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

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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.