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Vitamin K Epoxide Reductase Complex–Protein Disulphide Isomerase Assemblies in the Thiol–Disulphide Exchange Reactions: Portrayal of Precursor-to-Successor Complexes

Publié le 9 avril 2024 - International Journal of Molecular Sciences

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The human Vitamin K Epoxide Reductase Complex (hVKORC1), a key enzyme that converts vitamin K into the form necessary for blood clotting, requires for its activation the reducing equivalents supplied by its redox partner through thiol–disulphide exchange reactions. The functionally related molecular complexes assembled during this process have never been described, except for a proposed de novo model of a 'precursor' complex of hVKORC1 associated with protein disulphide isomerase (PDI). Using numerical approaches (in silico modelling and molecular dynamics simulation), we generated alternative 3D models for each molecular complex bonded either covalently or non-covalently. These models differ in the orientation of the PDI relative to hVKORC1 and in the cysteine residue involved in forming protein–protein disulphide bonds. Based on a comparative analysis of these models' shape, folding, and conformational dynamics, the most probable putative complexes, mimicking the 'precursor', 'intermediate', and 'successor' states, were suggested. In addition, we propose using these complexes to develop the 'allo-network drugs' necessary for treating blood diseases.