Histone deacetylase 1 controls the generation and maintenance of effector-like CD8+ T cells during chronic viral infection

E. Miyakoda[1], R. Rica[1], M. Waldherr[1], M. Schülein[1], L. Sandner[1], V. Stolz[1], D. Waltenberger[1], T. Krausgruber[2], C. Bock[2,3], N. Boucheron[1], W. Ellmeier[1], S. Sakaguchi[1]

[1]Medical University of Vienna, Division of Immunobiology, Institute of Immunology, Center for Pathophysiology, Infectiology and Immunology, Vienna, Austria, [2]CeMM Research Centre for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria, [3]Medical University of Vienna, Institute of Artificial Intelligence, Center for Medical Data Science, Vienna, Austria

Type selection

Choose your preferred presentation format: Oral presentation

General data

Track: Adaptive Immunity

Topic: Cytotoxic T cell differentiation and T cell exhaustion

Abstract text

Text: $CD8^+$ T cell exhaustion is a complex process that involves the differentiation of persistently activated $CD8^+$ T cells into functionally distinct cell subsets. Here, we investigated the role of the key epigenetic regulator histone deacetylase 1 (HDAC1) in the differentiation of exhausted T (Tex) cells during chronic viral infection. Wild-type and T cell-specific HDAC1-deficient mice were infected with lymphocytic choriomeningitis virus (LCMV) clone 13 to model T cell exhaustion in chronic viral infection. Beside monitoring viral titer and weight, Tex cell subset distribution was analyzed mainly in splenocytes isolated at d8 and d30 post infection through flow cytometry. Moreover, transcriptome analysis with a single cell resolution (scRNA-seq) was performed to investigate the differentiation of early exhausted T cells 8 days post infection. In addition, as a complementary approach, genome-wide chromatin accessibility analysis (ATAC-seq) was conducted on progenitor and non-progenitor subsets of early exhausted T cells. We uncovered that HDAC1 controls the generation and maintenance of effector-like $CX3CR1^+$ Tex cells in a $CD8^+$ T cell-intrinsic manner. Deletion of HDAC1 led to expansion of an alternative Tex cell subset characterized by high expression of T cell exhaustion markers, and this was accompanied by elevated viremia. HDAC1 knockout altered the chromatin landscape in progenitor Tex cells, abrogated the expression of effector-like signature genes and interfered with cell fate specification toward the $CX3CR1^+$ Tex cell subset. We conclude that HDAC1 is functionally required for controlling viral load during chronic infection by ensuring adequate $CX3CR1^+$ Tex cell subset differentiation.

Conflict of Interest statement

Do you have any conflict of interest to declare?: No

Affirmation

1. Consent to participate and present onsite: Yes

2. Consent to publication publication: Yes

3. Consent on treatment of contact details saved in this system: Yes