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Proteasome stress sensitizes malignant pleural mesothelioma cells to bortezomib-induced apoptosis

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Malignant pleural mesothelioma (MPM) is an aggressive cancer caused by exposure to asbestos. In an effort aimed at developing new pharmacologic strategies against this cancer, we assessed a panel of MPM lines with different sensitivity to bortezomib (Btz), for functional proteasome activity and levels of free and polymerized ubiquitin. We found that highly sensitive MPM lines display lower proteasome activity than more Btz-resistant clones, suggesting that reduced proteasomal capacity might contribute to the intrinsic susceptibility of MPM to Btz-induced apoptosis. Moreover, MPM equipped with fewer active proteasomes accumulated polyubiquitinated proteins, at the expense of free ubiquitin, a condition known as proteasome stress, which lowers the cellular apoptotic threshold and sensitizes MPM cells to Btz-induced toxicity. Taken together, our data suggest that an unfavorable load-versus-capacity balance represents a critical determinant of primary apoptotic sensitivity to Btz in MPM.

Notes