KSN 2016 Abstract Submission

Transplantation & Immunology

KSN2016ABS-1041

TARGETING HISTONE DEACETYLASE IN RENAL TUBULAR EPITHELIAL CELLS INHIBITS AMPLIFICATION OF TH1 CELL-MEDIATED INFLAMMATION

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Background: Objective: More studies are focusing on renal tubular epithelial cells (RTECs) as a new target to restore inflammatory environment as clarifying their immune regulatory function. Here, we investigated whether histone deacetylases (HDACs) are activated in RTECs during T cell-mediated inflammation and their blockade is able to reduce the inflammatory responses.

Methods: Human renal proximal tubular epithelial cell line HK-2 was cultured in the presence or absence of recombinant interferon gamma (IFN-g) 200 U/ml plus tumor necrosis factor alpha(TNF-a) 5 ng/ml. The HDAC activity was determined on the expression levels of acetylated H3 and a-tubulin by immune blot assay. To determine the functional activity of HDAC inhibitor SB939, we analyzed the immune stimulatory phenotype of HK-2 cells such as class II MHC molecule, CD80, CD86, and CD40 by flow cytometry. In addition, the culture supernatants were used for measuring cytokines and chemokines by ELISA assay.

Results: We found that HDAC activity was markedly increased in HK-2 cells by treatment of IFN-g/TNF-a within 12 hours. Treatment of pan-HDAC inhibitor SB939 in HK-2 cells completely prevented HDAC activity increased by IFN-g treatment. SB939 treatment predominantly inhibited up-regulating CD40 expression but not MHC class II, CD80, and CD86. In addition, MCP-1 was significantly inhibited more than IL-6 and TNF-a by SB939 treatment.

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Conclusion: Our results demonstrate that 1) HDAC activity is increased in RTECs in response to IFN-g, 2) which further facilitates T cell-mediated inflammatory responses through CD40 and MCP-1. Therefore, our study suggests that HDAC inhibitor has a therapeutic potential for the treatment of acute renal inflammatory diseases such as allograft rejection in transplantation.

Keywords: Renal tubular epithelial cells (RTECs), Cell-mediated allograft rejection, Histon deacetylases (HDACs), T lymphocytes, Interferon gamma