The molecular mechanism of the interaction between TCTP and the Bcl-2 proteins (Bcl-xL, Mcl-1)

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Résumé

The small (20 kDa) TCTP protein is known to interact with dozens of partners and impacts on various cellular and physiological processes. In the context of cancer, evidences suggest that downregulation of TCTP levels in tumors may contribute to restore the apoptosis pathway, leading to the death of malignant cells. In 2016, Thébault et al. released the crystal structure of the anti-apoptotic protein Bcl-xL in complex with a peptide from TCTP encompassing a BH3-like motif[1]. Although establishing the role of TCTP as an inhibitor of cell death through activation of Bcl-xL and related Bcl-2 proteins like Mcl-1, this work could not provide structural details in the context of the full length TCTP protein. Indeed, the BH3-like motif in TCTP which interacts with Bcl-xL and Mcl-1 is buried and folded as a beta-sheet in the full length protein, whereas the BH3-like peptide adopts a typical helical fold in complex with Bcl-xL, suggesting a major conformational change in TCTP upon binding. Consequently, we investigated the molecular mechanism by which full length TCTP associates with Mcl-1 and Bcl-xL using a panel of biophysical methods (NMR, SAXS, CD, SEC, DSF...). We demonstrated that full length TCTP binds to Mcl-1 in its BH3-binding groove. We uncovered the major changes in TCTP structure and dynamics required to form complexes with both Bcl-xL and Mcl-1. Namely, we have shown that only a minor, pre-existing TCTP state, named TCTP*, is competent for complex formation. The globular domain in TCTP* has μs-ms dynamics comparable to molten-globule states and has an unfolded, solvent-exposed BH3-like motif readily accessible for interaction with Mcl-1/Bcl-xL. Upon complex formation with Mcl-1, the core domain of TCTP also adopts a molten globule state. Overall, our work indicates that drug-design targeting TCTP in cancer

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should consider TCTP* when aiming to disrupt TCTP/Bcl-xL and TCTP/Mcl-1 interactions. In addition, this work enlightens how structural plasticity in full length TCTP can enable interactions with partners and promotes tumor maintenance and progression in the context of cancer. [1] Thébault, S. et al. TCTP contains a BH3-like domain, which instead of inhibiting, activates Bcl-xL. Scientific Reports, no. 6, pp. 19725, 2016.