The Protein Interaction Map of Apoptosis and Autophagy: From Basic Science to a Therapeutic Vision

Yuval Gilad, Ruth Shiloh, Naama Dekel, Avital Hay-Koren and Adi Kimchi.

Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel

Apoptosis and autophagy are distinct biological processes, each driven by a different set of protein-protein interactions, including some direct points of interface between apoptotic and autophagic proteins. Our laboratory studies the overall landscape of these proteomic maps and subsequently zooms into novel biochemical pathways discovered by the systems level approaches. To measure the global profile of protein interactions in cells, we have adapted the Protein fragment Complementation Assay (PCA), which monitors binding between proteins fused to complementary fragments of a luciferase reporter. A library encompassing 63 proteins from the basic machineries of autophagy and apoptosis, and some of their regulatory proteins, was constructed for the analysis of ~3600 protein-pair combinations. This generated a detailed landscape of the apoptotic and autophagic modules and the points-of-interface between them, identifying 46 previously unknown interactions. Two of these novel interactions were further investigated in detail. One deals with DAPK2, a Ser/Thr kinase that promotes cell death and autophagy. It was found here that DAPK2 interacts with 14-3-3τ, resulting in inhibition of DAPK2 dimerization and suppression of its biochemical and cellular activities. Another autophagic Ser/Thr kinase, ULK1, was found to interact with WIP12b, thus providing a direct link between a regulatory process and the basic machinery of autophagosome formation. This proof-of-concept underscores the power of the PCA platform for the discovery of novel biochemical pathways within the cell death network. The emerging landscape of the global map including the connectivity between apoptosis and autophagy is currently used for identifying the cell death signature of individual tumor cells. Novel platforms that measure the global functionality of the cell death network are being developed to follow the diversity among individual tumors, and identify alternative cell death pathways that are still active in the tumor.