BAG3

The ubiquitin-proteasome system (UPS) and autophagy are 2 major protein degradation pathways in eukaryotic cells. We previously identified a switch from UPS to autophagy with changes in BAG3 (B-cell lymphoma 2-associated-athanogene 3) expression after cerebral ischemia in mice. BAG3 is an antiapoptotic-cochaperone that is directly involved in cellular protein quality control as a mediator for selective macroautophagy. Here, we aimed to investigate the role of BAG3 in ischemic stroke.

Methods: Middle cerebral artery occlusion/reperfusion (MCAO/R) and oxygen-glucose deprivation/reoxygenation were used to mimic cerebral ischemia in vivo and in vitro. The UPS inhibitor MG132 and autophagy inhibitor 3-MA (3-methyladenine) were administered to mice to identify how BAG3 was involved after MCAO/R. Adeno-associated virus and lentiviral vector were used to regulate BAG3 expression in vivo and in vitro, respectively. Behavioral tests, 2,3,5-triphenyltetrazolium chloride staining, and Hematoxylin & Eosin staining were performed to evaluate cerebral injury following MCAO/R, and a Cell Counting kit-8 assay was conducted to assess oxygen-glucose deprivation/reoxygenation-induced injury in cells. Brain tissues and cell lysates were collected and analyzed for UPS activation, autophagy, and apoptosis.

Results: The UPS inhibitor alleviated MCAO injury in mice and increased autophagy and BAG3 expression, whereas the autophagy inhibitor exacerbated MCAO/R-induced injury. In addition, BAG3 overexpression significantly improved neurological outcomes, reduced infarct volume in vivo, and enhanced cell survival by activating autophagy and suppressing apoptosis in vitro.

Conclusions: Our findings indicate that BAG3 overexpression activates autophagy and inhibits apoptosis to prevent cerebral ischemia/reperfusion and hypoxia/reoxygenation injury, suggesting a potential therapeutic benefit of BAG3 expression in cerebral ischemia [1)]

Target-specific treatment modalities are currently not available for triple-negative breast cancer (TNBC), and acquired chemotherapy resistance is a primary obstacle for the treatment of these tumors. Here we employed derivatives of BT-549 and MDA-MB-468 TNBC cell lines that were adapted to grow in the presence of either 5-Fluorouracil, Doxorubicin or Docetaxel in an aim to identify molecular pathways involved in the adaptation to drug-induced cell killing. All six drug-adapted BT-549 and MDA-MB-468 cell lines displayed cross resistance to chemotherapy and decreased apoptosis sensitivity. Expression of the anti-apoptotic co-chaperone BAG3 was notably enhanced in two thirds (4/6) of the six resistant lines simultaneously with higher expression of HSP70 in comparison to parental controls. Doxorubicin-resistant BT-549 (BT-549rDOX20) and 5-Fluorouracil-resistant MDA-MB-468 (MDA-MB-468r5-FU2000) cells were chosen for further analysis with the autophagy inhibitor Bafilomycin A1 and lentiviral depletion of ATG5, indicating that enhanced cytoprotective autophagy partially contributes to increased drug resistance and cell survival. Stable lentiviral BAG3 depletion was associated with a robust down-regulation of Mcl-1, Bcl-2 and Bcl-xL, restoration of drug-induced apoptosis and reduced cell adhesion in these cells, and these death-sensitizing effects could be mimicked with the BAG3/Hsp70 interaction inhibitor YM-1 and by KRIBB11, a selective transcriptional inhibitor of HSF-1. Furthermore, BAG3 depletion was able to revert the EMT-like transcriptional changes observed in BT-549rDOX20 and MDA-MB-468r5-FU2000 cells. In summary, genetic and pharmacological interference with BAG3 is capable to resensitize TNBC cells to treatment, underscoring its relevance for cell death resistance and as a target to overcome therapy resistance of breast cancer [2)].

1)
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2)
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