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CD4^{+}T cell responses to a cytosolic viral antigen

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Robert Busch,[Aff1]

Aff1 Stanford University Medical Center, Stanford, USA

Keywords

Antigen presentation, cross-presentation, dendritic cells, EBNA-1, EBV, endogenous antigen, MHC class II

Context

Epstein-Barr virus (EBV) infects various human cells including B lymphocytes. EBV infection is prevalent among adults. $CD8^+$ T cell surveillance against key latent proteins such as EBNA1 seems inefficient. MHC class II-restricted $CD4^+$ T cell responses to EBV antigens have not been well studied, but they might contribute to immune surveillance. This study set out to measure the frequency of $CD4^+$ T cell responses to a panel of latent-phase EBV protein in healthy, EBV^+donors, to characterize the effector functions of such responses, and to examine the relevant antigen presentation pathways.

Significant findings

EBNA1 elicited blastogenic Th1 responses in T cells from all EBV^+ healthy donors. Cord blood T cells did not show this reactivity, suggesting that the measured EBNA1-specific responses were primed *in vivo*. Short-term T-cell lines responded to both soluble recombinant EBNA1 and vaccina virus-EBNA1-infected dendritic cells (DCs), as well as to autologous EBV-transformed B cells. DCs were also able to present EBNA1 shed by HLA-mismatched EBV-transformed B cells to the T-cell lines. The lines, enriched for $CD4^+$ T cells, lysed DR-matched EBV-transformed B cells, suggesting participation in immune surveillance. Presentation by EBV-transformed B cell lines probably did not reflect antigen shedding and re-endocytosis, but a distinct endogenous presentation pathway. In summary, EBNA1 peptides can be presented to $CD4^+$ T cells by MHC class II molecules in healthy, EBV^+ donors. The responding $CD4^+$ T cells lyse EBV-transformed B cells.

Comments

This study characterizes a novel immune surveillance mechanism directed against EBV. Some groups have reported abnormal immune responses to EBV in rheumatoid arthritis and EBV reactivation in inflamed joints, implicating EBV in the clinical picture of inflammatory arthritides. In healthy people, EBV replication and proliferation of transformed cells are kept in check by immune surveillance, but the mechanisms involved are unclear. EBNA1, the only EBV protein expressed in some forms of latent EBV infection, escapes recognition by MHC class I-restricted $CD8^+$ T cells because it is resistant to cytosolic degradation. The mechanism for surveillance proposed here is surprising as nuclear antigens are not usually thought to gain access to the MHC class II peptide-loading pathway. *In vitro*, EBNA1 presentation occurs by two distinct mechanisms. Either immature DCs acquire EBNA1 released from EBV-transformed B cells by endocytosis and present derived peptides on their MHC class II molecules, or B cells, incapable of efficient uptake of EBNA1 from neighbouring cells, present their own endogenous EBNA1 determinants. It is unknown whether similar dual modes of presentation exist for self antigens. If yes, this suggests a mechanism by which normally cryptic self antigens could become targets of autoimmunity in an inflamed microenvironment. Antigens normally presented endogenously in a nonstimulatory context could activate an autoimmune response if cell damage releases them for uptake by DCs.

Methods

Vaccinia virus vector, flow cytometry, enzyme linked immunospot assay, Chromium release, thymidine incorporation

References

1. Munz C, Bickham KL, Subklewe M, Tsang ML, Chahroudi A, Kurilla MG, Zhang D, O'Donnell M, Steinman RM: Human $CD4^+$T lymphocytes consistently respond to the latent Epstein-Barr virus nuclear antigen EBNA1. J Exp Med. 2000, 191: 1649-1660.