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Protein tyrosine phosphatases for targeted proteomics research

Tae-Sung Yoon[1], Dae-Gwin Jeong[1], Seung Jun Kim[1], Suk-Kyeong Jung[1], Jae Hoon Kim[2], Sang Jeon Chung[1], Seung-Ho Kim[1], Hwangseo Park[3], Seong-Eon Ryu[1]
[1]KRIBB, Systemic Proteomics Research Center, 111 Gwahangno, Yuseong-gu, Daejeon, 305-806, Korea (S), [2]Faculty of Biotechnology, College of Applied Life Science, Cheju National University, Jeju, 690-756, Korea, [3]Department of Bioscience and Biotechnology, Sejong University, 98 Kunja-Dong, Kwangjin-Ku, Seoul, 143-747, Korea, E-mail：yoonts@kribb.re.kr

Protein tyrosine phosphatases (PTPs) are an important family of signal transduction proteins, together with protein tyrosine kinases, controlling tyrosine phosphorylation which plays a major role in many cellular functions including cell survival, proliferation, and differentiation. There are at least 107 genes coding for PTPs in the human genome. Recently, about half of all PTP genes have been implicated in human disease and recognized as potential drug targets. PTPs have a conserved catalytic domain and show some subtle structural differences in the active-site residues. The detailed structural information of PTPs will enable us to verify the interaction between substrates and the active-site residues and provide a solid foundation for rational PTP inhibitor design. To this end, the catalytic domains of 56 human PTPs (RPTPalpha, RPTPbeta, LAR, SAP1, DEP1, RPTPkappa, RPTPmu, IA-2, IA-2beta, PTP-U2, PCPTP, RPTPsigma, PTPRT, PTP1B, TCPTP, STEP, SHP1, HePTP, SHP2, PTP-BAS, PTP36, PTPD1, MKP-1, MKP-2, hVH3/B23, PYST1, PYST2, hVH5, MKP-4, MKP-5, MKP-7, VHR, PIR1, HYVH1, BEDP, TMDP, VHY, DUSP20, DUSP17, DUSP21, VHX, MOSP, MGC1136, VHZ, MCE, SSH1, SSH2, PRL1, PRL2, PRL3, CDC14B, LMPTP, CDC25A, CDC25B, CDC25C, Eya2) were well expressed in E. coli and subjected to the crystallization screening. Among them, more than 16 PTPs were successfully crystallized and some of their structural analyses have been reported. Especially with our recent structural report of SSH2, comparative analysis between seven sub-families (MKPs, atypical DSPs, SSHs, PRLs, CDC14s, PTENs, MTMs) of DSPs or VH1-like PTPs (61 genes) would be possible. With these results, our targeted proteomics research efforts involving mass spectrometric analysis will be also discussed.

Keywords: protein tyrosine phosphatase, crystal structure, proteomics

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Joint center for structural genomics: Tools and resources for the community

Marc A Elsliger[1,6], Ashley M Deacon[2,6], Adam Godzik[3,6], Scott A Lesley[4,6], John A Wooley[5,6], Ian A Wilson[1,6]
[1]The Scripps Research Institute, The Joint Center for Structural Genomics, 10550 North Torrey Pine Rd, La Jolla, California, 92037, USA, [2]Stanford Synchrotron Radiation Laboratory, [3]The Burnham Institute, [4]The Genomics Inst. of the Novartis Research Foundation, [5]University of California, San Diego, [6]The Joint Center for Structural Genomics, E-mail：elsliger@scripps.edu

The Joint Center for Structural Genomics (www.jcsg.org) is one of the 4 large-scale Production centers funded by the NIGMS Protein Structure Initiative. A major goal of the JCSG is to ensure that the HT approaches, that we have developed and integrated into our pipeline over the past 8 years, not only advance the fields of structural genomics and structural biology, but also other biological sciences. Over the years, we have optimized our pipeline to maximize the productivity and minimize the effort, resources and cost associated with processing targets. By optimizing target flow through the pipeline, we are currently producing ~200 novel structures (< 30% seq. id. to any PDB) per year. To maintain and increase production schedules, we have developed sets of tools based on processing large amounts of data through the various stages of our experimental pipeline. Many of these tools, which cover key components of the gene-to-structure process, have recently been converted to open-access, web-based tools and applications. Key representative examples are the XtalPred (ffas.burnham.org/XtalPred), Structure Validation (smb.slac.stanford.edu/~crife) and Ligand Database (smb.slac.stanford.edu/public/jcsg/cgi/jcsg_ligand_check.pl) servers and the TOPSAN portal (www.topsan.org). We believe these resources are of high value to the general scientific community and we welcome feedback and comments. The JCSG is funded by NIGMS/PSI, U54 GM072898.

Keywords: structural genomics, high throughput, structural biology

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Crystal structure of RimO from *Thermotoga maritima*

Farhad Forouhar[1], Farhad Forouhar[1], Helen Neely[1], Munif Hussain[1], Rong Xiao[2], Jinfeng Liu[3], Thomas B Acton[2], Burkhard Rost[3], Gaetano T Montelione[2], John F Hunt[1]
[1]Columbia University, Biological Sciences, 1212 Amsterdam Ave., New York, NY, 10027, USA, [2]Rutgers University, Center for Advanced Biotechnology and Medicine, Northeast Structural Genomics Consortium, Piscataway, NJ 08854, USA, [3]Columbia University, Department of Biochemistry & Molecular Biophysics, Northeast Structural Genomics Consortium, New York, NY 10032, USA, E-mail：farhadf@biology.columbia.edu

RimO is a MiaB-like protein that belongs to the Radical-SAM superfamily whose members function as methylthiotransferases. It inserts a sulphur atom at the beta-carbon of the strickly conserved Asp89 of the ribosomal protein S12 followed by methylation using S-adenosylmethionine. The sequence alignment of MiaB and MiaB-like proteins suggest that they belong to a special group of enzymes within the Radical-SAM superfamily as they share three domains: UPF0004, Radical-SAM, and TRAM. Recent studies on MiaB revealed that UPF004 and Radical-SAM bind two iron-sulphur clusters (4Fe4S) by six conserved cysteines. Whereas the TRAM domain of MiaB interacts with tRNA, that of RimO likely interacts with Ribosomal S12. Here we report the crystal structure of RimO (TM1862) from Thermotoga maritima at 2.0 Å resolution. The structure reveals that an acidic patch lies at the interface of the Radical-SAM and the TRAM domains, which likely is the site that interacts with the Ribosomal protein S12.

Keywords: crystallography biological, crystal structure determination, structure