Best Practice & Research Clinical Haematology
Vol. 21, No. 3, pp. 405–420, 2008
doi:10.1016/j.beha.2008.06.002
available online at http://www.sciencedirect.com

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Immunotherapy targeting EBV-expressing lymphoproliferative diseases

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Epstein-Barr virus (EBV) is associated with non-Hodgkin's lymphoma (NHL), occurring in immunocompetent individuals as well as those with immunodeficiency. In patients with immunodeficiency, the nature of EBV infection in the malignant cell determines the pattern of antigen expression and the associated presence of targets for cellular immunotherapy. EBV-expressing lymphoma cells in the setting of immunodeficiency express type III latency, characterized by expression of all nine latent-cycle EBV antigens, and strategies to restore EBV-specific immune responses have resulted in effective anti-tumour activity. In contrast, EBV-associated NHL in immunocompetent individuals is characterized by type II latency, where a more restricted array of EBV-associated antigens is expressed. In this setting, T-cell therapies are limited by inadequate persistence of transferred T cells and by tumour-evasion strategies. A number of strategies to genetically modify the infused T cells and modulate the host environment are under evaluation.

Key words: EBV; post-transplant lymphoproliferative disease; cytotoxic T lymphocytes; chimeric antigen receptors.

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1521-6926/$ - see front matter

Epstein-Barr virus (EBV) is an enveloped herpes virus with a 172-kb double-stranded DNA genome.[1] In the immunocompetent host, EBV infection results in a mild self-limiting illness, and over 95% of the adult population worldwide are EBV seropositive, primarily after developing the infection during childhood.[2] EBV targets oral epithelial cells and B cells, and the CD21 receptor of the B lymphocyte allows the EBV to enter the cell. Like other herpes viruses, EBV is then able to maintain a latent infection with the virus genome retained in the host cells without production of infectious virions.

During a primary infection, many EBV-related antigens are expressed by infected cells, and vigorous cell-mediated immunity is induced to control the infection. Following primary infection in the oropharynx, EBV establishes lifelong latency in B cells where it persists as an episome creating a latent phase of infection with occasional productive replication in B cells and mucosal epithelium. There are at least four types of viral latency distinguished by EBV antigen expression, primarily on the surface of infected memory B cells, with the immunogenicity increasing with each latency type thus allowing the immunocompetent host to mount an appropriate immune response. Type I only express the virus nuclear antigen 1 (EBNA1), type II express the latent membrane proteins, LMP1 and LMP2, in addition to EBNA1, and type III express all the eight latency-associated proteins including the immunodominant EBNA3 viral antigens.[3] In addition, the viral small RNAs, EBERs are expressed abundantly in all types.

Using the latency model describing the predominant antigen expression and immunogenicity of the infected cells, EBV-related tumours can be categorized into the different latency types. EBV-positive Burkitt's lymphoma shows type I latency, while type II latency lymphomas include EBV-positive Hodgkin's disease (EBV-HD), nasopharyngeal carcinoma and extranodal natural killer (NK)/T-cell lymphomas. Most type I and type II latency EBV-related malignancies target immunocompetent patients. This is in contrast to EBV-related malignancies of type III latency, which express the full range of EBV antigens. This antigen expression pattern is found in EBV-related post-transplant lymphoproliferative disease (PTLD) occurring after haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT), or in other patients with primary or secondary immunodeficiency.

TYPE III LATENCY

Biology of type III latency lymphomas

Type III latency is characteristically associated with expression of multiple EBV antigens, and normally elicits a robust humoral and cell-mediated response in the immunocompetent host. Therefore, type III latency lymphomas occur in settings of immunodeficiency in which an adequate cell-mediated immune response against EBV related antigens is not observed. One example of this form of EBV-associated lymphoma is PTLD which presents following HSCT. It is predominantly derived from donor B cells and typically occurs within the first 6 months after transplant, prior to reconstitution of the EBV-specific immune response. Risk factors for developing this complication include T-cell depletion of the infused product, the use of human leukocyte antigen (HLA)-mismatched family members or unrelated donors, the use of anti-thymocyte globulin, and a diagnosis of primary immunodeficiency. While the overall incidence is low, incidences as high as 26% have been reported in patients with the risk factors listed above.[4,5]