Comment on Ishio et al, page 1541

Targeting vulnerabilities of adult T-cell leukemia

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In this issue of *Blood*, Ishio et al[1] identified the genes critical for proliferation and/or survival of adult T-cell leukemia-lymphoma (ATL) cells using whole-genome CRISPR library screening. They also discovered that the mTORC1 pathway is critical for ATL cells.

ATL is caused by human T-cell leukemia virus type 1 (HTLV-1) infection.[2] HTLV-1 is the first human retrovirus that causes multiple disorders, not only ATL but also inflammatory diseases like HTLV-1–associated myelopathy. ATL is an intractable lymphoproliferative disease. The prognosis of patients with acute type ATL treated with chemotherapy remains <1 year. Allogeneic hematopoietic stem cell transplantation is the only potentially curative approach, but the risk of relapse and severe GVHD is high. Therefore, the targeted therapy to ATL is needed to improve the prognosis of patients with ATL.

The authors identified 9 essential genes in ATL, including CDK6, CCND2, BATF3, JUNB, STAT3, and IL10RB genes, after excluding 305 essential genes identified in mantle cell lymphoma cell lines. These 9 genes are associated with various pathways, which contain AP-1 family (BATF3 and JUNB), G1-S cell-cycle transition (CDK6 and CCND2), and JAK/STAT pathway (STAT3 and IL-10RB). The previous study by this research group reported that BATF3 and IRF4 are essential transcription factors for ATL cells.[3] Thus, potential targets for ATL treatment converge at several critical pathways.

Based on these results, the authors demonstrated that the CDK6 inhibitor palbociclib induces cell-cycle arrest and apoptosis of ATL cells with wild-type p53. Furthermore, palbociclib with mTORC1 inhibitors effectively suppresses ATL cells. Thus, this study identified new targets for treatment of ATL.

HTLV-1 can infect many different types of cells, as its receptor is glucose transporter 1.[4] However, most of HTLV-1–infected cells found in vivo are $CD4^+CD25^+CCR4^+$ T cells, indicating that this cell-type specificity happens after infection of the host. Interestingly, Foxp3 expression is detected in all ATL cases.[5] Thus, ATL cells resemble regulatory T (Treg) cells. As the mechanisms of tropism to Treg cells, HTLV-1 bZIP factor (HBZ), which is the antisense transcript of HTLV-1, induces expression of Foxp3, CCR4, and BATF3.[3,6] Thus, HBZ converts infected T cells to a Treg-like phenotype. This strategy might be beneficial for survival and transmission of HTLV-1. Expression of the *tax* gene, which is encoded in the plus strand of the provirus, is frequently inactivated in ATL cells, whereas HBZ is expressed in all ATL cases, and knock-down of HBZ inhibits proliferation of ATL cells, indicating that ATL cells still depend on HBZ.

BATF3 and IRF4 interact with AP1-IRF composite elements motif, which is critical for Treg differentiation and suppressive function.[7] JunB promotes an IRF4-dependent transcription program.[8] Treg cells produce increased amounts of interleukin 10 (IL-10), which is critical for immune suppression by Treg cells. However, IL-10 promotes proliferation of HBZ-expressing cells through modulation of downstream signaling from IL-10 receptor.[5] HBZ interacts with STAT3. Furthermore, mTOR signaling plays an important role for generation and function of effector Treg cells.[9] Thus, several targetable molecules are linked to Treg cells.

HBZ hijacks networks that are critical for Treg cells. The vulnerable targets of ATL cells are the molecules that are important for Treg cells. Kogure et al[10] reported novel mutations in ATL cells using the whole-genome sequencing, one of which is a loss-of-function alteration targeting the long isoform of the CIC gene. Long isoform-specific inactivation of the CIC gene increases $CD4^+CD25^+Foxp3^+$ T cells in mice, indicating that this mutation is also associated with Treg cells.

These studies demonstrate that HTLV-1 targets Treg cells for its survival and transmission via functions of HBZ. ATL cells still rely on HBZ-modulated gene networks of Treg cells. These molecules that are indispensable for survival and proliferation of ATL cells should be ideal therapeutic targets of this intractable disease.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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