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Simultaneous inhibition of the ubiquitin-proteasome system and autophagy enhances apoptosis induced by ER stress aggravators in human pancreatic cancer cells.

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Abstract

In contrast to normal tissue, cancer cells display profound alterations in protein synthesis and degradation. Therefore, proteins that regulate endoplasmic reticulum (ER) homeostasis are being increasingly recognized as potential therapeutic targets. The ubiquitin-proteasome system and autophagy are crucially important for proteostasis in cells. However, interactions between autophagy, the proteasome, and ER stress pathways in cancer remain largely undefined. This study demonstrated that withaferin-A (WA), the biologically active withanolide extracted from Withania somnifera, significantly increased autophagosomes, but blocked the degradation of autophagic cargo by inhibiting SNARE-mediated fusion of autophagosomes and lysosomes in human pancreatic cancer (PC) cells. WA specifically induced proteasome inhibition and promoted the accumulation of ubiquitinated proteins, which resulted in ER stress-mediated apoptosis. Meanwhile, the impaired autophagy at early stage induced by WA was likely activated in response to ER stress. Importantly, combining WA with a series of ER stress aggravators enhanced apoptosis synergistically. WA was well tolerated in mice, and displayed synergism with ER stress aggravators to inhibit tumor growth in PC xenografts. Taken together, these findings indicate that simultaneous suppression of 2 key intracellular protein degradation systems rendered PC cells vulnerable to ER stress, which may represent an avenue for new therapeutic combinations for this disease.

KEYWORDS: ER stress; SNAREs; autophagy; proteasome; withaferin A

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