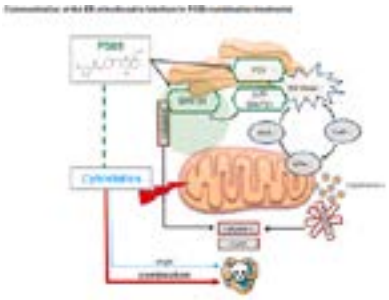
Targeting the ER-mitochondria interface sensitizes leukemia cells towards cytostatics

Olga Naglo
Ludwig-Maximilian University of Munich, Germany

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.



Recent Publications

1. Stoiber K, Nagło O, Pernpeintner C, Zhang S, Koeberle A, Ulrich M, Werz O, Müller R, Zahler S, Lohmüller T, Feldmann J and Braig S (2018) Targeting de novo lipogenesis as a novel approach in anti-cancer therapy. Br J Cancer. 118(1):43-51.
2. Koczian F, Nagło O, Vomacka J, Vick B, Servatius P, Zisis T, Hettich B, Kazmaier U, Sieber SA, Jeremias I, Zahler S and Braig S (2018) Targeting the ER-mitochondria interface sensitizes leukemia cells towards cytostatics. Haematologica. 2018 Oct 11. pii: haematol.2018.197368. doi: 10.3324/haematol.2018.197368.

Olga.Naglo@cup.uni-muenchen.de