Crystal Structure of Rv0813c Reveals a New Family of Putative FABPs

William Shepard[a], A. Haouz[b], A. Buschiazzo[b], J.M. Betton[b], S.T. Cole[b], P. Alzari[b], [a]*ESRF, 6 rue Jules Horowitz, BP 220, 38043 Grenoble cedex 9, France,* [b]*Institut Pasteur 25 rue du Dr. Roux, 75724 Paris cedex 15, France.* E-mail: shepard@esrf.fr

Rv0813c is a protein of unknown function that we have selected as a target for crystallographic studies in the context of a structural genomics effort on tuberculosis. The crystal structure of Rv0813c, a conserved protein in *M. tuberculosis*, reveals a new family of putative fatty acid binding proteins (FABPs). Rv0813c adopts a 10-stranded beta barrel fold, which closely resembles those of the FABPs found in eukaryotes. This is in fact the first FABP-like protein to be found in prokaryotes. However, Rv0813c lacks the double helix insert of FABPs that covers the entry to the binding site. The beta barrel forms a deep cavity, where a small ligand, which appears to be a morpholine, binds to the phenol hydroxyl group of Tyr192. This tyrosine corresponds to a RxY motif, which forms part of the binding site in FABPs. Furthermore, a network of H bonds, hydrophobic residues and an internal salt bridge surround the binding site and define the shape of the cavity. Most of these residues are well conserved in homologous proteins. Phylogenetic studies show that this family of FABP-like proteins is represented in GC-rich prokaryotes. The structural analysis of Rv0813 suggests that this cytoplasmic protein may have a role in fatty acid transport, storage or signaling. This work supports the notion that high resolution structural studies can provide strong leads as to the biochemical function(s) of the protein.

Keywords: structural genomics, mycobacteria, fatty acid binding protein