Differential functional activity and phenotype prediction from gene expression or mutations using models of signalling pathways

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INTRODUCTION

Understanding the aspects of the cell functionality that account for disease or drug action mechanisms is a main challenge. We propose a model of cell signaling that captures changes in the activity of signaling circuits that trigger cell functions. A web tool implementing the method has been developed and is freely available under hipathia.babelomics.org (A).

METHODS

Subpathway definition
Pathways are taken from KEGG [1]. A circuit is defined as the subpathway that connects a receptor node to an effector node, including any intermediary connected node in any path between them.

Signal activity
For a protein to pass the signal, it must be present and active. Signal activity is computed in two steps (B). First a node expression score is computed for each node (B1). Then signal activity is propagated (B2).

Functional analysis
Effector proteins trigger specific functions in the cell. From the matrix of effector circuits a matrix of functions can be inferred, containing an intensity value of signal for each function and for each sample. (C)

RESULTS

Results from an analysis of Breast Cancer are shown. 40 samples (20 normal + 20 tumor) were randomly taken from the TCGA [2] database and compared.

Levels of activity of the pathways allow to understand disease mechanisms.

RESULTS

When a pathway is selected on the pathways list, it is showed in the main window. At the moment, up to 60 pathways are available.

CONCLUSIONS

Models of pathway activity bridge the gap between conventional approaches based on single-gene biomarkers, and more realistic, model-based approaches.

REFERENCES