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Structural analysis of GNAT acetyltransferases and protein acetylation

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The Center for Structural Genomics for Infectious Diseases (CSGID) applies structural genomics approaches to biomedically relevant proteins from human pathogens and provides the infectious disease community with a high throughput pipeline for structure determination. Target proteins include drug targets, essential enzymes, virulence factors and vaccine candidates. Bacterial species generally have many acetyl-coenzyme A dependent GCN5-like Acetyl Transferases (GNATs), however, the substrates of most of them are unknown. Proteomic analysis has also revealed extensive post-translational modification of bacterial proteins, especially acetylation of lysine Ne. These observations led the CSGID to develop a high throughput substrate screen and initiate characterization of bacterial GNATs. One of the bacterial GNATs that acetylates lysine residues, is the Pseudomonas aeruginosa protein PA4794, that acetylates both peptides having a C-terminal lysine and the drug, chloramphenicol. Surprisingly, the acetylation of these two substrates by PA4794 is catalyzed by the enzyme using different active site residues and different kinetic mechanisms. Although it was expected that the GNATs would play a major role in protein acetylation, much of the lysine acetylation observed in bacteria is actually due to the metabolite acetylphosphate (1,2). Crystal structures and proteomics experiments revealed what makes some lysine residues particularly sensitive to acetylphosphate dependent lysine acetylation and what is required for subsequent enzymatic deacetylation. CSGID is funded with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contracts No. HHSN272200700058C and HHSN272201200026C and Midwest Center for Structural Genomics by grant GM094585

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