Lecture 2: “Role of Bcl-2 family protein in intracellular calcium dynamics”

Abstract:

Proteins belonging to the Bcl-2 family represent one of the main regulator of programmed cell death (PCD) also known as apoptosis. They control a key step in the apoptosis induction called the mitochondrial outer membrane permeabilization (MOMP). Initially discovered in chromosomal translocations in follicular lymphomas, Bcl-2 homologs have been now found in almost all metazoans. Indeed, genetic screen of cell death mutants performed in nematode and subsequent studies in drosophila, zebrafish and hydra identified a number of Bcl-2 related proteins. These proteins contain one to four B-cell homology domains as well as a hydrophobic C-terminus transmembrane domain. Although apoptosis control differ substantially between roundworms, insects and mammals, seminal experiments conducted in these models reinforced the belief that Bcl-2 family of proteins were evolutionary selected to control the survival of the cell at the level of the mitochondria.

However, a number of Bcl-2 related proteins localize not only to the MOM but are also found at the endoplasmic reticulum (ER). Indeed, Bcl-2 and related members bind to the ER membranes and control intracellular calcium fluxes through direct interactions with the calcium channel inositol 1,4,5-trisphosphate receptor (IP3R). Recently we showed that two Bcl-2 homologs named Nrz and Bcl-wav were able to orchestrate the first morphogenic movements, during early zebrafish embryonic development and thus independently from their roles in apoptosis. Nrz exerts this non canonical function at the ER by directly regulating IP3R permeability whereas Bcl-wav binds to VDAC channel at the MOM and enhance mitochondrial calcium uptake. Using high resolution confocal microscopy we demonstrated that these molecular interactions control actomyosin contractility and dynamics in the developing embryo.

Thus, the assumption that Bcl-2 family proteins appeared and were selected throughout metazoan evolution as sole MOMP regulators is now challenged.

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