

## Both HBZ Protein and mRNA upregulate TAp73 to promote the Warburg Effect in ATL cells

### Authors:

Toyoda K<sup>1</sup>, Yasunaga J<sup>1</sup>, Arima Y<sup>2,3</sup>, Tanaka A<sup>4</sup>, Tsujita K<sup>2,5</sup>, Watanabe M<sup>1</sup>, Sonoda M<sup>1</sup>, Shichijo T<sup>1</sup> and Matsuoka M<sup>1</sup>

<sup>1</sup> Department of Hematology, Rheumatology and Infectious Diseases, Faculty of Life Sciences, Kumamoto University School of Medicine, Kumamoto, Japan

<sup>2</sup> Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

<sup>3</sup> International Research Center for Medical Sciences (IRCMS), Kumamoto University, Kumamoto, Japan

<sup>4</sup> Department of Human Genetics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

<sup>5</sup> Center for Metabolic Regulation of Healthy Aging (CMHA), Kumamoto University, Kumamoto, Japan

**Presentation Type:** Research Based Oral Presentation

**Category:** Basic Science

### Background:

HTLV-1 bZIP factor (HBZ) is a viral oncogene constantly expressed in adult T-cell leukemia-lymphoma (ATL). HBZ protein and mRNA together function for proliferation and survival, and acquisition of immunophenotype in HTLV-1-infected cells. However, their comprehensive mechanisms remain unknown.

### Methods:

We carried out RNA-seq and ATAC-seq of murine primary CD4<sup>+</sup> T cells transduced with *HBZ* mutants functioning protein or mRNA independently. High-throughput sequencings were also performed using cell lines, and primary T cells of HBZ-transgenic mice (HBZ-Tg) and ATL patients. We analyzed metabolomics using HBZ-Tg with/without TP73 knockout.

### Results:

Both HBZ protein and RNA upregulated TAp73, the longest isoform of TP73. Bioinformatic analysis suggested that function of EZH2 was modulated by HBZ protein and RNA, resulting in upregulation of TAp73. Indeed, we found that both HBZ protein and RNA directly bound to EZH2. Interestingly, HBZ RNA enhanced expression of BATF3 to upregulate both TAp73 and another isoform of p73, DNp73 via IRF4/BATF3 machinery.

Consistent with these findings, TAp73 and DNp73 were upregulated in ATL patients. Notably, knockdown of TP73, especially in TAp73, led to cellular death of ATL cells. Knockout of TAp73, not DNp73, significantly lessened inflammation of HBZ-Tg, indicating that TAp73 is important in pathogenesis of HBZ. We also found that TAp73 was recruited to the promoters of MCT1 and MCT4, which are lactate transporters associated with the Warburg effect. We subsequently found that sirosingopine, a MCT1/4 dual inhibitor, impedes proliferation of ATL cells *in vitro* and *in vivo*.

**Conclusion:**

Both HBZ protein and RNA modulate the function of EZH2, enhance expression of TAp73, and promote the Warburg effect. These alterations may play critical roles in chromatin modification and cancer metabolism in ATL.

**Disclosure of Interest Statement:**

This study was funded by the Japan Agency for Medical Research and Development. No pharmaceutical grants were received in the development of this study.