Ritonavir induces endoplasmic reticulum stress and sensitizes sarcoma cells toward bortezomib-induced apoptosis

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The biosynthesis of immunoglobulin leads to constitutive endoplasmic reticulum (ER) stress in myeloma cells, which activates the unfolded protein response (UPR). The UPR promotes protein folding by chaperones and increases proteasomal degradation of misfolded protein. Excessive ER stress induces apoptosis and represents a molecular basis for the bortezomib sensitivity of myeloma. Most solid malignancies such as sarcoma, by contrast, are poorly bortezomib sensitive and display low levels of ER stress. We hypothesized that pharmacologic induction of ER stress might sensitize malignancies to bortezomib treatment. We show that the HIV protease inhibitor ritonavir induces ER stress in bortezomib-resistant sarcoma cells. Ritonavir triggered the UPR, decreased the degradation of newly synthesized protein, but did not directly inhibit proteasomal active sites in the therapeutic dose range in contrast to bortezomib. Whereas neither bortezomib nor ritonavir monotherapy translated into significant apoptosis at therapeutic drug levels, the combination strongly increased the level of ER stress and activated PERK, IRE1, and ATF6, synergistically induced CHOP, JNK, caspase-4, and caspase-9, and resulted in >90% apoptosis. In summary, ritonavir increases the level of ER stress induced by bortezomib, which sensitizes bortezomib-resistant cells to bortezomib-induced apoptosis. Ritonavir may therefore be tested clinically to improve the sensitivity of solid malignancies toward bortezomib treatment.

type: journal paper/review (English)
date of publishing: 7-2008
journal title: Molecular cancer therapeutics (7/7)
ISSN print: 1535-7163
pages: 1940-8