Deciphering and Engineering of Delftia acidovorans Haloacid Dehalogenase 2 for Effective Organohalogen Degradation Through Deep Learning and Molecular Dynamics Simulation

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PFAS (per- and polyfluoroalkyl substances) are organohalogens that are dubbed “forever chemicals” because they can remain in the environment for over 1,000 years. Chlorination-derived disinfection by-products (DBPs) are another type of organohalogens that pose a growing threat to water quality. Current degradation processes of these compounds generate smaller organohalogens that are toxic. DeHa2, a haloacid dehalogenase from Delftia acidovorans, offers a promising metal-independent biodegradation pathway to convert these compounds into less toxic products. However, its low catalytic efficiency and limited engineering guidelines hinder practical deployment. Here, we developed an integrated, structure-based computational framework to guide DeHa2 engineering. ProteinMPNN, a deep learning–based protein design model, was used with an auxiliary mutation-scoring module to identify target mutations in DeHa2 for improving organohalogen degradation efficiency. Molecular docking and molecular dynamics simulation were then performed to characterize binding and conformational dynamics, providing structural and mechanistic insights into the enzymatic activity. We found that the engineered variants MPNN_n3 and MPNN_m6 exhibited stronger predicted binding to monofluoroacetic acid (MFA) and monochloroacetic acid (MCA) than the wild-type enzyme. MPNN_n3 has the increased pocket compactness and polarity to enhance nucleophile accessibility, whereas MPNN_m6 contains hydrophobic features to favor chlorinated substrates. This workflow provides a cost-effective and accelerated strategy for enzyme engineering to advance PFAS/DBP bioremediation and mitigate associated environmental and health impacts.

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