News Release

Title

Elucidation of the formation mechanism of lymph node lesions in adult T-cell leukemia/lymphoma
- Epigenetic regulation of *HGF* expression in tumor cells and promising epigenetic therapy -

Key Points

- Adult T-cell leukemia/lymphoma (ATL) is one of the most lethal hematopoietic malignancies. Although ATL cells in peripheral blood tend to be sensitive to recently advanced treatments (e.g., mogamulizumab, an anti-CCR4 monoclonal antibody), ATL cells in lymph node still show resistance to any treatment.
- To clarify the mechanism of the formation of these treatment-resistant lesions, we compared the expression of cytokines and growth factors in lymph node and blood ATL cells. We found that HGF was an important factor for tumor formation and acts on ATL cells in an autocrine manner.
- The epigenetic status of *HGF* gene was different between lymph node and blood ATL cells. Bromodomain inhibitor (JQ1) suppressed HGF/c-Met signaling by inhibiting *HGF* expression and suppress cell proliferation and tumor formation in the mice xenograft model.
- Among ATL patients treated with mogamulizumab, the high HGF expression group showed a worse prognosis than low expression group.
- Our study demonstrated the potential of bromodomain inhibitors as promising candidates in the therapeutic strategy of patients with mogamulizumab resistance.

Summary

ATL is one of the refractory hematopoietic malignancies, and the elucidation of the formation mechanism of lymph node lesions that are particularly resistant to treatment and the development of strategy to get it over is an urgent issue. Comparative analysis of lymph node-derived and blood-derived ATL cell lines revealed that HGF expression was higher in lymph node ATL cells. It was also shown that HGF/c-Met signal promotes cell proliferation and invasion both *in vitro* and *in vivo*. As the differential *HGF* expression between lymph node and blood ATL cells was caused by the different epigenetic modofication of the gene expression regulatory region (enhancer and promoter). JQ1, a bromodomain inhibitor reduces *HGF* expression and downstream signaling activity, and suppressed cell proliferation and tumor formation. It was also found that serum HGF concentration is involved in prognosis in patients treated with mogamulizumab. Our data suggested that epigenetic regulation of HGF/c-Met signaling plays an important role in the formation of lymph node lesions in ATL, and targeting this pathway may be a useful therapeutic strategy to overcome resistant ATL lesions.

Research Background

Adult T-cell leukemia-lymphoma (ATL) is one of the lethal hematopoietic malignancies that progresses rapidly and is intractable. The lesions are wide-ranging, and at the time of diagnosis, approximately 90% of the cases have non-blood lesions, such as lymph nodes and organ infiltration. In recent years, in addition to conventional anti-cancer drugs, mogamulizumab, which targets CCR4 protein expressed in ATL cells, has been incorporated as standard therapy and has been improved outcome. Although ATL cells in peripheral blood tend to be sensitive to this monoclonal antibody, ATL cells in the lymph node still show resistance to any treatment. The mechanism of the formation of these treatment-resistant lesions is not clear, and new therapeutic approaches are needed. In this study, we performed a comparative analysis of the expression of cytokines and growth factors of ATL cells in lymph nodes and blood and investigated the mechanism of gene regulation involved in tumor formation and the use of therapeutic agents targeting epigenome.

Research Results

The protein array analysis of lymph node-derived and blood-derived ATL cell lines showed that HGF was a factor that is highly expressed in lymph node-derived cells and acts in an autocrine manner. It has been known that the HGF/c-Met pathway is involved in tumor growth and metastasis in some cancers and that aggressive ATL has a high HGF plasma concentration. However, the expression mechanism and differences in expression at the cell origin were not clear. In this study, the analysis of clinical specimens (lymph nodes/peripheral blood) from the same patient revealed that the proportion of ATL cells that express HGF is predominant in lymph nodes than in blood. HGF/c-Met signaling is activated in the lymph node ATL cells, and the induction of *HGF* gene into blood-derived cells, which do not express *HGF* upregulated downstream signal activity and promoted proliferation and invasion *in vitro*. In the mouse xenograft model, tumor formation and organ infiltration were observed. The analysis of *HGF* regulatory regions (enhancer and promoter) in lymph node and blood-derived ATL cell lines revealed that H3K27Ac, an active histone marker, and BRD4, a reader protein of H3K27Ac, were enriched in lymph node ATL cells and that this caused a difference in HGF expression between the two (Figure 1). Therefore, we evaluated the effect of JQ1, an inhibitor of BRD4. JQ1 significantly decreased *HGF* expression and inactivated downstream signals and suppressed cell proliferation. Furthermore, in the mice xenograft model, JQ1 treatment significantly reduced the tumor mass and inhibited organ infiltration compared with the control group (Figure 2). In clinical case analysis, serum HGF concentration was significantly higher in patients with non-blood lesions than patients with only blood lesion and among ATL patients who received mogamulizumab treatment, and both overall survival and progression-free survival were worse in HGF high group (Figure 3).

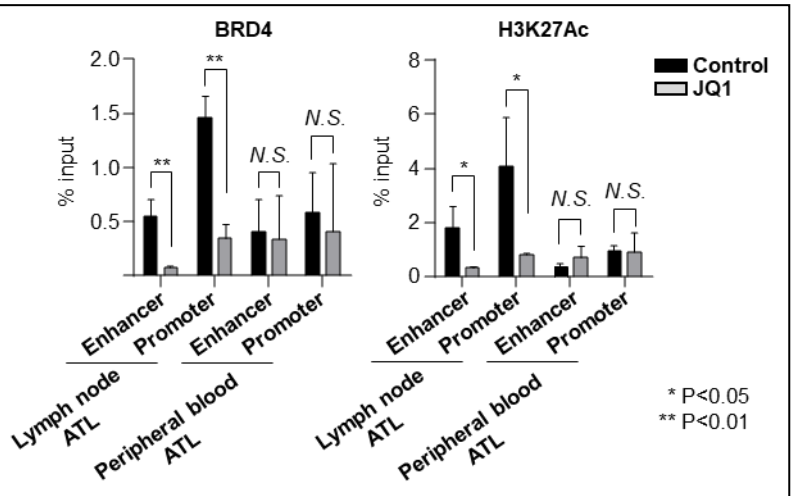

Figure 1. Status of *HGF* gene regulatory region

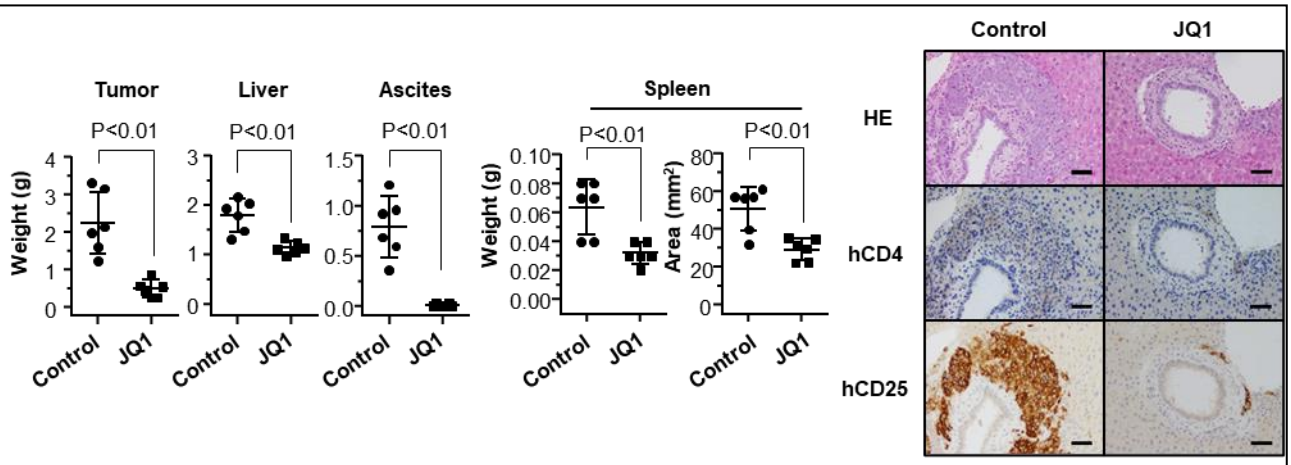

Figure 2. Inhibition of tumor growth by JQ1

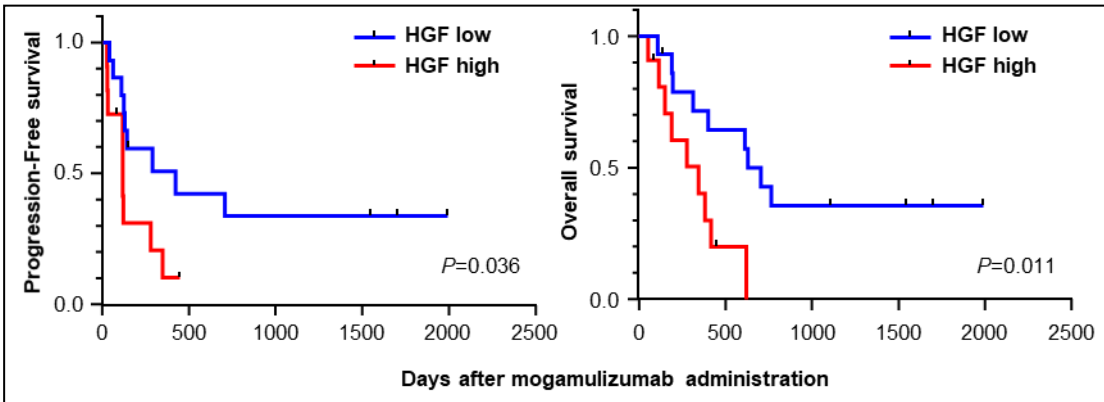

Figure 3. Prognosis of ATL patients who received mogamulizumab treatment

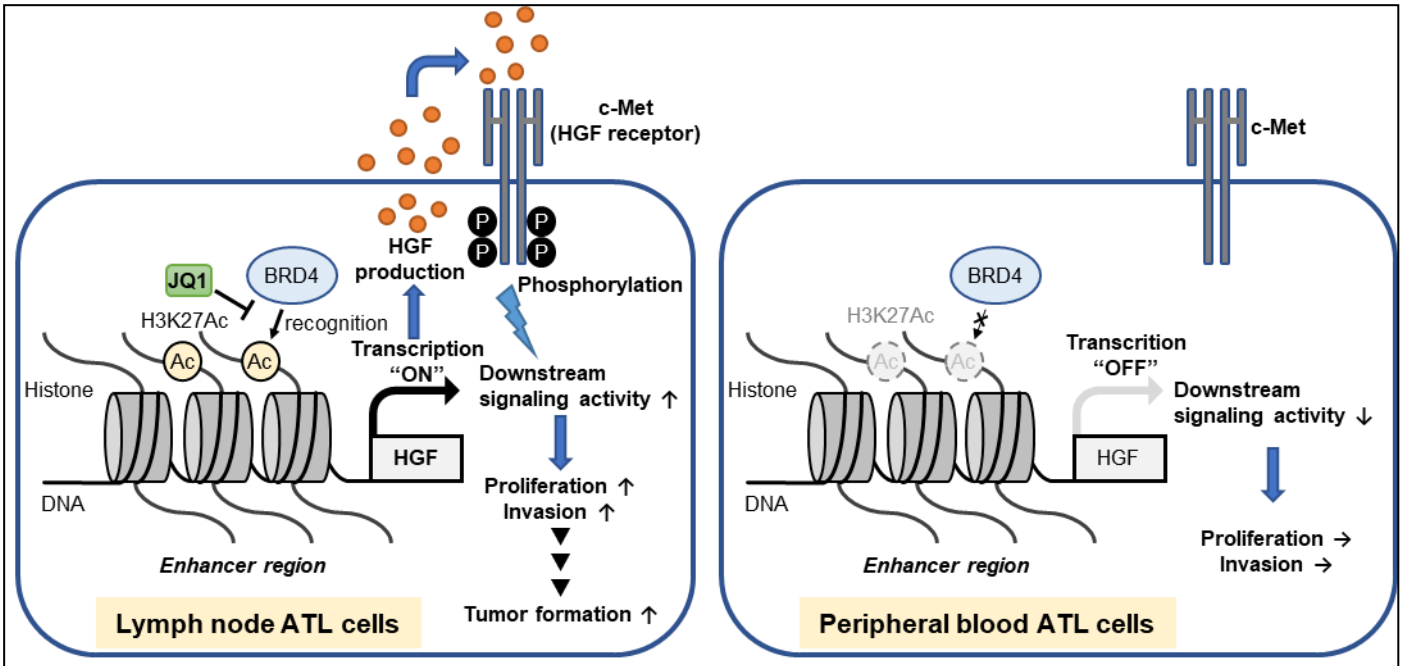

Figure 4. Epigenetic regulation of HGF expression and HGF/c-Met signaling in ATL cells

Research Summary and Future Perspective

Our data suggested that the epigenetic regulation of HGF expression in lymph node ATL cells promoted the formation of ATL tumors and may be associated with mogamulizumab resistance. We also found that a bromodomain inhibitor could be a novel, useful agent for patients with treatment-resistant lesions. Clinical trials of bromodomain inhibitors are currently used overseas for leukemia, lymphoma, and multiple myeloma in the hematopoietic field, and maybe introduced in Japan in the future. As the results of our study, it is expected to be useful in ATL as well, so we are aiming to develop a novel therapeutic strategy targeting epigenetic alterations.

Publication

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