Targeting their Interaction with the IP3 Receptors: New Tools to Overcome Bcl-2 Proteins-Associated Drug Resistance

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Apoptosis, also called “Programmed Cell Death”, plays a pivotal role in many biological processes and pathologies. The B-cell Lymphoma 2 (Bcl-2) proteins, often dysregulated in tumoral cells, are the main regulators of apoptosis.

Among this family, the function of the anti-apoptotic regulator bcl-b is still unclear. The bcl-b expression is found restricted to ovary, oocytes and B-cells whereas clinical studies have shown a strong correlation between Bcl-B expression and poor prognosis in multiple malignancies, such as Breast and Prostate carcinomas. Since the mechanisms of Bcl-B oncogenicity are poorly understood, we focused our efforts in the present study to find a relevant model overcoming this issue.

We analysed a subset of cancer cell lines for Bcl-B expression, and selected the MDA-MB-231 from breast carcinoma.
Subcellular fractionation in MDA-MB-231 cells revealed that Bcl-B is only present at the Endoplasmic Reticulum (ER) membrane, unlike most of the Bcl-2 proteins from the anti-apoptotic class.
We showed that Bcl-B is able to interacts with the Ligand Binding domain of the Inositol-1,4,5-triphosphate receptor type-I Ca2+ channel (IP3R1) and regulates IP3R1-mediated Ca2+ signalling.
Consistently with these results we demonstrated that an ER-targeted but not mitochondrial-targeted Bcl-B has apoptotic resistance properties against a Ca2+-induced challenge (Thapsigargin). Moreover, we showed that bcl-b knock-down sensitizes MDA-MB-231 cells to apoptosis either at steady state or upon Thapsigargin, but not Staurosporine treatment.

As a promising challenge, we are currently developing peptides to compete for Bcl-B at its interaction site on IP3R1. Using these peptides, we hope to prime to death cancer cells relying on Bcl-B for survival. This novel approach might be a leap forward in the treatment of tumours expressing the Bcl-B marker, considering that none of the available strategies targeting Bcl-2 proteins have selectivity toward Bcl-B.