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Unraveling Mitochondrial Cell Death Mechanisms: Insights from Computational Simulations

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Mitochondria play a crucial role in providing energy to cells and also serve as the foundation of apoptotic cell death under physiological stress. This dual function is essential for cellular homeostasis and the overall health of the organism. One of the critical events in apoptosis is mitochondrial outer membrane permeabilization (MOMP), which leads to the release of pro-apoptotic factors such as cytochrome c into the cytosol.[1,2] This release triggers the activation of caspases, which are proteases that execute cell death by cleaving key cellular components.

The B-cell lymphoma 2 (BCL-2) family proteins are key regulators of the MOMP pathway. This family consists of both pro-survival and pro-apoptotic members, and the balance between these opposing forces determines the cell's fate. Pro-survival members, such as BCL-2 and MCL-1, work to prevent MOMP, thereby inhibiting apoptosis. In contrast, pro-apoptotic members, such as BAX and BAK, promote MOMP and subsequent cell death.[3,4] Dysregulation of this balance is implicated in various diseases, including cancer, where cells evade apoptosis, and neurodegenerative diseases, where excessive apoptosis leads to cell loss.

Developing small molecules or peptides to modulate BCL-2 family protein activity represents a challenging but attractive therapeutic goal. Such interventions could restore the balance between pro-survival and pro-apoptotic signals, thereby reinstating the cell's ability to undergo apoptosis when necessary. This approach is particularly relevant in cancer therapy, where the inhibition of pro-survival BCL-2 proteins can make cancer cells more susceptible to apoptosis-inducing treatments.[6]

In this study, we focused on the interaction between MCL-1, a pro-survival BCL-2 family member, and BMF-1, its high-affinity inhibitor.[6] We investigated how oxidation affects this interaction, hypothesizing that oxidation could alter the binding affinity between these proteins. Using the umbrella sampling technique, we found that oxidation indeed reduced the binding free energy between MCL-1 and BMF-1. This reduction in binding affinity could potentially trigger apoptosis in cancerous cells by facilitating the release of pro-apoptotic factors and the activation of caspases.

Our findings provide valuable insights into the molecular mechanisms underlying oxidation-based therapies used in cancer treatment. Non-thermal plasma approaches, which generate reactive oxygen and nitrogen species, could exploit these mechanisms to induce apoptosis selectively in cancer cells while sparing healthy cells. These results highlight the importance of targeting mitochondrial pathways for developing new cancer therapies. Further exploration of these pathways could lead to significant advancements in cancer treatment, promoting selective apoptosis in cancer cells and enhancing the efficacy of existing therapeutic strategies.

References

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