DYNAMICS OF THE HELICES α8 AND α9 OF BCL-2 AFTER ITS ASSOCIATION WITH FKBP38 IN CNS NEURONS

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The intrinsic (mitochondrial) pathway of apoptosis is regulated negatively or positively by anti-apoptotic and pro-apoptotic members of the Bcl-2 family of proteins. An anti-apoptotic member of this family, Bcl-2, is among three dominant inhibitors of apoptosis. The mitochondrial localization of this protein is essential for its anti-apoptotic function. In many types of neurons of human central nervous system (hCNS), mitochondrial targeting of Bcl-2 uses FKBP38, an integral *mitochondrial outer membrane (MOM) protein [1]*. The behavior of Bcl-2 after its association with FKBP38 remains little understood. Here, computational structural biology tools were used to gain structural insights into the dynamics of Bcl-2 after its association with FKBP38 in healthy (nonapoptotic) cells and under apoptotic conditions. The combination of remote homology modeling meta-predictor PHYRE with the iterative threading assembly refinement (I-TASSER) protocol and the MEMOIR system for homology modeling of membrane proteins were used to predict the full-length structure of FKBP38. The modeling of the atomistic 3D-structure of the FKBP38/Bcl-2 complex was performed in a stepwise fashion using a four - staged computational molecular docking protocol PIPER – ROSETTADOCK – GalaxyRefineComplex – ROSETTADOCK (abbreviated by $PRG_{RC}R$). The modeling showed the existence of two hinge regions within the loops between helices α7, α8 (hinge region 1, HR1, Asn192Gly193Gly194) and α8, α9 (hinge region 2, HR2, Gly203). We suggested the insertion of helix α9 into the mitochondrial outer membrane due to rotations of helices α8 and α9 about these hinge regions. To address this issue, a 'Hinge Bending-GalaxyRefine-GalaxyRefineComplex-RosettaDock strategy' (abbreviated as $H_BG_RG_{RC}R$), was used. With this strategy, the dihedral angles of the backbone of the hinge groups residues were first subjected to changes at 30° intervals until the attainment of the virtual insertion of helices α9 of Bcl-2 into the membrane followed then by the refinement procedure using the GalaxyRefine and GalaxyRefineComplex protocols. The application of this strategy has shown the insertion of the α9 helix into the MOM.

References

1. Shirane-Kitsuji M., Nakayama K.I., 2014. Mitochondria: FKBP38 and mitochondrial degradation. //Int J Biochem Cell Biol. 2014. Vol. 51. 19–22.