m07a.o03

Serendipitous discovery of a human phosphate binding apolipoprotein

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Keywords: atherosclerosis, chemical warfare agents, gene missing

We report the serendipitous discovery of a human plasma phosphate binding protein (HPBP). This 38 kDa protein is co-purified with paraoxonase (HPON1) [1]. Paraoxonase, named for its ability to hydrolyse the insecticide paraoxon, is the matter of intensive research owing to its capability to inactivate various organophosphorous esters, including nerve agents and pesticides, representing both a terrorist threat and an environmental hazard. The association between HPON1 and HPBP is modulated by phosphate and calcium concentrations. Due to initial difficulties in obtaining heavy atom derivatives, the protein envelope was initially determined *ab initio* at 25 Å resolution [2]. Subsequenly, the HPBP X-ray structure was solved at 1.9 Å résolution [3,4]. This structure is similar to the prokaryotic phosphate solute-binding proteins (SBPs) associated with ATP binding cassette transmembrane transporters, though phosphate-SBPs have never been characterized or predicted from nucleic acid databases in eukaryotes. However, HPBP belongs to the family of ubiquitous eukaryotic proteins named DING, meaning that phosphate-SBPs are also widespread in eukaryotes. The absence of complete genes for eukaryotic phosphate-SBP from databases is intriguing, but the astonishing 90% sequence conservation of genes between evolutionary distant species suggests that the corresponding proteins play an important function. HPBP is the first identified transporter capable of binding phosphate ions in human plasma. Thus its is thought to become a new predictor and a potential therapeutic agent for phosphate-related diseases such as atherosclerosis.

[1] Renault F., Chabrière E., Andrieu J.P., Dublet B., Masson P., Rochu D. *J. Chromatog. B,* 2006, 836, 15-21.
[2] Fokine A., Morales R., Contreras-Martel C., Carpentier P., Renault F., Rochu D., Chabriere E. *Acta Cryst.* 2003, D55, 2083.
[3] Morales R., Berna A., Carpentier P., Contreras-Martel C., Renault F., Nicodeme F., Chesne-Seck M.L., Bernier F., Dupuy J., Schaeffer C., Diemer H., Van-Dorsselaer A., Fontecilla-Camps J.C., Masson P., Rochu D., Chabriere E. *Structure* 2006, 14, 601-609.
[4] Contreras-Martel C., Carpentier P., Morales R. , Renault F., Chesne-Seck M.L., Rochu D., Masson P., Fontecilla-Camps J.C., Chabriere E. *Acta Cryst.* 2006, F62, 67.

m07a.o04

Chaperone-subunit complex recognition by the type 1 pilus assembly platform FimD

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Keywords: biomolecular recognition, protein disorder, bacterial pili

In uropathogenic *Escherichia coli* strains, type 1 pili enable bacterial attachment to mannose units of the glycoprotein receptor uroplakin Ia on the surface of urinary epithelium cells, thus mediating the first critical step in the infection process. Type 1 pili are filamentous protein complexes that are attached to the assembly platform FimD in the outer membrane. During pilus assembly, FimD binds complexes between the chaperone FimC and type 1 pilus subunits in the periplasm and mediates subunit translocation to the cell surface [1]. We have determined the X-ray and NMR structures of the N-terminal domain of FimD ($FimD_N$) before and after binding of a chaperone-subunit complex (FimC-$FimH_P$). The structures, together with *in vivo* complementation studies, provide snapshots of the initial step of type 1 pilus formation at the assembly platform site [2]. $FimD_N$ is composed of a flexible N-terminal segment of 24 residues, of a structured core with a novel fold and of a C-terminal hinge segment. In the ternary complex ($FimD_N$-FimC-$FimH_P$), residues 1_24 of $FimD_N$, which are flexibly disordered in the absence of ligands, adopt a defined conformation and specifically interact with both FimC and the $FimH_P$ subunit, acting as a sensor for loaded FimC molecules. This unique mechanism enables recognition and discrimination of different chaperone-subunit complexes by the bacterial pilus assembly platform. In addition to the above results (which were rated of exceptional interest by Faculty of 1000 Biology [3]), the latest structural findings on the system will be described.

[1] Capitani G., Eidam O., Glockshuber, R. & Grütter, M.G. *Microbes Infect.* 2006, in press.
[2] Nishiyama M., Horst R., Eidam O., Herrmann T., Ignatov O., Vetsch M., Bettendorff P., Jelesarov I., Grütter M.G., Wüthrich K., Glockshuber R., Capitani G. *EMBO J.*, 2005, 24, 2075.
[3] Faculty of 1000 Biology: evaluations for Nishiyama et al., *EMBO J*, 2005, 24, 2075: *http://www.f1000biology.com/article/15920478*.