Apoptotic effects of proteasome and histone deacetylase inhibitors in prostate cancer cell lines

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Received November 22, 2013
Accepted February 14, 2014
Published May 9, 2014
DOI http://dx.doi.org/10.4238/2014.May.9.17

ABSTRACT. Prostate cancer is one of the most common types of urological cancers. Despite the implementation of effective radiotherapy and chemotherapy methods, prostate cancer cells can still show resistance to treatment. In recent years, a combination of proteasome and histone deacetylase inhibitors has been used to treat various malignancies. In this study, we examined the cytotoxic and apoptotic effects of the proteasome inhibitor bortezomib (Velcade/PS-341) and histone deacetylase inhibitor trichostatin A (TSA), used either alone or in combination, on the human prostate LNCaP and PC3 cell lines. We investigated the cytotoxic activity of these inhibitors using a WST-1 assay, IkBα and caspase-3 mRNA levels by real-time polymerase chain reaction, and caspase-3 activity and activation of phosphorylated (p-IkBα) protein by Western blotting. Low-dose bortezomib and TSA synergistically induced apoptosis in both prostate cancer cell
lines. Combination treatment with TSA with bortezomib effectively inactivated NFkB signaling, upregulated the predominant endogenous apoptotic factor caspase-3, and disrupted the NFkB pathway in the androgen-independent PC3 cell line. In contrast, androgen-dependent LNCaP cells showed upregulation of caspase-3 through a pathway other than NFkB. This study examined the possible clinical use of bortezomib and TSA, together with reduced doses of chemotherapeutic agents with high cytotoxicity, to determine their apoptotic effects on the NFkB pathway in prostate cancer cell lines. Therefore, combination bortezomib and TSA treatment may represent a novel therapeutic strategy for prostate cancer.

**Key words:** Apoptosis; Bortezomib; NFkB pathway; Prostate cancer; Trichostatin A