PubMed

Display Settings: Abstract

Full Text Mol Cancer Ther

Mol Cancer Ther. 2013 Aug;12(8):1568-78. doi: 10.1158/1535-7163.MCT-12-1010. Epub 2013 May 8.

NF-κB inhibition by bortezomib permits IFN-γ-activated RIP1 kinase-dependent necrosis in renal cell carcinoma.

Thapa RJ, Chen P, Cheung M, Nogusa S, Pei J, Peri S, Testa JR, Balachandran S.

Immune Cell Development and Host Defense Program, Fox Chase Cancer Center, Philadelphia, PA, USA.

Abstract

Advanced renal cell carcinoma (RCC) is an invariably fatal cancer. Currently, small-molecule inhibitors that target cell growth, angiogenesis, or nutrient-sensing pathways represent the primary pharmacologic interventions for this disease, but these inhibitors only delay tumor progression and are not curative. The cytokine IFN-γ showed the potential to provide lasting remission in several phase I/II trials for advanced RCCs, but subsequent trials, including a multicenter phase III study using IFN-γ as a monotherapy for RCCs, were less promising. Notably, these trials were designed to exploit the indirect immunomodulatory effects of IFN-γ, whereas its direct antitumor properties--including its ability to trigger programmed cell death in tumors-remain mostly untapped. Here, we show that the proteasome inhibitor bortezomib (PS-341, Velcade) sensitizes otherwise resistant RCC cells to direct necrotic death by IFN-γ. Mechanistically, we show that bortezomib functions, at least in part, by inhibiting prosurvival NF-κB signaling. In the absence of this signal, IFN-γ triggers programmed necrosis (or "necroptosis") dependent on the kinase RIP1. When taken together with the observation that NF-κB signaling is elevated in RCCs, these results provide rationale for the combined use of IFN-γ and bortezomib in the treatment of metastatic RCCs.

PMID: 23657944 [PubMed - in process] PMCID: PMC3746800 [Available on 2014/8/1]

Publication Types, Grant Support

LinkOut - more resources