HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

P1272 GP130/STAT3 AXIS IS A POTENTIAL THERAPEUTIC TARGET FOR HISTONE DEACETYLASE INHIBITOR-RESISTANT CUTANEOUS T-CELL LYMPHOMA

Topic: 20. Lymphoma Biology & Translational Research

Yuto Takahashi[1], Akihiro Kitadate[2], Sho Ikeda[2], Sayaka Iwama[1], Ko Abe[2], Yuka Matsuda[1], Hiroyuki Tagawa[2], Hideki Wakui[1], Naoto Takahashi[2]

[1] Department of Life Science, Graduate School of Engineering Science, Akita University, Akita, Japan;[2] Department of Hematology, Nephrology, and Rheumatology, Akita University Graduate School of Medicine, Akita, Japan

Background: Histone deacetylase inhibitors (HDACis), such as vorinostat and romidepsin, are promising agents for various T-cell lymphomas, including cutaneous T-cell lymphoma (CTCL), peripheral T-cell lymphoma, and adult T-cell lymphoma/leukemia. Despite the promising anti-lymphoma activity of HDACis, resistance remains a significant clinical problem. Therefore, novel therapeutic strategies to overcome HDACi resistance are required. In this study, we generated HDACi-resistant CTCL cell lines and investigated the mechanisms of HDACi resistance.

Aims: The aim of the study was to identify the mechanism of resistance to HDACis in CTCLs and to explore new therapeutic targets.

Methods: CTCL cell lines My-La, MJ, and Hut78 were used in the study. Vorinostat-resistant cell lines MyLa resistant, HUT78 resistant, and MJ resistant were prepared by repeatedly exposing cells to increasing concentrations of vorinostat. To maintain drug resistance, cells were continuously cultured in a medium containing 2.5 μM vorinostat. Following this, we conducted a comprehensive gene expression analysis using a microarray platform to investigate deregulated genes in the resistant cell lines.

Results: CTCL cell lines resistant to vorinostat were also resistant to romidepsin, suggesting that vorinostat-resistant cell lines were cross-resistant to other HDACis. Next, we selected genes whose expression was upregulated more than two-fold in the three resistant cell lines and performed pathway analysis. Pathway analysis revealed that upregulated genes were significantly enriched in cytokine-mediated signaling pathways. Among the upregulated genes, we focused on IL6ST/gp130, which forms a heterogeneous complex with IL6 and IL6 receptor and activates the JAK/STAT pathway. Further, flow cytometric analysis revealed that surface gp130 expression was significantly upregulated in resistant cell lines. Moreover, resistant cell lines showed an increased sensitivity to a gp130 inhibitor (SC144), and gp130 activation could activate the JAK/STAT pathway. Accordingly, we examined the expression level of the activated form of STAT3, that is p-STAT3, and found that p-STAT3 was significantly upregulated in resistant cell lines. To investigate whether p-STAT3 upregulation is involved in the acquisition of vorinostat resistance, we performed STAT3 knockdown using an siRNA. We confirmed that STAT3 knockdown significantly decreased the survival of resistant cell lines. Moreover, resistant cell lines showed increased sensitivity to the STAT3-selective inhibitor, C188-9. We also examined the expression level of p-STAT5; however, it was downregulated in resistant cell lines, which was opposite to that of p-STAT3. Finally, we examined gp130 and p-STAT3 protein expression in CTCL skin samples, which were obtained from the same patients before and after vorinostat treatment. We found that gp130 and p-STAT3 expression significantly increased in the specimens at the time of relapse after vorinostat treatment.

Summary/Conclusion: Activation of STAT3 in HDACi-resistant CTCL cells was enhanced via gp130, which contributed to their resistance. These results suggested that STAT3 could be a new therapeutic target in HDACi-resistant CTCL, and gp130/STAT3 inhibition could be an important therapeutic strategy.