Chapter 14
Pathway Resources at the Rat Genome Database:
A Dynamic Platform for Integrating Gene, Pathway and Disease Information

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ABSTRACT

The set of interacting molecules representing a biological pathway or network is a central concept in biology. It is within the pathway context that the functioning of individual molecules acquires purpose and it is the integration of these molecular circuitries that underlies the functioning of biological systems. In order to provide the research community with a dynamic platform for accessing pathway information, the Rat Genome Database (RGD – http://rgd.mcw.edu) is using a multi-tiered approach. In this chapter, the pathway resources that RGD currently offers are presented. Issues covered include: the biological pathway, the concept and the ontology, pathway literature curation and annotation of genes, interactive pathway diagrams, and tools and resources to access and navigate between pathway data. A case study is presented; future directions are discussed.

INTRODUCTION

Pathways represent a central biological concept. The reactions biological macromolecules carry out and the interactions they establish with one another form small circuitries referred to as pathways or networks. Their cross-talk, synergy and co-regulation underlie the functioning of biological systems. When the molecular functioning falters such that the network gets perturbed, the malfunctioning can propagate to the point where

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the system as a whole is affected as manifested in the diseased state. In order to comprehensively capture the pathway universe as well as its alterations, the Rat Genome Database (RGD) has delineated several goals. Objectives include the ability to associate individual genes with the pathway or pathways in which they participate as well as to retrieve this information in an easy and efficient manner, the ability to visualize individual pathways in a manner that is both dynamic and integrated and finally, the ability to easily navigate between these components.

To achieve these goals, RGD is employing a multi-tiered approach, as delineated below:

1. It is developing an ontology solely dedicated to pathways, the Pathway Ontology (PW) in order to integrate the various types of biological pathways – metabolic, regulatory, signaling, drug, disease as well as altered pathways – and the relationships between them, within a hierarchical structure.
2. It is using the published scientific review literature to identify the individual components of particular pathways and the identified set of genes is annotated to the PW term for the rat, human and mouse complement.
3. It is building and publishing interactive pathway diagrams that can be accessed and linked via their unique PW term identifier. Elements in the diagram link to entries in RGD as well as other databases, whenever applicable.
4. It is using and building tools to provide easy access to and navigation between the objects stored in the database, analyses and downloads, and links to various outside resources.
5. It is actively seeking to add new dimensions to the current provision of pathway information.

BACKGROUND

The Pathway Concept - Reactions, Interactions and Regulation

A pathway is represented by a set of interacting molecules. The set may have 'boundaries' i.e., a beginning and an end as in the conversion of a particular compound into another in a metabolic pathway. For instance, in the glycolysis pathway of carbohydrate metabolism, glucose (the beginning) is broken down to pyruvate (the end) via 10 enzymatic reactions (Voet, Voet & Pratt, 2008). In signaling and regulatory pathways, the boundaries represent a consensus established by researchers for ease of communication as these circuitries fluidly transition from, to and between one another, a delicate balance choreographed by modulatory loops and molecules (Marks, Klingmüler & Müller-Decker, 2009; Kholodenko, 2007; Santos, Verveer & Bastiaens, 2007; Hunter, 2000; Schlessinger, 2000). For instance, insulin – a hormone of central relevance to normal physiological homeostasis – upon binding to its receptor, 'activates' the insulin signaling pathway which in turn triggers downstream intracellular pathways to modulate cellular and nuclear gene expression events. The conformational changes in the insulin receptor resulting from binding to its ligand lead to autophosphorylation of distinct tyrosine residues, followed by additional conformational changes, activation of the tyrosine kinase function of the receptor and modification of downstream substrates. What follows is a cascade of protein-protein recognitions and interactions that trigger the two main conduits of the insulin signal – the phosphatidylinositol 3-kinase-Akt and the extracellular signal-regulated Raf/Mek/Erk signaling pathways. Several phosphatases and regulatory proteins act to tightly control the activity of the insulin receptor; substrates are also targeted for regulation (Taniguchi, Emanuelli & Kahn, 2006).

The reactions are chemical modifications carried out by enzymes. The modification of the sub-