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HcaR Ligand and DNA Interactions in the Regulation of Catabolic Gene Expression

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Precise tuning of gene expression by transcriptional regulators determines the response to internal and external chemical signals and adjusts the metabolic machinery for many cellular processes. As a part of ongoing efforts by the Midwest Center for Structural Genomics, a number of transcription factors were selected to study protein-ligand and protein-DNA interactions. HcaR, a new member of the MarR/SlyA family of transcription regulators from soil bacteria Acinetobacter sp. ADP1, is an evolutionarily atypical regulator and represses hydroxycinnamate (hca) catabolic genes. Hydroxycinnamates containing an aromatic ring play diverse, critical roles in plant architecture and defense. HcaR regulates the expression of the hca catabolic operon, allowing this and related bacterial strains to utilize hydroxycinnamates: ferulate, p-coumarate, and caffeate as sole sources of carbon and energy. HcaR appears to be capable of responding to multiple aromatic ligands. These aromatic compounds bind to HcaR and reduce its affinity to the specific DNA sites. As a result, the transcription of genes encoding several catabolic enzymes is up-regulated. The HcaR structures of the apo-form and in a complex with several ligands: ferulic acid, 3,4 dihydroxybenzoic acid, vanillin and p-coumaric acid have been determined to understand how HcaR accommodates various aromatic compounds using the same binding pocket. We also have identified a potential DNA site for HcaR in the regulatory region upstream of the genes of the hca catabolic operon in Acinetobacter sp. ADP1 and have confirmed DNA binding by EMSA. The co-crystal structure of HcaR and palindromic 24-mer DNA has been determined for this DNA site. The crystal structures of HcaR, the apo-form, ligand-bound forms, and the specific DNA-bound form provide critical structural basis of protein-ligand (substrates or product) and protein-DNA interactions to understand the regulation of the expression of hydroxycinnamate (hca) catabolic genes. Our studies allow for better understanding of DNA-binding and regulation by this important group of transcription factors belonging to the MarR/SlyA families. This work was supported by National Institutes of Health grant GM094585 and by the U. S. Department of Energy, Office of Biological and Environmental Research, under contract DE-AC02-06CH11357.

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