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Molecular dynamics simulation approach to explore atomistic molecular mechanism of peroxidase activity of apoptotic cytochrome *c* mutants

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ABSTRACT

Mutations in cytochrome *c* (Cyt *c*) have been reported in tuning peroxidase activity, which in-turn cause Cyt *c* release from mitochondria and early apoptosis. However, the molecular tuning mechanism underlying this activity remains elusive. Herein, multiple 20 ns molecular dynamics (MD) simulations of wild type (WT), Y67F and K72W mutated Cyt *c* in aqueous solutions have been carried out to study how the changes in structural features alters the peroxidase activity of the protein. MD simulation results indicate that Y67F mutation caused, (i) increased distances between critical electron-transfer residues, (ii) higher fluctuations in omega loops, and (iii) weakening of intraprotein hydrogen bonds result in open conformation at heme crevice loop in Cyt *c* leading to an enhanced peroxidase activity. Interestingly, the aforementioned structural features are strengthened in K72W compared to WT and Y67F, which triggers K72W mutated Cyt *c* into a poor peroxidase. Essential dynamics results unveil that first two eigenvectors are responsible for overall motions of WT, Y67F and K72W mutated Cyt *c*. This study thus provides atomic level insight into molecular mechanism of peroxidase activity of Cyt *c*, which will help in designing novel Cyt *c* structures that is more desirable than natural Cyt *c* for biomedical and industrial processes.

1. Introduction

Computational studies have provided significant insights concerning the details of molecular motion. Last decade witnessed the shifting of structure-function paradigm to structure-dynamics-function triad, to investigate the dynamic behavior of biomolecules on different timescale along with the accurate knowledge of tertiary or quaternary structure to understand the protein function [1]. In addition to its well established role as an electron carrier, cytochrome *c* (Cyt *c*), the hemoprotein, has attracted increasing interest recently, because of its essential role in the peroxidase activity and early apoptosis [2,3]. The Cyt *c* mediated apoptogenic pathway is important for a large variety of biological events, including brain development, immune system homeostasis, genotoxic-induced cell death and consequently, playing essential role in protecting living organisms from diseases such as cancer [4–9]. Disruptions in the apoptosis regulation can lead to numerous pathologies, including neurodegenerative disorders, autoimmunity and cancer [1,2]. Apoptosis is executed by activation of subfamily of cysteine proteases known as caspases. In mammalian cells, a major caspase activation pathway is the Cyt *c* initiated pathway. After its release into the cytosol, Cyt *c* interacts with apoptotic protease activating factor-1 (Apaf-1), which then binds to pro-caspase-9 to create a protein complex known as apoptosome [10,11]. The apoptosome cleaves the pro-caspase to its active form, caspase-9, which in turn induces cell death through a series of biochemical reactions. Post-translational modifications such as tyrosine nitration, phosphorylation, methionine sulfoxidation and mutations

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