Journal of Proteomics & Bioinformatics - Open Access
www.omicsonline.com Abstract No.009 JPB/Vol.S2/July 2008/Special Issue

Discrimination Between DNA Sequences and Between Coregulator Amino Acids by Feast/Famine Regulatory Proteins (FFRPs)

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Homologues of *Escherichia coli* leucine-responsive regulatory proteins (Lrp) are referred to as Feast/Famine Regulatory Proteins (FFRPs). They compose a unique group of transcription factors systematically distributing throughout archaea and eubacteria.

An archaeal FFRP, FL11 from *Pyrococcus* sp. OT3 was crystallized in its dimer form in complex with a DNA duplex, TGAAAWWWTTTCA. Ala34-Thr37 in the loop connecting alpha helices 2 and 3, and two other residues, Leu24 and His39, in each monomer contacted 5 bps at each terminus of the target DNA. These contacts and DNA bending by propeller twisting at WWW confirmed specificity of the interaction. Dimer-binding sites were identified in the promoters of approximately 200 transcription units, i.e. 20% of all units, coding, for example, proton ATPase and NAD(P)H dehydrogenase, synthesizing ATP by degrading amino acids.

In the presence of lysine, four FL11 dimers were shown to assemble into an octamer, thereby covering the *fl11* promoter. The FL11 octamer was crystallized in complex with eight lysine molecules. Between each pair of dimers two lysine molecules were present. Asp104 of one dimer contacted the N-terminus of a lysine molecule, and Thr132 and Thr135 of the other dimer contacted its C-terminus. Some other residues of the two dimers, including of Gln98 and Asp122, interacted with the lysine side-chain.

In the "feast" mode in the presence of lysine, when *P*. OT3 grows on amino acids, the FL11 octamer will terminate transcription of *fl11*, as was shown *in vitro*, thereby derepressing transcription of many metabolic genes. In the "famine"

Proceedings of The Joint 2nd Pacific Rim International Conference on Protein Science and 4th Asian-Oceania Human Proteome Organization, Cairns- Australia, 22-26 June 2008

Journal of Proteomics & Bioinformatics (JPB) Volume S2:011-012(2008)
ISSN:0974-276X JPB, an open access journal

mode in the absence of lysine, approximately 6000 FL11 dimers present per cell will arrest growth. This regulation resembles another global regulation by *E. coli* Lrp in response to the availability of leucine, and hints at the prototype of transcription regulations, once achieved in the last common ancestor of all extant organisms.

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ISSN:0974-276X JPB, an open access journal