Targeting the ER-mitochondria interface sensitizes leukemia cells towards cytostatics

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Combination chemotherapy has proved to be a favorable strategy to treat acute leukemia. However, the introduction of novel compounds remains challenging and is hindered by a lack of understanding their mechanistic interaction with established drugs. In the present study, we demonstrate a highly increased response of various acute leukemia cell lines, drug resistant cells and patient-derived xenograft (PDX) cells by combining the recently introduced protein disulfide isomerase (PDI) inhibitor PS89 with cytostatics. In leukemic cells, a proteomics based target fishing approach disclosed that PS89 impacts a whole network of ER homeostasis proteins. We elucidate that the strong apoptosis induction in combination with cytostatics is orchestrated by the PS89 target B-cell receptor-associated protein 31 (BAP31), which transduces apoptosis signals at the ER-mitochondria interface. Activation of caspase-8 and cleavage of BAP31 stimulate a pro-apoptotic crosstalk including ER calcium release and increased ROS levels resulting in amplification of mitochondrial apoptosis. This study promotes PS89 as a novel chemo sensitizing agent for acute leukemia treatment and uncovers that targeting the ER-mitochondria network of cell death is a promising approach in combination therapy.

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