

The impact of the C-terminal peptide extension in retinal IMPDH(546) variant in response to allosteric regulation with purine nucleotides

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Abstract

Inosine monophosphate dehydrogenase (IMPDH) controls the gateway to guanine nucleotides. The IMPDH-catalyzed conversion of IMP to XMP is the rate-limiting step in guanine nucleotide biosynthesis. XMP is converted to GMP by the action of GMP synthetase. Humans have two IMPDH genes, hIMPDH1 and hIMPDH2. Polymerization and enzyme activity are regulated in part by binding of purine nucleotides to an allosteric regulatory domain. In solution, the basic units of IMPDHs are homotetramers that can dimerize in different ways to form octamers or higher-order oligomers. In this report, we are aimed to evaluate the mode of allosteric regulation of two of the retinal isoforms, mainly IMPDH1(514) and IMPDH1(546), via their structural variation. The monomeric units of the each enzyme were associated to create large macromolecular structures under the influence of GTP the formation of macromolecular structures was prevented. Our results indicated that induction or inhibition of IMPDH1(514 and 546 variants) by the allosteric modulators (ATP and/or GTP, respectively) occurs mainly via structural association/disassociation of the structural building blocks of the monomeric subunits.

Key Words: IMPDH1, retinal isoforms, structure