Reticulophagy

Selective degradation of the endoplasmic reticulum (ER; reticulophagy) is a type of autophagy involved in the removal of ER fragments. So far, amino acid starvation as well as ER stress have been described as inducers of reticulophagy, which in turn restores cellular energy levels and ER homeostasis.

Zielke et al. explored the autophagy-inducing mechanisms that underlie the autophagic cell death (ACD)-triggering compound loperamide (LOP) in glioblastoma cells. Interestingly, LOP triggers the upregulation of the transcription factor ATF4, which is accompanied by the induction of additional ER stress markers. Notably, knockout of ATF4 significantly attenuated LOP-induced autophagy and ACD. Functionally, LOP also specifically induces the engulfment of large ER fragments within autophagosomes and lysosomes as determined by electron and fluorescence microscopy. LOP-induced reticulophagy and cell death are predominantly mediated through the reticulophagy receptor RETREG1/FAM134B and, to a lesser extent, TEX264, confirming that reticulophagy receptors can promote ACD. Strikingly, apart from triggering LOP-induced autophagy and ACD, ATF4 is also required for LOP-induced reticulophagy. These observations highlight a key role for ATF4, RETREG1 and TEX264 in response to LOP-induced ER stress, reticulophagy and ACD, and establish a novel mechanistic link between ER stress and reticulophagy, with possible implications for additional models of drug-induced ER stress [1].

1)
Zielke S, Kardo S, Zein L, Mari M, Covarrubias-Pinto A, Kinzler MN, Meyer N, Stolz A, Fulda S, Reggiori F, Kögel D, van Wijk SJL. ATF4 links ER stress with reticulophagy in glioblastoma cells. Autophagy. 2020 Oct 28:1-17. doi: 10.1080/15548627.2020.1827780. Epub ahead of print. PMID: 33111629.