Crystal structure of GTP cyclohydrolase I complexed with its feedback regulatory protein GFRP

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In animals, tetrahydrobiopterin (BH4) is an essential cofactor for key enzymes producing nitric oxide and neurotransmitters such as catecholamines and serotonin and thus involved in diverse body functions including neurotransmission, blood pressure regulation, immune function, and the conversion of phenylalanine to tyrosine. GTP cyclohydrolase I (GTPCHI) is a zinc containing enzyme that converts GTP to a precursor of BH4 at the rate-limiting step in the biosynthesis of BH4. In the presence of phenylalanine, GTP cyclohydrolase I feedback regulatory protein (GFRP) forms a stimulatory 360 kDa-complex with GTPCHI. The crystal structure of the stimulatory complex reveals that the GTPCHI decamer is sandwiched by two GFRP homo-pentamers. Each GFRP pentamer forms a symmetrical five-membered ring similar to beta-propeller. Five phenylalanine molecules are buried inside each interface between GFRP and GTPCHI, thus enhancing the binding of these proteins. The complex structure suggests that phenylalanine-induced GTPCHI-GFRP complex formation enhances GTPCHI activity by locking the enzyme in the active state.