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

T. Voitsitskyi [1,2], O. Gnatyuk [1], F. Naeimaeirouhani [3], O. Skorokhod [3], G. Dovbeshko [1,3], G. Gilardi [3]

[1] Institute of Physics, National Academy of Sciences of Ukraine, Kyiv, Ukraine, [2] Receptor.AI Inc., London, UK [3] Department of Life Sciences and Systems Biology, University of Torino, Torino, Italy

Introduction

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 [1] 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.

Methods

The predicted structure of the CYP4F11 protein, generated by AlphaFold2 [2], 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 [1].

Subsequently, the modified structure was minimized using the Universal force field (UFF) [3] with the help of cheminformatics software RDKit v. 2023.09.1. The CYP4F11 unmodified AlphaFold2 structure was also minimized for a fair comparison. The secondary structure fractions were calculated using the dictionary of protein secondary structure (DSSP) v. 4.0.4. [4].

Results

Independently, the FTIR-spectrometry experiment indicates a decrease in the amount of alpha-phase by 0.23% and an increase in beta-phase by 2.12% in 4-HNE modified CYP4F11, in accordance with our computational analysis (Fig. 1).

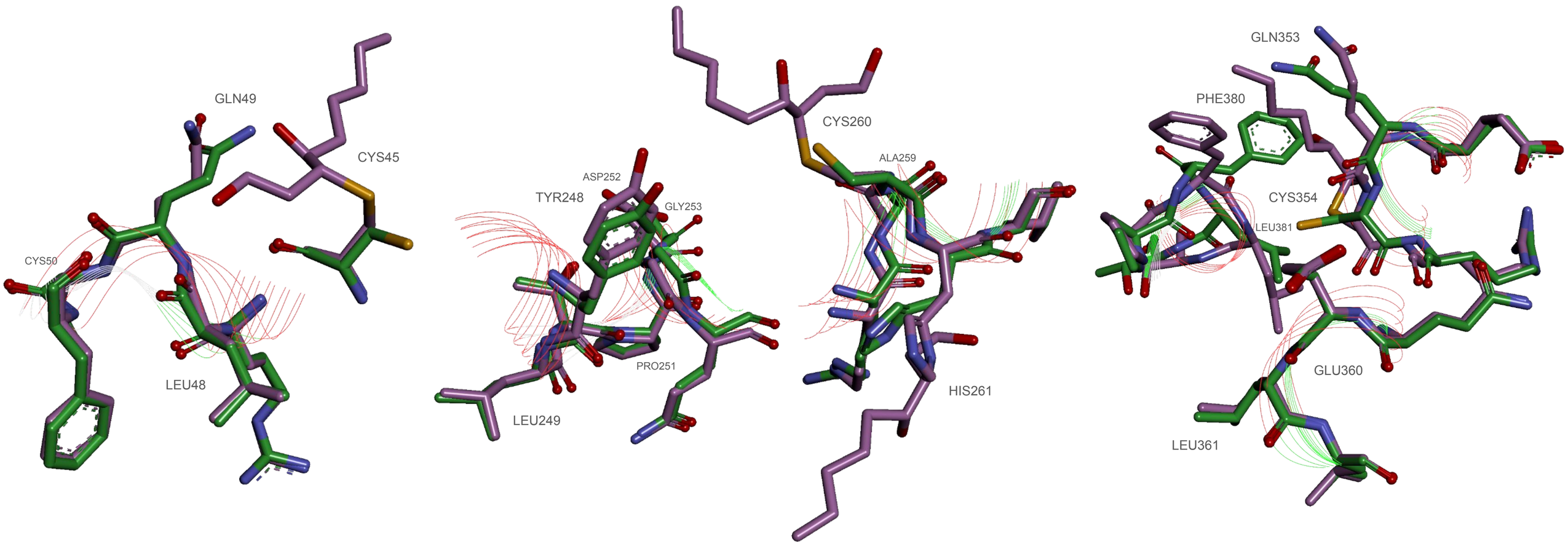

Figure 1. Predicted changes in the modified structure (purple) relative to the original (green). The modification at CYS45 induces changes in the secondary structure at positions 48-50 from helix to coil (left); The modifications at CYS260 and HIS261 induce changes in the secondary structure at positions 248-249, 251-253, and 259-260 from helix to coil (center); The modification at CYS354 induces changes in the secondary structure at positions 360-361 from helix to coil and at positions 353-354, 380-381 from coil to helix (right). The red thin lines indicate helix, green and gray - coil. The 4-HNE is shown in purple, conjugated with CYS45, CYS260, HIS261, and CYS354.

References

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