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The Structure of Ce-FAR-7 from *C. Elegans* Indicates How This Family of Nematode Fatty Acid and Retinoid Binding Proteins Bind Their Cargo. Rositsa Jordanova[a], Matthew R. Groves[a], Elena Kostova[a], Christian Woltersdorf[b], Eva Liebau[b], Paul A. Tucker[a]. [a]*European Molecular Biology Laboratory, Hamburg Outstation, Hamburg, Germany.* [b]*Institute of Animal Physiology, University of Muenster, Muenster, Germany.*
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Parasitic nematodes cause serious diseases in humans and animals, economically impacting agricultural industries. Chemoprophylaxis offers short-term benefits, but due to rapid development of drug resistance in parasites there is a pressing need for novel treatments of nematode infections. Lipid binding proteins (LBPs) play an important role in parasitic nematode's limited lipid metabolism. Several structurally novel families of LBPs in nematodes have been described, including the fatty acid and retinoid binding protein family (FAR). In *C. elegans*, used as a model for studying parasitic nematodes, eight Ce-FAR proteins have been described. Here we report the first high resolution structure of a FAR protein – the 1.8 Å crystal structure of Ce-FAR-7. Ce-FAR-7 has nine helices, packed into a novel fold containing two hydrophobic binding pockets. Pocket P1 can accommodate fatty acids with different length of the aliphatic chain, whereas P2 is more suitable for bulkier ligands like retinoids and other signaling lipids. Our results suggest that retinol binding can be upregulated by casein kinase 2, via phosphorylation of Thr26 positioned at the bottom of the pocket P2. GFP localization in vivo shows, that Ce-FAR-7 is intracellular and present in all development stages of the nematode. It is mainly localized in the excretory cell and head hypodermis region of the worm. However, during starvation its localization changes and Ce-FAR-7 is expressed in the body hypodermis. In conclusion, our study provides the basic structural and functional information for investigation of inhibitors of lipid binding by FAR proteins, which could result in new generation of anti-nematode drugs.

Keywords: fatty acid and retinoid binding; nematode metabolism; phosphorylation

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Structural and Functional Analysis of PhnP from Carbon-Phosphorous Lyase Pathway. Kateryna Podzelinska[a], Shu-Mei He[b], Matthew Wathier[b], Alexander Yakunin[c], Michael Proudfoot[c], Bjarne Hove-Jensen[d], David L. Zechel[b], Zongchao Jia[a]. *Departments of* [a]*Biochemistry and* [b]*Chemistry, Queen's University, Kingston, Canada, the* [c]*Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada, and the* [d]*Department of Biology, University of Copenhagen, Copenhagen, Denmark.*
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Free phosphate availability in nature can be a limiting factor for bacterial growth. During phosphate limitation, bacteria exhibit many hundred fold upregulation of a C-P lyase pathway to obtain phosphate from phosphate esters and organophosphonates. The C-P lyase operon consists of 14 genes (phnCDEFGHIJKLMNOP). Based on mutational and sequence analysis, gene products PhnC to PhnE are thought to be involved in transport of substrates, PhnF is a transcription repressor protein, PhnO is an aminoalkylphosphonate N-acetyltransferase, PhnG to PhnM are enzymes involved in C-P bond cleavage, and PhnN is a ribose 1,5-bisphosphokinase. Mutational studies suggest that PhnP is required in the presence of a functional phnN product for phosphonate utilization. In order to determine the role of PhnP in the C-P lyase pathway, structural studies have been undertaken. The three-dimensional crystal structure of PhnP was determined at 1.4 Å resolution and exhibits significant similarity to Zn-dependent ribonucleases. Phosphodiesterase substrate screen has identified 2'3'-cyclic nucleotides as substrates for PhnP, and cellulose TLC showed that 3'- nucleotides are the products. Interestingly, PhnP contains both Zn and Mn as determined by IPC-MS analysis. Kinetic studies revealed that PhnP enzymatic activity is Mn- but not Zn-dependent. Mutagenesis was used to elucidate the roles of active site residues, and the enzymatic mechanism was proposed. (Supported by NSECR and CIHR)

Keywords: phosphodiesterase; C-P lyase; organophosphonate metabolism

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Crystal Structure of the Full-length Sorbitol Operon Regulator SorC from *Klebsiella Pneumoniae*: Structural Evidence for a Novel Transcriptional Regulation Mechanism. Daniele de Sanctis[a,b], Colin E. McVey[b] , Francisco J. Enguita[c], Maria Armenia Carrondo[b]. [a]*Structural Biology Group, European Synchrotron Radiation Facility, Grenoble, France.* [b]*Instituto de Tecnologia Química e Biológica, Oeiras, Portugal.* [c]*Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Portugal.*
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SorC transcriptional regulators are common regulators in prokaryotes. Here we report the first crystal structure of a full-length SorC, the sorbitol operon regulator SorC from Klebsiella pneumoniae, the prototype of its family. SorC was found to be a homotetramer (which seems to be the biologically active form) that is able to recognize its DNA operator. The tetramer can be regarded as a dimer of dimers, with each dimer being composed of two identical subunits in different conformations. The DNA-binding domains divergently protrude from the core of the tetramer, suggesting that SorC may bind its operator in two distinct regions. The sugar-binding domain presents the same fold identified in members of the SorC family that shows some features identified as specific for sugar recognition. An in