Clinical Cancer Research

Cancer Therapy: Preclinical

The Dual Inhibition of RNA Pol I Transcription and PIM Kinase as a New Therapeutic Approach to Treat Advanced Prostate Cancer


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Abstract

Purpose: The MYC oncogene is frequently overexpressed in prostate cancer. Upregulation of ribosome biogenesis and function is characteristic of MYC-driven tumors. In addition, PIM kinases activate MYC signaling and mRNA translation in prostate cancer and cooperate with MYC to accelerate tumorigenesis. Here, we investigate the efficacy of a single and dual approach targeting ribosome biogenesis and function to treat prostate cancer.

Experimental Design: The inhibition of ribosomal RNA (rRNA) synthesis with CX-5461, a potent, selective, and orally bioavailable inhibitor of RNA polymerase I (Pol I) transcription, has been successfully exploited therapeutically but only in models of hematologic malignancy. CX-5461 and CX-6258, a pan-PIM kinase inhibitor, were tested alone and in combination in prostate cancer cell lines, in Hi-MYC- and PTEN-deficient mouse models and in patient-derived xenografts (PDX) of metastatic tissue obtained from a patient with castration-resistant prostate cancer.

Results: CX-5461 inhibited anchorage-independent growth and induced cell-cycle arrest in prostate cancer cell lines at nanomolar concentrations. Oral administration of 50 mg/kg CX-5461 induced TP53 expression and activity and reduced proliferation (MK67) and invasion (loss of ductal actin) in Hi-MYC tumors, but not in PTEN-null (low MYC) tumors. While 100 mg/kg CX-6258 showed limited effect alone, its combination with CX-5461 further suppressed proliferation and dramatically reduced large invasive lesions in both models. This rational combination strategy significantly inhibited proliferation and induced cell death in PDX of prostate cancer.

Conclusions: Our results demonstrate preclinical efficacy of targeting the ribosome at multiple levels and provide a new approach for the treatment of prostate cancer. Clin Cancer Res; 22(22); 5539–52. ©2016 AACR.

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Footnotes

- Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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