Investigating the impact of missense mutations in hCES1 by in silico structure-based approaches - DTU Orbit (25/12/2018)

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Genetic variations in drug-metabolizing enzymes have been reported to influence pharmacokinetics, drug dosage and other aspects that affect therapeutic outcomes. Most particularly, non-synonymous single-nucleotide polymorphisms (nsSNPs) resulting in amino acid changes disrupt potential functional sites responsible for protein activity, structure, or stability, which can account for individual susceptibility to disease and drug response. Investigating the impact of nsSNPs at a protein's structural level is a key step in understanding the relationship between genetic variants and the resulting phenotypic changes. For this purpose, in silico structure-based approaches have proven their relevance in providing an atomic-level description of the underlying mechanisms. The present review focuses on nsSNPs in human carboxylesterase 1 (hCES1), an enzyme involved in drug metabolism. We highlight how prioritization of functional nsSNPs through computational prediction techniques in combination with structure-based approaches, namely molecular docking and molecular dynamics simulations, is a powerful tool in providing insight into the underlying molecular mechanisms of nsSNPs phenotypic effects at microscopic level. Examples of in silico studies of carboxylesterases (CESs) are discussed, ranging from exploring the effect of mutations on enzyme activity to predicting the metabolism of new hCES1 substrates as well as to guiding rational design of CES-selective inhibitors.

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