INHIBITION OF CASEIN KINASE II (CK2) ENHANCES IKAROS TUMOR SUPPRESSOR ACTIVITY AND SHOWS THERAPEUTIC EFFICACY IN A PRECLINICAL LEUKEMIA MODEL

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Casein kinase II (CK2) promotes cell cycle progression and cellular proliferation in leukemia. Overexpression of CK2 results in the development of high-risk leukemia, that is resistant to chemotherapy. The mechanism by which CK2 promotes cellular proliferation and malignant transformation is unknown. Our published data showed that CK2 phosphorylates the Ikaros tumor suppressor protein, which results in loss of its function as a transcriptional repressor. To determine the therapeutic efficacy of CK2 inhibitors, we tested their effect on Ikaros tumor suppressor function in vitro in human pre-B acute lymphoblastic leukemia (ALL) and in vivo using a preclinical human-mouse pre-B ALL xenograft model. Using qChIP (quantitative chromatin immunoprecipitation assay) we have identified CDC7 and CDK2 as in vivo Ikaros target genes. The use of a luciferase reporter assay demonstrated that Ikaros represses transcription of CDC7 and CDK2. Increased expression of Ikaros via retroviral transduction in pre-B ALL cells resulted in transcriptional repression of CDC7 and CDK2, along with increased binding of Ikaros to their promoters. These results suggest that Ikaros functions as a transcriptional repressor of CDC7 and CDK2, and thus, as a negative regulator of cell cycle progression in ALL. We tested whether the inhibition of CK2 enhances Ikaros-mediated transcriptional repression of CDC7 and CDK2 in pre-B ALL. Treatment of the pre-B ALL cell line, Nalm6, with a specific CK2 inhibitor, resulted in transcriptional repression of CDC7 and CDK2, along with cell cycle arrest. We used a preclinical xenograft model of pre-B ALL to assess the therapeutic efficacy of CK2 inhibition. Treatment with a specific CK2 inhibitor resulted in the transcriptional repression of CDC7 and CDK2 and a strong anti-leukemia effect that led to prolonged survival of treated mice. Our data suggest that CK2 inhibition enhances the Ikaros-mediated repression of cellular proliferation in ALL. These results demonstrate the efficacy of CK2 inhibition as a treatment for ALL and provide a mechanistic rationale for the use of CK2 inhibitors as a targeted treatment of pre-B ALL in clinical trials.

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