Unveiling how point mutations affect NUDT15 dynamics with in silico approaches.

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Abstract

NUDT15 is a member of NUDIX (nucleoside diphosphates linked to a moiety x) protein family that catalyzes the hydrolysis of nucleotides and deoxynucleotides, including thioguanine analogues. One of their major role in the human body is a as sanitizer enzyme in purine metabolism. However, this protein is also implicated in the metabolism of thiopurine drugs. Recent studies have shown that genetic variants are related to a poor prognosis in inmoplastic and immunologic disorders under thioguanine drug treatment. Despite of this, the role of NUDT15 in physiology and molecular biology is quite unclear, as well as the mechanism of action of this enzyme. By using a combination of biomolecular modeling techniques and unrestrained molecular dynamics simulations, the monomeric wild type NUDT15, as well as some of the most important variants have been studied. Our findings reveal not only how nucleotide binding stabilizes the enzyme, but also how two loops are responsible for keeping the enzyme in a packed close conformation. Mutations in α2 helix affect a network of hydrophobic and π-interactions that are responsible of active site enclosing. This knowledge contributes to set to the understanding of NUDT15 dynamics and will be valuable for the design of new chemical probes and drugs targeting this protein.

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