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Functional CBS modules make IMPDHs octameric

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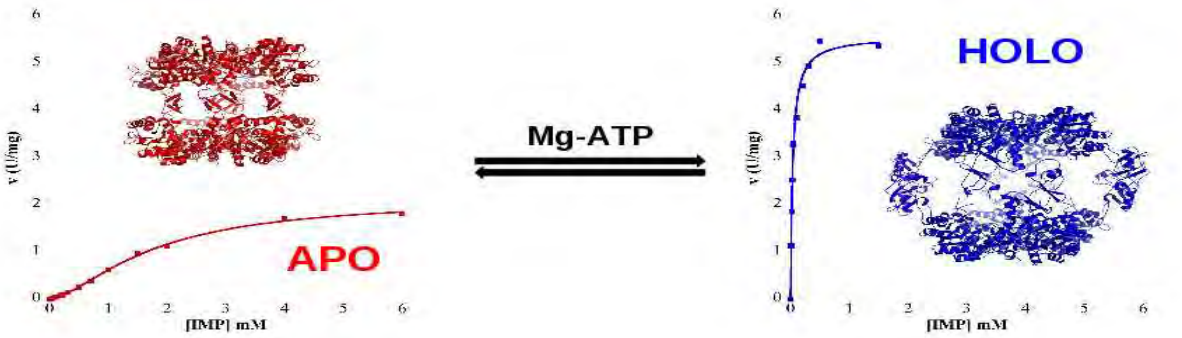
Inosine-5'-monophosphate dehydrogenase (1, 2) (IMPDH) is a major target for antiviral, antiparasitic, antileukemic and immunosuppressive therapies. It is an ubiquitous and essential enzyme for the biosynthesis of guanosine nucleotides. Up to now, IMPDHs have been reported as tetrameric enzymes harbouring a catalytic domain and a tandem of cystathionine-ß-synthase (CBS) modules. The latter had no precise function assigned despite their nearly absolute conservation among IMPDHs and consistent indication of their importance in vivo. The aim of our study was to provide evidence for the role of the CBS modules on the quaternary structure and on the regulation of IMPDHs. A multidisciplinary approach involving enzymology, site-directed mutagenesis, analytical ultracentrifugation, X-ray crystallography, SAXS, cryo-electron microscopy and molecular modelling allowed us to demonstrate that the Pseudomonas aeruginosa IMPDH is functionally active as an octamer and allosterically regulated by MgATP via each CBS module. Revisiting deposited structural data, we found this newly discovered octameric organization conserved in other IMPDH structures. Meanwhile, we demonstrated that the human IMPDH1 formed two distinct octamers that can pile up into isolated fibres in the presence of MgATP while its pathogenic mutant D226N, localised into the CBS domains, appeared to form massively aggregating fibres. The dramatic impact of this mutation could explain the severe retinopathy adRP10. Our data (3) revealed for the first time that IMPDH has an octameric architecture modulated by MgATP binding to the CBS modules, inducing large structural rearrangements. Thus, the regulatory CBS modules in IMPDHs are functional and they can either modulate catalysis or/and macromolecular assembly. Targeting the conserved effector binding pockets identified within the CBS modules might be promising to develop antibacterial compounds or drugs to counter retinopathy onset.

[1] *L. Hedstrom, Chem. Rev., 2009, 109, 2903-2928.,* ***[2]*** *K. W. Pankiewicz, B. M. Goldstein, 2003, ACS Symposium Series.,* ***[3]*** *G. Labesse, T. Alexandre, L. Vaupre et al., 2013, Structure, 21, 975-985.*



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