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Changing network signaling by viruses

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Context

Epstein-Barr virus (EBV) causes infectious mononucleosis as well as lymphoproliferative disorders in immunosuppressed patients. It is associated with various malignancies, such as Burkitt's lymphoma, Hodgkin's lymphoma, and nasopharyngeal carcinoma. Among EBV-gene-encoded proteins, latent membrane protein (LMP)1 is essential for EBV-mediated transformation, and induces most of the changes associated with EBV infection. LMP1 signals via tumor necrosis factor (TNF) receptor associated factors (TRAFs). This family of proteins includes CD40. This study tested the hypothesis that LMP1 expression may rescue some of the humoral immune responses in CD40 deficient (CD40-/-) mice, where immunoglobulin (Ig) class switching and germinal center (GC) formation is defective, if LMP1 interacts in part with the CD40 signal pathway. To address the question of whether and how LMP1 mimics CD40 signaling to induce B cell activation and differentiation *in vitro* and *in vivo*.

Significant findings

The LMP1 transgene specifically expressed on B220+ B cells led to enhanced expression of intercellular adhesion molecule-1 (ICAM-1/CD54), CD23, Fas/CD95, major histocompatibility complex (MHC) class II antigen (I-A), CD80, and CD86 when compared to normal B cells. Thymidine uptake was detected in LMP1tg B cells without stimulation, whereas IL-4 alone induced significant enhancement of [^{3}H]thymidine uptake of LMP1tg B cells. In addition, elevated NF-?B-binding activity was seen in both LMP1tg and CD40-/- LMP1tg B cells without stimulation, whereas this activity was induced in control mice only after stimulation by lipopolysaccharide (LPS) or CD40 ligation. Anti-NP IgM production was observed in all immunized mice, including CD40-/- mice after immunization. CD40-expressing LMP1tg mice and their littermates produced high-affinity anti-NP IgG1, in contrast to CD40-/- LMP1tg mice, which produced only low-affinity antibodies.

Spleen sections were taken at day 7 after immunization and stained by anti-? and anti-?1 antibody. B cell foci stained by anti-? antibody could be observed in immunized control animals and LMP1tg mice, but only a few ?+ cells were also anti-?1+. In CD40-/- and CD40-/- LMP1tg mice, immunoblast-like

cells intensely stained by anti-? were detected only in small clusters, but were anti-?1 negative. Well-developed GCs were observed in the lymphoid follicles of immunized control mice after 14 days, whereas CD40-/- LMP1tg mice failed to develop GCs, consistent with the production of low-affinity anti-NP IgG1. Typical GC formation was not detected in the follicles of LMP1tg although they produced high-affinity anti-NP IgG1.

Comments

This report documents nicely how EBV infection can influence signal transduction of CD40 and provides evidence for a variety of phenomena of B cell activation seen in EBV infected individuals. Although the data focus mainly on anti-NP responses and were obtained in an artificial system, they provide significant insights into how LMP1 can partially substitute for CD40 activity with regard to B cell development. However, expression of LMP1 appears to be able to prevent GC formation and, therefore, can disable the induction of an effective immune response to EBV. Taking into account how HIV acts, this study adds to our understanding of how EBV has apparently learned to sufficiently interact with the immune system. Since escaping the GCs allows EBV to reduce selective processes in these organs with the appearance of lymphoblasts in the circulation, it is tempting to speculate on implications of these findings for autoimmunity.

Methods

This study analyzed B cell functions and humoral immune responses of LMP1 transgenic (LMP1tg) mice in normal and (CD40-/-) backgrounds. This transgene was under the control of the Ig promoter/enhancer to ensure that only B cells expressed LMP1.

The *in vitro* proliferation, antibody secretion, and nuclear factor ?B (NF-?B) activation of LMP1-expressing B cells were analyzed.

In vivo experiments tested the effect of LMP1 on a defined *in vivo* antibody response. LMP1tg and CD40-/- LMP1tg mice were immunized with alum-precipitated (4-hydroxy-3-nitrophenyl) acetyl-conjugated chicken ?-globulin (NP-CGG). Immunization of the animals was monitored by analyzing specific Ig titers and by immunohistology of spleen sections taken at 7 and 14 days after immunization. Since it is known that most primary anti-NP antibodies bear ?1 chains after Ig class switching in the Igh--sup/sup-- mice, PALS-associated B cell foci have been stained by anti-? and anti-?1 antibodies in the CD40-/-LMP1tg and the LMP1tg mice.

References

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