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Computational Investigation of Plasma-Induced Oxidative Modifications on Heat Shock Protein Structure

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Cold atmospheric plasma (CAP) has emerged as a promising therapeutic tool in cancer treatment, primarily due to its ability to induce oxidative stress, promote apoptotic and immunogenic cell death in cancer cells, and stimulate immune responses against tumors [1]. Numerous *in vitro* studies have demonstrated the anticancer properties of CAP against various types of malignancies, including those resistant to conventional therapies [2]. The investigation of CAP-modified pharmaceutical compounds and biomolecules has further expanded its potential applications in oncology. Our previous research revealed that plasma-assisted modifications of lysozyme led to amino acid oxidation, which subsequently triggered apoptosis in cancer cells [3].

Understanding the interaction between plasma and protein structures remains critical, as exemplified by studies on SARS-CoV-2-CTD [4], and Mdm2-p53 [5]. Molecular dynamics simulations have provided valuable insights into the permeation of reactive oxygen and nitrogen species (RONS) across modified cell membranes [6]. These simulations have also been employed to study the transport of reactive species through aquaporins [7]. Nevertheless, the impact of plasma on heat shock proteins, particularly Hsp60, represents a fascinating area for further exploration.

Heat shock proteins (Hsps) are highly conserved protein families found in both prokaryotic and eukaryotic organisms. They function as a coordinated network to fold newly synthesized polypeptides, refold unstable proteins, disassemble protein aggregates, facilitate the assembly of protein complexes, and degrade misfolded proteins [8]. Hsp60 expression has been associated with gastric cancer progression and prognosis [9], as well as lymph node metastasis in prostate cancer [10]. Notably, Suh et al. demonstrated that reactive oxygen species (ROS) generated by alcohol can oxidize cysteinyl residues in Hsp60, potentially contributing to mitochondrial dysfunction [11].

It is highly likely that heat shock proteins (Hsps) might play a significant role in plasma-induced mitochondrial damage. To simulate the effects of plasma, we oxidized the amino acids of Hsp60 (hereafter referred to as Hsp) to evaluate the root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and solvent-accessible surface area (SASA) of both native and oxidized Hsp protein.

Our study demonstrates that the structure of Hsp undergoes noticeable modifications due to plasma-assisted oxidation, particularly in Trp, Tyr, and Met amino acids. RMSD analysis reveals a slight increase in structural flexibility for Hsp-oxd-2 (one Trp, 6 Tyr, and 10 Met residues oxidized), while the structure becomes more rigid in Hsp-oxd-1 (one Trp and 6 Tyr residues oxidized). These findings suggest that the oxidation of Met residues plays a crucial role in enhancing Hsp flexibility.

These results suggest that disruptions to chaperone-assisted protein quality control, caused by oxidation or exposure to electric fields, may contribute to the onset and progression of various diseases.

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