Cureus

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Poster

Development of a Cytotoxic Peptide Based on the C-terminal Domain of Bax

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Categories: Oncology
Keywords:

How to cite this poster
Boohaker R J, Khaled A (2012) Development of a Cytotoxic Peptide Based on the C-terminal Domain of Bax. Cureus 4(10): e448.

Abstract

The Bcl-2 family proteins maintain the balance of life and death in the cell. Bax, a pro-apoptotic member, translocates to the mitochondrial membrane in response to diverse death stimuli, initiated a cascade of programmed vents that lead to cell death. Tumor progression involves deregulation of this process in part through mutations that cause aberrant expression of anti-apoptotic members of the Bcl-2 family that normally sequester and inhibit Bax. This study seeks identify functional domains of Bax that can be developed into therapeutic peptides to promote the death of cancer cells resistant to existing chemotherapeutics. Our goal was to generate a peptide, much like antimicrobial peptides, that could target and disrupt mitochondrial membranes. To this end, we discovered that the C-terminal, alpha-9 helix of Bax (CT20p), when tagged to EGFP or a destabilization domain (DD), could bind mitochondria and cause cell death. The peptide's lethal mode of action was linked to increased mitochondrial membrane potential, and eventual membrane rupture without the characteristic membrane asymmetry associated with apoptosis. Targeted mutagenesis of two adjacent lysines at the carboxyl end of CT20p demonstrated that these residues enabled mitochondrial membrane association. Expression of the CT20 peptide in the presence or absence of endogenous Bax resulted in cytotoxicity, suggesting that the death mechanism involved could be independent of the Bcl-2 family. These findings suggest that peptide composition of the alpha 9-helix of Bax is sufficient to induce mitochondrial membrane binding and cell death via a mechanism not typically associated with apoptosis. This indicated that CT20p has the potential to be developed into a viable therapeutic agent in the treatment of a broad range of cancer types.

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Published 10/12/2012

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