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R. E. L. A. T. E. D

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02-17-2006

G protein-coupled receptors (GPCRs) are a large superfamily of integral membrane proteins that transduce signals across the cell membrane. Because of the breadth and importance of the physiological roles undertaken by the GPCR family, many of its members are important pharmacological targets. Although the knowledge of a protein's native structure can provide important insight into understanding its function and for the design of new drugs, the experimental determination of the three-dimensional structure of GPCR membrane proteins has proved to be very difficult. This is demonstrated by the fact that there is only one solved GPCR structure (from bovine rhodopsin) deposited in the Protein Data Bank library. In contrast, there are no human GPCR structures in the Protein Data Bank. To address the need for the tertiary structures of human GPCRs, using just sequence information, the authors use a newly developed threading-assembly-refinement method to generate models for all 907 registered GPCRs in the human genome. About 820 GPCRs are anticipated to have correct topology and transmembrane helix arrangement. A subset of the resulting models is validated by comparison with mutagenesis experimental data, and consistent agreement is demonstrated.

In an important step toward accelerating drug discovery, researchers have created computer models of more than 900 cell receptors from a class of proteins known to be important drug targets. The models, which are now freely available to noncommercial users, promise to help scientists narrow their research inquiries, potentially speeding up the discovery of new drug compounds. The research appears in the February 17, 2006 issue of the Public Library of Science Computational Biology.

"This is the first time anyone has modeled them all with an algorithm that improves the accuracy of the structure," said Jeffrey Skolnick Georgia Research Alliance Eminent Scholar in Computational Systems Biology at the Georgia Institute of Technology. "I think

BIOINFORMATICS

- PRIDE: proteomics identifications database
- Human Protein Atlas: tissue profiling
- CPAS: proteomic data publishing
- 2DDB for quantitative proteomics
- BlastPro to identify metastatic cancer marker
- Complex patterns in proteins
- FOLDpro: protein fold recognition
- Secondary-structure guided superposition
- Convergence of proteomic pattern
- Human protein reference database - 2006

PROTEOMICS FUNDINGS

- Clinical Proteomics Assessment - update
- Advanced Proteomic Platforms - update
- NCI Proposal for FY 2007 and Proteomics
- Proteomics in NIDDK's Diseases
- Development of Disease Biomarkers
- Non-Invasive Methods for Diagnosis
- Diabetes Endocrinology & Metabolism
- Technology for Proteomics & Glycomics
- Structural Biology of Membrane Proteins
- PSI Materials Repository

it's going to have significant impact, because it's a major class of drug design."

One of the hottest areas in drug research, rational drug design uses three-dimensional computer simulations to study how different drugs and their cellular targets interact with each other. This technique can help research teams discover which compounds are most likely to achieve the desired results, potentially accelerating the speed of drug research and allowing for the discovery of reactions that may not have been found through traditional means.

G protein-coupled receptors are targeted by an estimated one-third of all drugs and convey chemical signals from the outside of cells to the inside. But because they tend to fall apart once they're removed from the outer membrane of the cell, scientists have only been able to solve the three-dimensional structure for a few of them. And those aren't even good drug targets. Until now, researchers wanting to model any of the others have had to base their models on the structures of the existing, non-pharmacological receptors. Since those receptors, according to Skolnick, are evolutionarily distant from the proteins thought to be good drug targets, the models aren't very accurate.

Using an algorithm they developed known as TASSER, a team of researchers led by Skolnick, then at the University of Buffalo, created three-dimensional structures of all the GPCRs below 500 amino acids in the human genome.

"The solved GPCRs are of the same approximate shape as the ones known to be good drug targets, only they differ in details. But it's the details, the packing of the helices, their angles, their size, that differentiate the drug binding sites of GPCRs from one another," said Skolnick. "TASSER appears to have the capacity to give us a reasonable picture of the structure of these proteins."

Of the 907 models TASSER has helped create, Skolnick estimates that about 820 are accurate enough to be useful to researchers.

"There's still room for significant improvement. They're like cartoons – they kind of look like reality sometimes, but they can be used to help design experiments," said Skolnick.

The mission of the Center for the Study of Systems Biology at Georgia Tech, of which Skolnick is the director, is to essentially simulate life on a computer by building accurate three-dimensional models of the components of life, such as individual proteins and collections of proteins.

"The idea is to simulate these proteins, introduce a drug structure and see how they interact," said Skolnick.

The next step for Skolnick is solving the structure of proteins that have been implicated as a factor in various types of cancer.

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- Fluids proteomic patterns for lung cancer

PROTEOMICS JOBS

- Proteomics, Postdoc
M. D. Anderson Cancer Center
- Proteomics Data Analysis, Investigator
Novartis Institutes for BioMedical Research
- Proteomics, Postdoc
La Jolla Institute for Molecular Medicine
- Faculty Scientist in Systems Biology
Ohio State University
- Proteomics, Faculty
Princeton University

CONFERENCES

Upcoming Conferences

- OncoProteomics World Congress
April 27-28, 2006; So San Francisco, CA
- Tissue and Fluid Biomarkers
May 1-2, 2006; Philadelphia, PA
- Annual Int'l HapMap Project
May 8-10, 2006; Cambridge, MA
- BSPR/EBI Proteomics Meeting
Jul 12-14, 2006; Cambridgeshire, UK
- GPBM/IUBMB: Proteomics for Medicine
July 12-16, 2006; Novosibirsk, Russia

Selected Proteomics Abstracts

- PITTCON 2006 - new
- USHUPO 2006 - new
- ABRF 2006 - new
- HUPO 2005
- 230th ACS
- 53rd ASMS
- AUA 2005
- ASCO 2005
- Digestive Disease Week 2005
- AACR 2005
- Experimental Biology 2005

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All times are ET. Now is 15:50

02-17-2006

[PLoS Comput Biol]
(2006) 2(2): e13

Zhang Y, DeVries ME, Skolnick J

Structure Modeling of All Identified G Protein–Coupled Receptors in the Human Genome

G protein–coupled receptors (GPCRs), encoded by about 5% of human genes, comprise the largest family of integral membrane proteins and act as cell surface receptors responsible for the transduction of endogenous signal into a cellular response. Although tertiary structural information is crucial for function annotation and drug design, there are few experimentally determined GPCR structures. To address this issue, we employ the recently developed threading assembly refinement (TASSER) method to generate structure predictions for all 907 putative GPCRs in the human genome. Unlike traditional homology modeling approaches, TASSER modeling does not require solved homologous template structures; moreover, it often refines the structures closer to native. These features are essential for the comprehensive modeling of all human GPCRs when close homologous templates are absent. Based on a benchmarked confidence score, approximately 820 predicted models should have the correct folds. The majority of GPCR models share the characteristic seven-transmembrane helix topology, but 45 ORFs are predicted to have different structures. This is due to GPCR fragments that are predominantly from extracellular or intracellular domains as well as database annotation errors. Our preliminary validation includes the automated modeling of bovine rhodopsin, the only solved GPCR in the Protein Data Bank. With homologous templates excluded, the final model built by TASSER has a global C_α root-mean-squared deviation from native of 4.6 Å, with a root-mean-squared deviation in the transmembrane helix region of 2.1 Å. Models of several representative GPCRs are compared with mutagenesis and affinity labeling data, and consistent agreement is demonstrated. Structure clustering of the predicted models shows that GPCRs with similar structures tend to belong to a similar functional class even when their sequences are diverse. These results demonstrate the usefulness and robustness of the in silico models for GPCR functional analysis. All predicted GPCR models are freely available for noncommercial users on our Web site (<http://www.bioinformatics.buffalo.edu/GPCR>).

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- » Moving novel genomic testing from the lab into the clinic
- » High accuracy of non-invasive screening for Down syndrome
- » LOC & POC: An intelligent chip for patient testing
- » Clinicians presented new data on a point of care proteomic assay

quest for early detection

- » Prognostic value of urinary albumin protein for cardiovascular risk

- » Three proteins the first diagnostic indicator for ALS identified
- » Multiple plasma biomarkers to predict risk of coronary artery disease
- » TNF protein level predicts graft vs. host disease
- » New protein biomarkers for urothelial cancer
- » CSF biomarkers predict progression to Alzheimer's
- » Preterm birth risk quickly and accurately detected with proteomic profiling
- » Blood test to detect liver cancer early using SELDI-TOF mass spectrometry

CPRMap |+| Clinical Proteomics Research Map |+

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DISEASES & CONDITIONS^[+], Heart and Vascular , Neurodegenerative & Brain^[+], Pulmonary , Obstetric & Gynecologic , {Alzheimer's, Bladder, Breast, Colorectal, Diabetes, Kidney, Liver, Ovarian, Prostate }

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