

### **Enzymes of nucleotide metabolism adapted to regulatory function**

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Phosphoribosyltransferases (PRTases) are key enzymes of nucleotide metabolism. They catalyze the interconversion of 5-phosphoribose- $\alpha$ -1-pyrophosphate (PRPP) and a  $\beta$ -1-substituted ribose-5-phosphate. All PRTases of nucleotide metabolism are members of the “PRT” protein family, which has a common core domain for binding PRPP. Two PRT family members do not have primary catalytic functions, but are regulators of transcription in some gram positive bacteria. PurR is a transcription repressor of purine biosynthetic genes, and PyrR is an attenuator of pyrimidine biosynthetic genes. By sequence analysis, both regulatory proteins are most closely related to hypoxanthine/guanine PRTases. The crystal structures of PurR and PyrR confirm the PRT homology and demonstrate how the PRT fold has been adapted from a catalytic to a regulatory function. PurR has no detectable catalytic activity, but exploits a PRPP-binding site to repress transcription by binding to specific sequences in the upstream control region of purine genes in a PRPP-dependent manner. PurR recognizes a pseudo-palindromic sequences separated by 35 base pairs, presumably through a fused helix-turn-helix domain. PyrR has low-level uracil PRTase activity, but its biological function is to regulate pyrimidine biosynthesis in a UMP-dependent manner. The structure of *Bacillus caldolyticus* PyrR showed that it binds GMP and UMP with similar base-specific hydrogen bonds. Subsequent studies established that GMP and UMP have opposite effects on transcription.

### **GENE EXPRESSION PROFILES IN HPRT-DEFICIENT MOUSE BRAIN.**

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Although there is a well-understood and direct effect of altered purine metabolism in Lesch Nyhan Disease on some of the biochemical hallmarks of the disorder; i.e. hyperuricemia, the mechanisms by which HPRT gene mutations and the resulting deficient expression of HPRT enzyme activity lead to CNS dysfunction are less well understood. We have hypothesized that at least part of the CNS pathogenesis results from aberrant expression of genes that regulate some of the complex systems interactions of HPRT with many other neurotransmitter, metabolic and other pathways in the brain. We have used whole mouse genome microarray chips to carry out extensive transcriptional studies in the wild type and HPRT-deficient mouse striatum and liver and in human HPRT-deficient fibroblasts derived from patients with LND. We have identified modest but broad aberrations in the expression of genes associated with a number of metabolic pathways, including purine biosynthesis, protein biosynthesis and other cellular functions. We interpret our findings to be consistent with the concept that the abnormal

expression of some of these secondarily aberrant genes may contribute to the CNS dysfunction of LND, and that LND may serve as a model for understanding the ways in which apparently “simple” single gene disorders can reflect multigenic pathogenic mechanisms.