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Mechanistic Structural Insights into the UV Induced Apoptosis via Bcl-2 proteins

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Abstract : Ultraviolet C (UVC) radiation induces apoptosis in mammalian cells and it is suggested that the mechanism by which this occurs is the mitochondrial pathway of apoptosis through the release of cytochrome c from the mitochondria into the cytosol. The Bcl-2 family of proteins pro-and anti-apoptotic is the regulators of the mitochondrial pathway of apoptosis. Upon UVC irradiation, the proliferation of apoptosis is enhanced through the downregulation of the anti-apoptotic protein Bcl-xl and up-regulation of Bax. Although the participation of the Bcl-2 family of proteins in apoptosis appears responsive to UVC radiation, to the author's best knowledge, it is unknown how the structure and, effectively, the function of these proteins are directly impacted by UVC exposure. In this background, we present here a structural rationale for the effect of UVC irradiation in restoring apoptosis using two of the relevant proteins, namely, Bid-FL and Bcl-xl ΔC, whose solution structures have been reported previously. Using a variety of biophysical tools such as circular dichroism, fluorescence and NMR spectroscopy, we show that following UVC irradiation, the structures of Bcl-xlΔC and Bid-FL are irreversibly altered. Bcl-xLΔC is found to be more sensitive to UV exposure than Bid-FL. From the NMR data, dramatic structural perturbations (α-helix to β-sheet) are seen to occur in the BH3 binding region, a crucial segment of Bcl-xlΔC which impacts the efficacy of its interactions with pro-apoptotic tBid. These results explain the regulation of apoptosis by UVC irradiation. Our results on irradiation dosage dependence of the structural changes have therapeutic potential for the treatment of cancer.

Keywords : Bid, Bcl-xl, UVC, apoptosis
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