SUMMARY

KPT-0127 Induces Selective Apoptosis of Malignant Cells by CRM1 Inhibition and Elevation of Regulatory Proteins p53, p21, FOXO and IκB

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CRM1 (Kpt) is a key nuclear export protein which controls multiple tumor suppressor proteins (p53, p21, p27 and IκB) and proliferation pathways including p16, p15, FOS/ JUN, Wnt/catenin and NFκB. It was previously reported that maximal inhibition of p38 signaling and reduction of IκB and NFκB activities is required for maximal p53 induction in a variety of cancer cells. While p53 induction has been observed, its role in resistance to chemotherapy is not known. p53 is also critical for tumor suppression, and restoring p53 activity in cancer cells could potentially reverse chemoresistance and/or make the cells sensitive to chemotherapies designed to induce p53 activation. We have recently demonstrated that inhibition of CRM1 in a variety of cancer cells results in selective induction of p53 and its downstream targets p21 and p27, while only p21 induction is observed in normal fibroblasts. Importantly, CRM1 inhibition specifically causes cell cycle arrest of cancer cells, while normal cells maintain their cell cycle activity. We have shown that CRM1 inhibition induces cell cycle arrest in cell lines of both hematologic and solid origin. CRM1 inhibition specifically caused p53 induction and cell cycle arrest in all hematologic cell lines tested, while cell cycle arrest was not observed in a variety of solid tumor cell lines. These results indicate that CRM1 inhibition may be specific for hematologic malignancies. We have also shown that CRM1 inhibition can improve drug sensitivity to a variety of chemotherapeutic agents, including Bortezomib (aka Velcade), a selective proteasome inhibitor. We have shown that CRM1 inhibition can restore drug sensitivity and restore chemotherapies ineffective. Induction of nuclear expression of chemotherapy targets, TSP and p53, combinations with standard therapies for hematological cancers.

KPT-0127 kills lymphoproliferative leukemic cells but not normal BM cells. Foamy-leaked human CLL cells (resistant after Fludarabine-based chemotherapy treatment) or normal BM cells were treated with vicin with varying doses of KPT-0127 and viability was determined using Cyt assay. KPT-0127 selectively kills human CLL cells but normal healthy lymphocytes.

KPT-0127 Induces Caspase-3 Activation in Malignant Cell Lines

KPT-0127 Causes Caspase-3 activation (A). Jurkat and Burkitt’s Lymphoma cell lines were treated for 24 hours with KPT-0127 and caspase 3/7 activity was determined (B) and (C).

KPT-0127 Causes Cell Cycle Arrest in 1937 Lymphoma Cells

KPT-0127 causes G0/G1 and G2/M arrest. L363 Lymphoma cells were treated with vehicle (A) or KPT0127 at indicated doses (B). Cells were fixed in ethanol and stained with propidium iodide to assess the left scatter DNA content by flow cytometry.

KPT-0127 Increases Nuclear Levels of p53, p21 and FOXO

KPT-0127逛街 nuclear localization of functional p53 and phospho-p53, and in vivo, in leukemic MMS-1 cells, KPT-0127 arrested U17D cells. However, in KPT-0127 treated tumors, nuclear retention of p53 was not observed. The role of p53 in the induction due to block of CRM1 mediated nuclear export. In KPT-0127 treated cases cancer cells arrest due to nuclear retention of p53.

KPT-0127 Inhibits the Growth of Small & Large Myeloma Xenografts

KPT-0127 Inhibits the Growth of Malignant B cells and Human CLL Cells but not Normal BM cells

KPT-0127 Inhibits the Growth of Small & Large Myeloma Xenografts

KPT-0127 Enhances the Cytotoxicity of Bortezomib and Doxorubicin

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KPT-0127 Demonstrates Potent & Selective Cancer Cell Cytotoxicity

KPT-0127 kills human lymphoproliferative leukemic cells but not normal BM cells. Foamy-leaked human CLL cells (resistant after Fludarabine-based chemotherapy treatment) or normal BM cells were treated with vicin with varying doses of KPT-0127 and viability was determined using Cyt assay. KPT-0127 selectively kills human CLL cells but normal healthy lymphocytes.

Conclusions

1. Induction of nuclear export through blockade of CRM1 induces retention of multiple tumor suppressor proteins and proliferation control in the nucleus.

2. KPT-0127 is a Selective Inhibitor of Nuclear Export (SINE) with preferential toxicity for malignant versus normal cells independent of p53 status

3. KPT-0127 is well tolerated in vivo and inhibits the growth of small (130µm) and large (1350µm) myeloma xenografts

4. SINE may represent a novel approach to the treatment of hematologic malignancies with both single agent activity and in combination with other anticancer drugs.

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