Universal force field minimization for predicting secondary structure changes in proteins due to post-translational modifications

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Human enzyme posttranslational modifications are important features of numerous diseases. Lipid peroxidation product 4-hydroxynonenal (4-HNE) is able to functionally modify specific proteins with implications for various diseases. Human monooxygenase CYP4F11 enzyme is involved mainly in lipid metabolism and xenobiotic degradation. CYP4F11 modification by 4-HNE was shown previously in malaria model, where phagocytosed malarial pigment hemozoin produced non-enzymatically 4-HNE in human monocytes. Enzyme activity was shown to be inhibited [Skorokhod, 2023] but the structural changes were not studied yet.

The aim of the work is to investigate the modifications, elicited by 4-HNE in human CYP4F11 enzyme applying computational modelling.

The predicted structure of the CYP4F11 protein, generated by AlphaFold, was utilized. Specific residues (C45, C260, H261, H347, C354, K451) were manually modified by Michael addition with 9-carbon aldehyde 4-HNE, based on previously identified modification sites determined through mass spectrometry [Skorokhod, 2023].

Subsequently, the modified structure was minimized using the Universal force field (UFF) with the help of cheminformatics software RDKit v. 2023.09.1. The CYP4F11 unmodified AlphaFold structure was also minimized for fair comparison. The secondary structure fractions were calculated using the dictionary of protein secondary structure (DSSP) v. 4.0.4.

Independently, FTIR-spectrometry experiment indicates a decrease in the amount of alpha-phase by 2.5% and an increase in beta-phase by 3.3% in 4-HNE modified CYP4F11, in accordance with our computational analysis.

Skorokhod O, Triglione V, Barrera V, Di Nardo G, Valente E, Ulliers D, Schwarzer E, Gilardi G. Posttranslational Modification of Human Cytochrome CYP4F11 by 4-Hydroxynonenal Impairs ω-Hydroxylation in Malaria Pigment Hemozoin-Fed Monocytes: The Role in Malaria Immunosuppression. Int J Mol Sci. 2023 Jun 16;24(12):10232. doi: 10.3390/ijms241210232. PMID: 37373382