IMiD/CELMoD-induced growth suppression of adult T-cell leukemia/lymphoma cells via cereblon through downregulation of target proteins and their downstream effectors

ABSTRACT

Adult T-cell leukemia/lymphoma (ATL) is an aggressive T-cell neoplasia associated with human T-cell leukemia virus type 1 (HTLV-1) infection and has an extremely poor prognosis. Lenalidomide (LEN; a second-generation immunomodulatory drug [IMiD]) has been employed as an additional therapeutic option for ATL since 2017, but its mechanism of action has not been fully proven, and recent studies reported emerging concerns about the development of second primary malignancies in patients treated with long-term IMiD therapy. Our purpose in this study was to elucidate the IMiD-mediated anti-ATL mechanisms. Thirteen ATL-related cell lines were divided into LEN-sensitive or LEN-resistant groups. CRBN knockdown (KD) led to a loss of LEN efficacy and IKZF2-KD-induced LEN efficacy in resistant cells. DNA microarray analysis demonstrated distinct transcriptional alteration after LEN treatment between LEN-sensitive and LEN-resistant ATL cell lines. Oral treatment of LEN for ATL cell-transplanted severe combined immunodeficiency (SCID) mice also indicated clear suppressive effects on tumor growth. Finally, a novel cereblon modulator (CELMoD), iberdomide (IBE), exhibited a broader and deeper spectrum of growth suppression to ATL cells with efficient IKZF2 degradation, which was not observed in other IMiD treatments. Based on these findings, our study strongly supports the novel therapeutic advantages of IBE against aggressive and relapsed ATL.