMAL HUMAN GENE FUNCTION

A key step to integrating knowledge about gene function is to develop a unified method to describe the properties of their products. The Gene Ontology (GO) Consortium (Harris, Clark et al. 2004) has developed a successful interdisciplinary project to catalogue and standardize a vocabulary of terms depicting biological activity and localization of expressed products. Each term is supported by a text-based description that illustrates and defines a biological property, with which any number of gene products may be associated. This annotation strategy has achieved considerable coverage of a large number of genes from a wide variety of model organism databases (http://geneontology.org).

This qualitative relational classification of descriptive GO terms provides vital bearings on the functional landscape of sequence molecules. GO maintains actively three distinct ontologies of terms, namely, 'Molecular Function', 'Biological Process' and 'Cellular Component'. GO's stated objective is to keep its ontologies strictly orthogonal to each other, thus minimizing the descriptive overlap of these vocabularies.

Both 'Molecular Function' and 'Biological Process' terms represent some form of biological activity associated with gene products – a 'process' can be seen as a recognized series of 'functions'. Some activity terms deal with the movement of biological entities (for example, 'protein transporter activity' (GO:0008565)), a significant proportion with a molecular conversion of some kind (for example, 'adenylosuccinate lyase activity' (GO:0004018)), while others are concerned with assembly (for example, 'actin cable formation' (GO:0045011)). In many ways, GO activity terms relate to a structural change that has a biological implication.

The 'Cellular Component' ontology describes subcellular and extracellular locations, representing a higher level of structural complexity, starting from macromolecular assemblies. For example, the GO term 'actin cable' (GO:0030482) is defined as 'a long bundle of actin filaments, comprising filamentous actin and associated proteins, found in cells'.

In practice, GO terms describe where gene products locate themselves as well as an indication as to what their role is and how this is carried out. The wording employed in GO terms also provides a unique insight into the conceptual relationship of structure and activity and the difficulties often encountered in

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