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Cold Atmospheric Plasma as a Modulator of Immune Checkpoints: Targeting PD-1 and PD-L1/PD-L2 interaction via Molecular Dynamics

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The PD-1/PD-L1/PD-L2 immune checkpoint is pivotal in regulating immune responses, preventing excessive immune activation. However, its exploitation by cancer cells allows evasion of immune surveillance, promoting tumor progression [1,2]. Programmed cell death protein 1 (PD-1), expressed on T-cells, interacts with its ligands, programmed death-ligand 1 (PD-L1) and 2 (PD-L2), on tumor cells, delivering an inhibitory "don't eat me" signal that suppresses T-cell activity [3]. Cold atmospheric plasma (CAP), a partially ionized gas producing reactive oxygen and nitrogen species (ROS/RNS), has gained attention as an alternative option in cancer therapy. CAP's ability to induce oxidative stress and modulate protein interactions positions it as a candidate for disrupting immunosuppressive checkpoints [3,4].

This study utilized molecular dynamics (MD) simulations to explore CAP's effects on PD-1/PD-L1 and PD-1/PD-L2 binding interactions. High-resolution structures of the complexes were sourced from the Protein Data Bank (PDB) and subjected to simulated oxidation conditions mimicking CAP's ROS effects. Key residues (e.g., methionine, lysine, tyrosine, cysteine) in the binding interfaces were oxidized at varying levels, and enhanced sampling techniques, including umbrella sampling was employed to determine binding free energies. Results indicated that higher oxidation levels significantly reduced binding affinities, weakening PD-1 interactions with both PD-L1 and PD-L2. This suggests that CAP disrupts the immunosuppressive signal, potentially enhancing cytotoxic T-cell responses against tumors.

The study provides critical molecular insights into CAP's immunomodulatory potential, positioning it as a complementary approach to existing immunotherapies like anti-PD-1/PD-L1 antibodies. By elucidating the mechanisms underlying CAP's effects, this computational framework supports further experimental studies and clinical development of CAP as a non-invasive cancer therapy [5]. Future work will focus on validating these findings in vitro and in vivo exploring precise mechanisms of activating immune cells over the cancer cells.

References

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