HO-1 and GSH mediate cancer cell resistance to Bortezomib: role of Nrf2

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Antioxidants are recognized to provide cancer cells with resistance to anticancer therapies and a leading role of glutathione (GSH) and heme oxygenase-1 (HO-1) has been demonstrated. Proteasome inhibitor Bortezomib (BTZ) commonly used in the therapy of multiple myeloma and has been also proposed for the treatment of solid tumors. However, cell responses to proteasome inhibition are not clear and Nrf2 activation, inducing antioxidant genes, can limit BTZ efficacy.

We treated a very aggressive neuroblastoma cell line (HTLA-230) with a low dose of BTZ (2.5nM). The inhibition of proteasome activity was marked up to 24 h (-80% vs CTR) but no changes in viability were detected. HO-1 expression was induced already after 6h, up to 24h of BTZ treatment and Nrf2 binding to HO-1 promoter was definitely up-regulated by BTZ. GSH level was increased about two-fold after 24h of BTZ treatment. HO-1 silencing increased ROS generation and decreased cell number after 6 h but GSH depletion was the most effective factor in inducing cell death after 24h of BTZ treatment. Therefore, a synergistic effect between HO-1 silencing and GSH depletion was observed at the longer experimental time.

Moreover, preliminary results showed Nrf2 inhibition had a similar efficacy in increasing BTZ toxicity

In conclusion, we suggest that Nrf2-dependent pathways can be targeted to improve Bortezomib efficacy, overcoming the resistance of high-risk neuroblastoma to anticancer therapy.

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