

# Comparison of Insulin signaling pathways among 4 species and 3 tissues of

Noriko Hiroi<sup>1,4,5</sup>, Eugene Schuster<sup>1</sup>, Jonathan Ward<sup>1,2</sup>, Matt Piper<sup>3</sup>,  
Akiya Jouraku<sup>4,6</sup>, Akira Funahashi<sup>4,6</sup>  
David Gems<sup>3</sup>, Linda Partridge<sup>3</sup>, Nicolas Le Novère<sup>1</sup> and Janet Thornton<sup>1,3</sup>

1. EMBL-European Bioinformatics Institute (EBI), UK.
  2. European Molecular Biology Laboratory (EMBL), Germany.
  3. University College London (UCL), UK
  4. Keio University, Japan
  5. The University of Tokyo, Japan
  6. The Systems Biology Institute, Japan
- \*email: [noriko.hiroi@ebi.ac.uk](mailto:noriko.hiroi@ebi.ac.uk)

## Introduction

The insulin signaling pathway is one of the most important metabolic systems in multicellular organisms, and is required for controlling energy production and storage. Dysfunction of this pathway triggers severe forms of diabetes. It has been shown recently that insulin signaling has been shown to be involved in the control of longevity and aging, probably via amelioration of molecular damage generated by super oxide etc. The complexity of the insulin signaling pathway and downstream networks requires a system level analysis. We compare here the insulin signaling maps of worm, fruit fly mouse and human in addition to three mouse tissues. These maps are based on information from systematically curated databases of pathways, and should provide a sound basis for future analysis.

## Difference among species

Each map contains around 500 nodes (i.e. states) and 700 edges (transitions between states). The state transition diagrams were represented using CellDesigner (<http://celldesigner.org/>), which uses the Systems Biology Markup Language (SBML, <http://sbml.org/>) as a native model format. The graphical convention follows roughly the nascent Systems Biology Graphical Notation standard (<http://sbgn.org/>). The insulin pathway for each species was constructed from Reactome, KEGG, and literature, and orthologous relationships were taken from Ensembl.

To analyse the difference between maps, we used BiNoM (<http://bioinfo-out.curie.fr/projects/binom/>), an extension for the network analysis software Cytoscape (<http://www.cytoscape.org/>). There are 64 nodes and 55 edges that differ

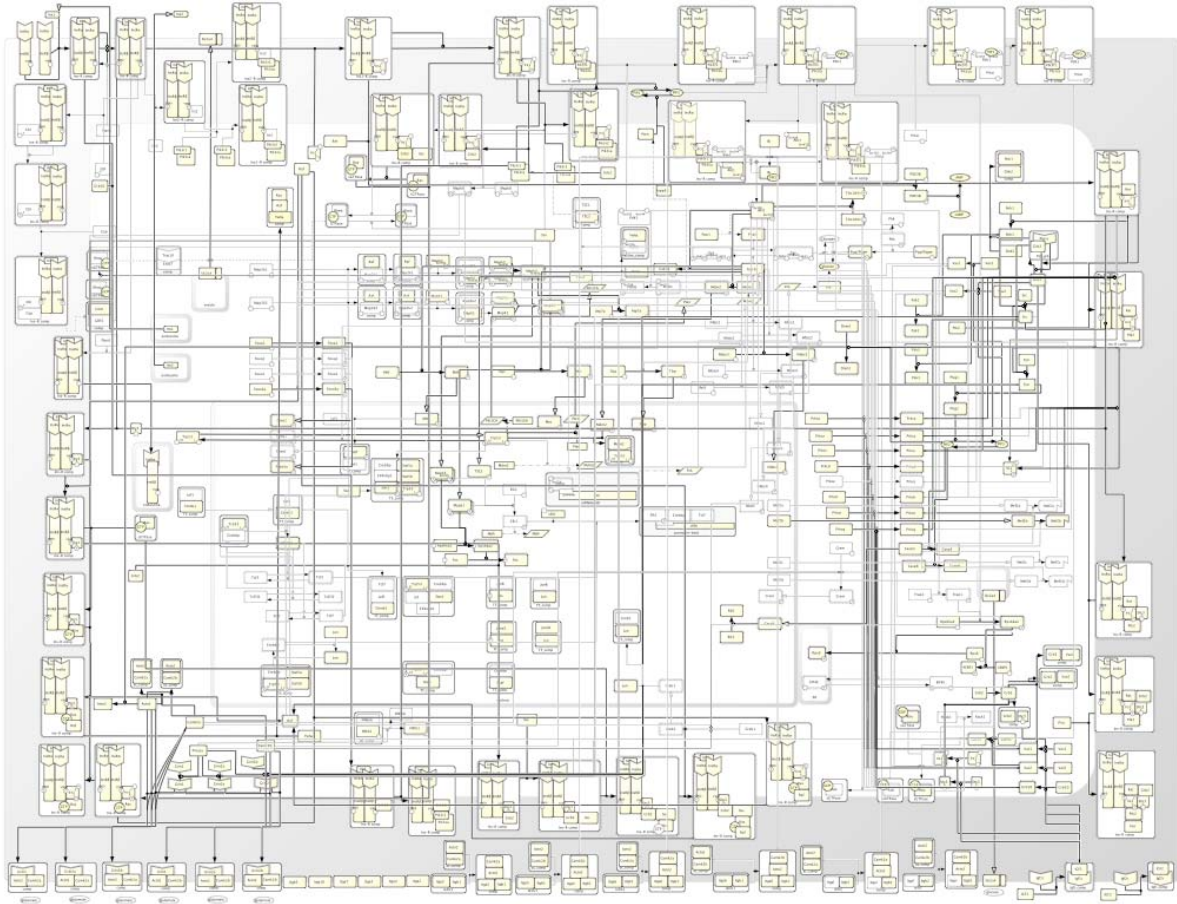
between the mouse and human maps. However, all of these differences are due to orthologues being given alternative names and that, according to current knowledge, these two species possess identical network structures. Our study therefore suggests that the mouse is a good animal model for the analysis of human insulin signaling.

There are 31 nodes and 27 edges in the mouse map that do not have an equivalent in the nematode map. The differences involve transcription factors (Foxq1, Foxa1), a control factor of the translocation of glucose transporter (Cbl), a kinase which is a highly connected node of this signaling network (Akt1) and their reactions. These network components could potentially affect two of the basic functions of the insulin signaling pathway, with Cbl involved in glucose uptake and with Foxa1, Foxq1, affecting gluconeogenesis, both contributing to up-regulation of intracellular glucose. Akt1 is a highly connected node, and is likely to be involved in multiple functions due to the central role of PI3K signaling in many biological processes. The importance of Akt1 as a signaling hub in the insulin signaling network requires further investigation.

The differences between mouse and fruit fly are three times greater than the differences between mouse and nematode. These differences include transcription factors and their regulatory molecules (Foxa3a, Mdm2), molecules regulated by Akt1 (PDE3B, Tbc1d), and IGF1-Vav1 pathway, etc. These data suggest that the differences between mouse and fruit fly involves cell proliferation via Mdm2, and cell migration via the IGF1-Vav1 mechanisms, and could contribute to the different developmental mechanisms of mammals and insects.

### **Difference between tissues**

We also built 3 different maps of mouse tissues: liver, skeletal muscle, and fat cells. These tissues have different metabolic mechanisms that are adapted to their function. Liver tissues take up glucose, muscle stores glycogen, and fat cells store lipids. Our maps suggest that the main combination of ligand and receptor differs for each cell type. Ins1 plays an important role in the liver cells, Ins2 in muscle cells, and IGF2 in fat cells. It should be noted that these differences could have arisen from incomplete datasets, and this fact should be borne in mind when discussing the results and designing further investigations.



**Figure 1.** A comprehensive map of Insulin signaling pathway (Liver cell, mouse). This map includes 550 states of reactants and 725 edges between the states of reactants. The colored molecules are confirmed their expression by experiments in a liver cell. The edges between expressed molecules are drawn with thick black lines.

### **Acknowledgement**

We thank Dr. Andrei Zinovyev (the Institute Curie, France) for kind introduction and supports to use BiNoM.