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Co-inhibition of BET and proteasome enhances ER stress and Bim-dependent apoptosis with augmented cancer therapeutic efficacy

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Abstract

Agents that inhibit bromodomain and extra-terminal domain (BET) protein have been actively tested in the clinic as potential anticancer drugs. Proteasome inhibitors such as carfilzomib (CFZ) are FDA-approved for the treatment of patients with advanced multiple myeloma and have been tested against other cancers. The current study focuses on the combination of a BET inhibitor (e.g., JQ1) and a proteasome inhibitor (e.g., CFZ) as a novel cancer therapeutic strategy and the underlying mechanisms. The tested combination (JQ1 with CFZ) synergistically decreased cell survival and enhanced apoptosis *in vitro* and inhibited tumor growth *in vivo*. The dramatic induction of apoptosis was accompanied by enhanced elevation of Bim and ER stress. Bim knockout significantly attenuated apoptosis induced by the combination, suggesting a critical role of Bim induction in mediating the enhanced induction of apoptosis by BET and proteasome co-inhibition. The combination significantly increased Bim mRNA levels with limited effect on Bim protein stability, suggesting a primary transcriptional regulation of enhanced Bim expression. Our findings warrant further investigation of this combinatorial strategy as an effective regimen against cancer in the clinic.