

COMPUTATIONAL STRUCTURAL BIOPHYSICS STUDY OF THE EFFECT OF METAXIN 1 AND METAXIN 2 ON APOPTOSIS

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In a number of cell types, the proapoptotic protein Bak is implicated in the execution phase of intrinsic (mitochondrial) apoptosis. Bak is already mitochondrial in healthy (nonapoptotic cells) and becomes fully membrane integrated during early steps of apoptosis, followed by Bak oligomerization and cell destruction. Little is known about the partners and mechanisms implicated in the activation of Bak. It has been recently shown that, after the induction of apoptosis, Bak switches from its association with metaxin 2 (Mtx2) and VDAC2 to a closer association with metaxin 1 (Mtx1) and this change of partners is under the control of a tyrosine phosphorylation of Mtx1 [1] but the mechanisms remain unclear. Here, computational structural biophysics tools were used to gain structural insights into the interactions between the Bcl-2 family proteins, Bak and tBid, and VDAC2, Mtx1, Mtx2 in healthy (nonapoptotic) cells and under apoptotic conditions. We first performed the modelling of the VDAC2/Mtx1/Mtx2 complex, which we suggested to be formed in healthy cells, and then the interaction of this complex with Bak and tBid. Also, the interaction of Mtx1 with Bak and tBid was calculated. The modeling of the atomistic 3D-structures of the complexes was performed in a stepwise fashion using a four - staged computational molecular docking protocol PIPER – ROSETTADOCK – GalaxyRefineComplex – ROSETTADOCK. We established a strong binding of Bak to the VDAC2 of the VDAC2/Mtx1/Mtx2 complex, and even a stronger binding of tBid to VDAC2 of this complex, suggesting the displacement of Bak from this complex by tBid. Besides, we revealed a rather strong binding of Bak with Mtx1, and somewhat stronger binding of tBid to Mtx1, suggesting the displacement of Bak in the Mtx1/Bak complex by tBid.

References

1. Cartron P.F., Petit E., Bellot G., Oliver L., Vallette F.M., Metaxins 1 and 2, two proteins of the mitochondrial protein sorting and assembly machinery, are essential for Bak activation during TNF alpha triggered apoptosis, *Cell. Signal.* 2014. Vol. 26. P.1928–1934.