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Biosynthesis and Secretion of Bacterial Siderophores

Research Interests

Protein-protein interactions are necessary for most cellular processes. Finding ways to 'disarm' the virulence of pathogenic bacteria by disrupting protein-protein interactions in vivo may eventually lead to a powerful new class of antibiotics. Ferric iron (Fe^{3+}) is an essential nutrient for most bacteria, but this element is very scarce in the extracellular environment. To obtain scarce yet essential iron, bacteria employ molecules called siderophores that chelate Fe^{3+} with high affinity. Bacteria synthesize siderophores in the cytoplasm and secrete them to scavenge iron from their environment. We still know very little about how proteins involved in bacterial siderophore biosynthesis and secretion co-ordinate their functions through protein-protein interactions. We are currently using E. coli K12 as a model organism in order to investigate how proteins involved in the biosynthesis and secretion of the E. coli siderophore enterobactin form specific complexes to enhance biosynthesis of this siderophore and its subsequent transport through the Gram-negative cell envelope. This will help us better understand how pathogenic bacteria use siderophores as virulence factors to cause diseases in host organisms.

We use analytical fluorescence spectroscopy, analytical ultracentrifugation (AUC), isothermal titration calorimetry (ITC), and circular dichroism (CD) to perform biophysical characterizations of interactions between recombinant proteins from the enterobactin biosynthetic pathway. We are also studying the enterobactin membrane transporter EntS, to better understand its structure and function in relation to the enterobactin biosynthetic machinery. Novel protein-protein complexes that we identify will be crystallized when possible. We can then employ X-ray crystallography to characterize their interaction interfaces at the atomic level. Such information will aid in the development of compounds (small molecules, peptide aptamers) that could specifically disrupt protein-protein interaction interfaces.

Selected Publications

Khalil, S. and Pawelek, P.D. (2009) "Ligand-Induced Conformational Rearrangements Promote Interaction between the Escherichia coli Enterobactin Biosynthetic Proteins EntE and EntB." Journal of Molecular Biology, 393 658-671.

Lei, Y., Pawelek, P.D., and Powlowski, J. (2008) "A shared binding site for NAD+ and coenzyme A in an acetaldehyde dehydrogenase involved in bacterial degradation of aromatic compounds." Biochemistry, 47 6870-6882.

Carter, D.M, Miousse, I.R., Gagnon, J.-N., Martinez, E., Clements, A., Lee, J., Hancock, M.A., Gagnon, H., Pawelek, P.D., and Coulton, J.W. (2006) "Interactions Between TonB from Escherichia coli and the Periplasmic Protein FhuD." Journal of Biological Chemistry, 281 35413-35424.

Pawelek, P.D., Croteau, N., Ng-Thow-Hing, C., Khursigara, C.M., Moiseeva, N., Allaire, M., and Coulton, J.W. (2006) "Structure of TonB in Complex with FhuA, E. coli Outer Membrane Receptor." Science, 312 1399-1402.

Carter, D.M., Gagnon, J.-N., Damlaj, M., Mandava, S., Makowski, L., Rodi, D.J., Pawelek, P.D., and Coulton, J.W. (2006) "Phage Display Reveals Multiple Contact Sites Between FhuA, an Outer Membrane Receptor of Escherichia coli, and TonB." Journal of Molecular Biology, 357 236-251.

Eisenhauer, H.A., Shames, S., Pawelek, P.D., and Coulton, J.W. (2005) "Siderophore Transport Through Escherichia coli Outer Membrane Receptor FhuA with Disulfide-Tethered Cork and Barrel Domains." Journal of Biological Chemistry, 280 30574-30580.

Khursigara, C.M, De Crescenzo, G., Pawelek, P.D., and Coulton, J.W. (2005) "Deletion of the Proline-Rich Region of TonB Disrupts Formation of a 2:1 complex with FhuA, an Outer Membrane Receptor of Escherichia coli." Protein Science, 14 1266-1273.