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Proteasome inhibitors target FOXM1 and induce p53-independent apoptosis in human cancer cells

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Proteasome inhibitors are currently in the clinic or in clinical trials, but the mechanism of their anticancer activity is not completely understood. The oncogenic transcription factor FoxM1 is one of the most overexpressed genes in human tumors, while its expression is usually halted in normal non-proliferating cells. Previously, we established that thiazole antibiotics Siomycin A and thiostrepton inhibit FoxM1 and induce apoptosis in human cancer cells. We found that they also act as proteasome inhibitors in vitro. More importantly, we also found that well-known proteasome inhibitors such as MG115, MG132 and Velcade inhibit FoxM1 transcriptional activity and FoxM1 expression. Furthermore, we found that well-known proteasome inhibitors such as MG132 and bortezomib as well as the recently discovered proteasome inhibitor thiostrepton induced p53-independent apoptosis in human cancer cell lines that correlated with p53-independent induction of proapoptotic Noxa, but not Puma proteinOur data confirm that proteasome inhibitors generally induce p53-independent apoptosis in human cancer cells. We investigated the therapeutic potential of the combination of thiostrepton and proteasome inhibitor bortezomib (Velcade) on various human tumor cell lines. Combination of sublethal concentrations of thiostrepton and bortezomib induced potent apoptosis and inhibition of long-term colony formation in a wide variety of human cancer cell lines. The synergistic relationships between thiostrepton and bortezomib combination was also quantitatively demonstrated by low combination index between 0.1 and 0.8. The synergy between these drugs was based on their proteasome inhibitory activities of both drugs, because structurally similar thiostrepton modification, thiostrepton methyl ester that did not have inhibitory activity failed to increase apoptosis in combination with bortezomib. Thiazole antibiotic, thiostrepton was identified as an inhibitor of oncogenic transcription factor FoxM1, later demonstrated to exhibit proteasome inhibitory activity. We found that polymeric micelle-encapsulated thiostrepton reduced tumor growth rate in xenografts induced by human breast and liver cancer cell lines Encapsulation of thiostrepton into polymeric micelles can aid its solubilization and increase its accumulation into tumor sites. Furthermore, its anti-cancer effects on breast cancer xenografts were found to be through reducing cell proliferation and inducing cell death. Thiostrepton is sulfur containing highly modified macrocyclic antibiotic with a central pyridine/tetrapyridine/ dehydropiperidine ring with up to three thiazole substituents' on positions 2, 3 and 6, which has macrocyclic loop connecting thiazole rings at position 2 and 3 described as ring A. In addition, it has a quinaldic acid macrocycle also connected to thiazole on position 2 described as ring B. Structural modification of thiostrepton to thiostrepton methyl ester (with open B ring) did not demonstrate proteasome inhibitory activity. These data suggest that B ring of thiostrepton and similar thiazole antibiotic Siomycin A that is absent in other thiazole antibiotics determines the proteasome inhibitory activity of these drugs.