Yuanpeng Janet Huang et al., J Proteomics Bioinform 2014, 7:8
http://dx.doi.org/10.4172/0974-276X.S1.071

OMICS Group Conferences
Accelerating Scientific Discovery

4th International Conference on
Proteomics & Bioinformatics
August 04-06, 2014 Hilton-Chicago/Northbrook, Chicago, USA

Targeting the human cancer pathway protein interaction network by structural genomics

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Structural genomics provides unique opportunities for characterizing and understanding systems biology. As a step towards better integrating protein 3D structural information in cancer systems biology, we have constructed a Human Cancer Pathway Protein Interaction Network (HCPIN) by analysis of several classical cancer-associated signaling pathways and their proposed physical protein-protein interactions. The current version of HCPIN was constructed by identifying "core proteins" associated with classical cancer-associated cellular processes using the KEGG database, and then expanded to include binding partners of these "core proteins" based on physical protein-protein interaction data (e.g. co-IP, Y2H data) obtained from the Human Protein Reference Database (HPRD). The HCPIN database includes some 4,400 human proteins, with some 15,000 putative pair-wise physical interactions. Many well-known cancer-associated proteins (e.g. p53, NF-kB, EGF receptor, etc) play central roles as "hubs" or "bottlenecks" in the HCPIN. While some 50% of residues in these proteins are in sequence segments that meet criteria sufficient for approximate homology modeling (Blast E-val < 10^{-6}), < 30% of residues in these proteins are structurally covered using high-accuracy homology modeling criteria (i.e. Blast E-val < 10-6 and at least 80% sequence identity) or by actual experimental structures. Since these human protein structures will be used for many different kinds of biophysical studies, we have defined our goal as structural coverage of HCPIN at the 80% sequence identity level, rather than the 30% level used in our other PSI work. The NESG HCPIN website (available at www.nesg.org) provides a comprehensive description of this biomedically important multi-pathway network. It is a useful tool for cancer biology research, providing experimental and homology models of HCPIN proteins, information about their protein partners, and access to extensive expression and sample production data generated by the NESG.

The NESG is targeting > 1,000 human proteins (> 3,000 domains) from the HCPIN for sample production and 3D structure determination. About 100 human protein structures from the HCPIN, including a few complexes, have been determined and deposited in the PDB to date, with several more in final stages of refinement. Information provided on the NESG HCPIN website also includes the experimentally-identified binding partners of each HCPIN protein, as well as information about disorder/order transitions that may occur upon complex formation. These data will drive our efforts to determine structures of HCPIN proteins and their complexes in PSI3:Biology. We will present the NESG progress on the HCPIN protein production and a brief survey of HCPIN protein structures solved by NESG.

Biography

Yuanpeng Janet Huang received her PhD in Molecular Biophysics and Bioinformatics in 2001. Since then, she jointed the Northeast Structural Genomics Consortium (NESG) at Center for Advanced Biotechnology and Medicine, Rutgers-the State University of New Jersey. Dr. Huang is currently an associated research professor at Rutgers, working on structural genomics for cancer protein pathway and develop new methods for structural determination by NMR. She has co-authored over 50 scientific peer-reviewed publications.

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