A Novel Therapeutic Approach for Efficient Elimination of HTLV-1–Infected Cells

■ Researcher Information

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■ Research Ideas & Biomedical Seeds

■ Research Originality and Advantages

We identified a selective growth-suppressive mechanism in HTLV-1–infected cells through induction of endoplasmic reticulum (ER) stress, revealing a novel therapeutic target not previously recognized.

■ Novel Antigen Design, Appropriate Animal Models, and Modalities

HIV integrase inhibitor: MK-2048

■ Major Findings

We demonstrated that MK-2048 selectively activates the PERK–ATF4–CHOP pathway of the unfolded protein response (UPR) in HTLV-1–infected cells, thereby inducing apoptosis.

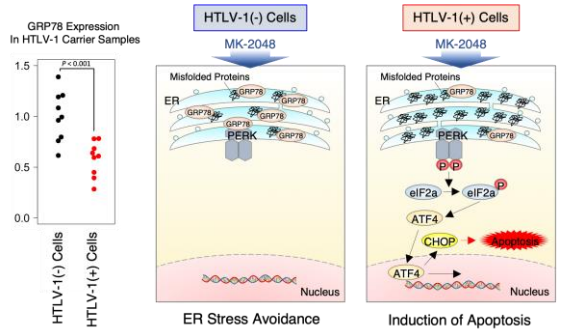
Normal cells maintain homeostasis by alleviating physiological stress through UPR. However, when UPR fails to function properly or excessive stress occurs, apoptosis is induced. Activation of the PERK–ATF4–CHOP pathway represents a mechanism of action distinct from existing therapeutics, and MK-2048 is expected to serve as a promising candidate anti-HTLV-1 agent capable of selectively eliminating HTLV-1–infected cells. Blood Adv. 4(9):1845-1858. (2020)

■ Background and Unmet Medical Needs

Human T-cell leukemia virus type 1 (HTLV-1) infection causes fatal diseases such as adult T-cell leukemia/lymphoma (ATL). In particular, patients with acute and lymphoma subtypes have an extremely poor prognosis, with a 4-year overall survival rate of less than 20%. Meanwhile, no effective vaccine is currently available, and many patients develop resistance to existing chemotherapies, leaving treatment options limited. Therefore, there is a strong unmet medical need for the development of novel therapeutics with distinct mechanisms of action.

■ Research Overview

In HTLV-1 carrier samples analyzed in this study, expression of GRP78, a key regulator involved in alleviating endoplasmic reticulum (ER) stress, was significantly decreased in HTLV-1–infected cells, suggesting increased vulnerability of infected cells to ER stress.
MK-2048 selectively activated the UPR/PERK–ATF4–CHOP pathway in HTLV-1–infected cells and induced apoptosis.



■ Future Perspectives

Although the clinical development of MK-2048 as an HIV integrase inhibitor has been completed, its potential for drug repositioning is currently being investigated at the basic research level.