PROTEASOME STRESS SENSITIZES MALIGNANT PLEURAL MESOTHELIOMA CELLS TO BORTEZOMIB-INDUCED APOPTOSIS

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Proteasome inhibitors (PIs) are emerging as a promising new class of drugs active against cancers that are refractory to current chemotherapies. Based on promising results in preclinical *in vitro* and *in vivo* models (1-2), clinical trials have been carried out to evaluate the efficacy of the first-in-class PI bortezomib (Btz) towards malignant pleural mesothelioma (MPM), an aggressive cancer arising from the mesothelium of the serous cavities following exposure to asbestos. Unexpectedly, only minimal therapeutic benefits were observed, thus implicating that this tumor harbors inherent resistance mechanisms (3-4). Identifying the molecular bases of this primary resistance is, therefore, crucial to develop novel pharmacologic strategies aimed at increasing the vulnerability of MPM to Btz. To this purpose, we assessed a panel of four human MPM lines with different sensitivity to Btz, for functional proteasome activity and the 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 mesothelioma cells to PIs-induced apoptosis. Most importantly, MPM equipped with fewer active proteasomes accumulated higher levels of polyubiquitinated proteins, at the expense of free ubiquitin, a condition known as proteasome stress, which lowers the cellular apoptotic threshold and sensitizes mesothelioma cells to Btz-induced toxicity as shown herein. Taken together, our data suggest that, as for the prototypical PIs-responsive cancer multiple myeloma (5-6), an unfavorable load-versus-capacity balance also represents a critical determinant of primary apoptotic sensitivity to Btz in MPM.

References

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