

Flavopiridol inhibits adult T-cell leukemia/lymphoma cell growth by IRF4 downregulation via super-enhancer suppression

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Background:

Adult T-cell leukemia/lymphoma (ATL) is an intractable hematological malignancy with extremely poor prognosis. Recent studies have revealed that super-enhancers (SE) play important roles in controlling tumor-specific gene expression and are potential therapeutic targets for neoplastic diseases, including ATL. Cyclin-dependent protein kinase (CDK)9 is a component of the complex comprising transcription factors that bind the SE region. Flavopiridol is a CDK9 inhibitor which exerts antitumor activity not only by inhibiting phosphorylation of RNA polymerase II but also by suppression of tumor-specific genes expression mediated by SE as expected. Therapeutic efficacy of flavopiridol for hematological malignancies has been demonstrated but its efficacy for ATL remained unknown. In the present study, we verified the efficacy of flavopiridol against ATL and impact on SEs.

Methods:

ATL-derived cell lines and clinical samples of ATL patients were used. The effects of flavopiridol on cell proliferation and transcription in ATL cells were analyzed using Cell Titer Glo Reagent and RNA sequence. The status of SE was evaluated using chromatin immunoprecipitation (ChIP) sequence and ROSE assay. Immunocompromised mice inoculated ATL cells were used to verify *in vivo* efficacy of flavopiridol.

Results:

Flavopiridol inhibited the proliferation of ATL cell lines and samples from ATL patients. RNA sequencing and ChIP sequencing revealed that the expression of IRF4 was suppressed, and SE regulated IRF4 in ATL cell lines. Previous studies showed that IRF4 suppression inhibited ATL cell proliferation. Hence, IRF4 is a putative flavopiridol target in ATL therapy. Moreover, flavopiridol suppressed ATL in a mouse xenograft model.

Conclusion:

The present study disclosed that flavopiridol inhibits ATL cell growth by suppressing SE-mediated IRF4 expression. Flavopiridol has therapeutic efficacy against ATL and its mode of action has been partially elucidated here. This work indicated that flavopiridol is promising for the clinical treatment of ATL.

Disclosure of Interest Statement:

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