Letter to the Editor

Targeting Proteasomal Protein Degradation in Cancer—Letter

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In the recently published Molecular Pathways article (1), Molineaux summarized the recent progress in the development of proteasome inhibitors for the treatment of cancer. He stated that inhibition of NF-κB is one of the major mechanisms mediatisng the antitumor effect of proteasome inhibition. This notion has been supported by the finding that proteasome is responsible for the degradation of IκB, which is a major inhibitor of the NF-κB signaling pathway (2). It is therefore believed that proteasome inhibition would lead to the accumulation of IκB and thereby block the NF-κB signaling. However, this concept has recently been challenged. Dolcet and colleagues first reported that the U.S. Food and Drug Administration (FDA)-approved proteasome inhibitor bortezomib activates constitutive NF-κB in endometrial carcinoma cell line (3). Markovina and colleagues also showed that the proteasome inhibitor fails to inhibit constitutive NF-κB activity in myeloma cell lines (4). Hideshima and colleagues later showed that bortezomib and another proteasome inhibitor (lactacystin) promote nonproteasomal degradation of IκB through activation of IKKβ and RIP2, resulting in enhanced NF-κB DNA binding in human multiple myeloma cell lines and primary tumor samples (5). Li and colleagues further showed that bortezomib may induce IκBβ degradation through calpain activation, which lead to increased p65 (a NF-κB subunit) nuclear translocation and NF-κB activity (6). Above all, pharmacologic inhibition of IKKβ or calpain enhances the cytotoxic effect of bortezomib (5, 6). Collectively, these findings suggest that proteasome inhibitor may paradoxically induce NF-κB activation, which serves as an autoregulatory prosurvival mechanism to counteract the cytotoxicity of proteasome inhibition.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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