The transmembrane domain of the proapoptotic protein Harakiri: NMR structural studies in micellar systems

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Harakiri (Hrk)[1], a proapoptotic member of the Bcl-2 protein family, contains a single BH (Bcl-2 Homology) domain named BH3 and plays a key role in programmed cell death. BH3-only proteins control apoptosis[2] by interacting with pro-survival partners, a mechanism related to the insertion of several proapoptotic members into the mitochondrial membrane prompting caspase activation and subsequent cell disintegration. Hrk is a 91 amino acid-long protein with a predicted transmembrane domain of approximately 30 residues (Hrk-TM). Not all of the members of the BH3-only subfamily contain such domain, suggesting that Hrk membrane insertion is implicated in its proapoptotic function. We have studied the conformational behavior of Hrk-TM by NMR to understand the molecular basis governing membrane interaction. Hrk-TM is insoluble in aqueous solution, resulting from its hydrophobic nature, and strongly aggregates in alcohol/water mixtures. In contrast, detergent/alcohol mixed micelles have been found to nicely accommodate Hrk-TM allowing structural studies by high resolution NMR. The obtained data indicate that Hrk-TM is inserted in the micelle and adopts an alpha helix fold with disordered N- and C-termini.

[1]Inohara, N.; Ding, L.; Chen, S.; Núñez, G., *The EMBO Journal*, **1997**, Vol.16 No.7, 1686-1694.
[2]Willis, S.N.; Adams, J.M., *Current Opinion in Cell Biology*, **2005**, 17, 617-625.

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