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Structure of *Mycobacterium tuberculosis* PyrR: A Persistence Gene and Drug Target. C. Vasquez¹, K.A. Kantardjieff¹, B-S. Rho², T. Legin³, C.Y. Kim², B.W. Segelke³, T. Terwilliger², B. Rupp³, ¹Keck Center for Molecular Structure, CSU Fullerton, ²Los Alamos National Laboratory, ³Lawrence Livermore National Laboratory.

Mtb pyrR regulates expression of genes and operons of pyrimidine nucleotide biosynthesis (*pyr* genes), an essential step in the progression of TB. When intracellular levels of uridine nucleotides are elevated, a pyrR-UMP complex binds specific sequences on *pyr* mRNA, causing transcriptional attenuation. *PyrR* is upregulated during hypoxic stress, characteristic of the environment found in the granuloma harboring *Mtb*. The 1.9Å structure of *Mtb* pyrR has been determined by molecular replacement in space group P 3₁21, with cell dimensions at 120K of $a = 64.57 \text{ \AA}$, $c = 156.74 \text{ \AA}$, freeR=0.244, R=0.206, and two molecules in the asymmetric unit. The homodimer forms a positively charged mRNA binding cleft. Each monomer consists of a core parallel β -sheet domain, reminiscent of the related UPRTases, and a distinct antiparallel β -sheet hood domain. The weak UPRTase activity of *Mtb* pyrR is explained by structural determinants of the active site. Virtual ligand screening has identified potential drug leads.



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