Charting the SH2 pool

September 13 2012

New research published in BioMed Central's open access journal *Cell Communication and Signaling* describes a large set of interactions (interactome) which maps the range of phosphotyrosine (pTyr)-dependent interactions with SH2 domains underlying insulin (Ins), insulin-like growth factor-1 (IGF-1) and fibroblast growth factor (FGF) signaling pathways.

In the control of cell signaling pathways SH2 domains can be thought of as a master connector and tyrosine kinases the switch. SH2 domains interact with phosphorylated tyrosine containing peptides on receptors and other signaling molecules and couple the kinase to the next protein in the signaling chain.

The human genome contains 111 SH2 domain containing proteins which bind to activated protein tyrosine kinases (PTK). These cell signaling pathways are involved in embryonic development and their mis-regulation is implicated in a wide range of cancers, immunodeficiences and even diabetes.

A panel of 50 SH2 domains was screened for binding against a set of 192 human phosphotyrosine peptides from the FGF and Ins/IGF-1 pathways and found an extensive interactome consisting of over 500 interactions, most of which are novel.

The pool also highlighted the selectivity of individual SH2 domains. Six general classes of SH2 domain specificity were found which demonstrate not only the evolutionary similarities between SH2 domains

in the same family of proteins but across families as well. The study also found subtle differences which could potentially control specificity.

Dr Piers Nash, from The University of Chicago, who led this study observed, "Our study of pTyr binding by SH2 domains is a valuable insight into the selectivity that underpins complex signaling networks. Understanding these signaling systems is a vitally important step towards explaining pathologies such as diabetes and cancer, as well as normal physiology and development."

He continued, "Every cell in our body is an immensely powerful computational device capable of integrating millions of factors and responding with remarkable fidelity. What lies beneath this computational power is not static wires, but dynamic interactions that leverage a finite number of genes to generate an almost infinite number of combinatorial interactions between the protein components that are at the heart of cellular signaling. Mapping the immensely complex set of interactions between the parts laid out by the genetic code represents a next frontier for biomedical science. "

More information: SRC Homology 2 Domain Binding Sites in Insulin, IGF-1 and FGF receptor mediated signaling networks reveal an extensive potential interactome Bernard A Liu, Brett W Engelmann, Karl Jablonowski, Katherine Higginbotham, Andrew B Stergachis and Piers D Nash, *Cell Communication and Signaling* (in press)

Provided by BioMed Central