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The Development of Prophylactic EBV Vaccines

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Epstein-Barr virus (EBV) is an important global human pathogen found in over 90% of the world's population [1]. EBV infection usually occurs in young children and causes no or only nonspecific symptoms [2]. However, EBV is the major cause of infectious mononucleosis (IM) [3]. EBV is an oncogenic virus associated with various human malignancies of both epithelial and lymphoid origin such as nasopharyngeal carcinoma (NPC), a subset of gastric carcinoma (GC), Burkitt's lymphoma (BL), Hodgkin lymphoma (HL) and post-transplant lymphoproliferative disorder (PTLD) [4,5]. Almost 200,000 cases of EBV-associated malignancies occur each year worldwide [6]. Currently, no vaccine has been licensed to prevent EBV infection or EBV-associated diseases. There is an urgent need for the development of EBV vaccines. Although a vaccine to prevent EBV infection was proposed as long ago as 1973 [7], the development of an EBV vaccine has been agonizingly slow.

EBV major envelope glycoprotein gp350 has been widely considered as an attractive candidate for a prophylactic EBV vaccine. The reason for choosing gp350 is that EBV causes infection predominantly by binding gp350 to the CD21 receptor on the surface of B lymphocytes [8]. Numerous studies have demonstrated the efficacy of gp350-based vaccines [9-11]. Prophylactic EBV vaccines have been evaluated in controlled clinical trials [12] vaccinated adults, children and infants in China with a single dose of vaccinia virus expressing gp350. The gp350 vaccination was able to elicit neutralizing antibodies in the 9 EBV-seronegative children (100%), and only 3 of the 9 vaccinated children were infected with EBV during 16 months of follow-up. The vaccine could not effectively elicit EBV antibodies in EBV-seropositive and vaccinia virus-seropositive adults, hinting that this gp350 vaccine might be recommended for EBV-seronegative children. However, vaccinia virus is unlikely to be accepted as a vaccine vector because of its potential side effects.

In a phase I/II study, recombinant gp350 expressed in Chinese hamster ovary (CHO) cells exhibited the ability to induce neutralizing antibodies in healthy volunteers [13]. The subjects receiving soluble gp350 in no adjuvant developed lower levels of EBV antibodies than those receiving soluble gp350 in alum/monophosphoryl lipid A. These results demonstrated that the adjuvant could enhance the humoral immunity in vaccine recipients. A phase II, randomized, double-blind placebo-controlled trial of soluble gp350 was performed in 181 EBV-seronegative children [14]. EBV-neutralizing antibodies were detected in 70% of the vaccinated subjects at 6 months after the first immunization. The vaccine also reduced the rate of IM by 78% in vaccinated children but failed to prevent EBV infection. The gp350 vaccine may be able to reduce EBV-associated diseases, but not necessarily prevent virus infection. Finally, a similar vaccine was given to 16 EBV-seronegative children with chronic kidney disease awaiting transplantation [15]. EBV-neutralizing antibody was detected in 4 of the 13 vaccinated subjects. Four vaccinated subjects became asymptomatically infected with EBV and one even developed PTLD. The dose of gp350 used in this trial may be relative low and thus could not induce protective immunity. The patients' immunosuppressed state may also cause the failure of this trial.

A different vaccine strategy is to control the expansion of EBV-infected B cells by inducing T-cell response to EBV latent antigens [16]. A phase I trial utilized an EBNA3A peptide epitope (FLRGRAYGL) restricted by HLA B*08:01 [17] with tetanus toxoid in an oil and water emulsion [18]. Of the 14 enrolled subjects, four received placebo, two were immunized with high dose of EBNA3A peptide and the remaining eight recipients were immunized with low dose of peptide. Most of the vaccine recipients developed T-cell response to EBNA3A peptide after vaccination. The vaccine also effectively protected the subjects from the development of IM.

Prophylactic EBV vaccines have many promising prospects, but some problems in the vaccine development have to be solved. A vaccine that does not prevent EBV infection might still be efficient to reduce EBV-associated disease. For example, in the phase II trial performed in 181 EBV-seronegative children [14], the gp350 vaccine could elicit EBV neutralizing antibodies and reduce the rate of IM, but failed to prevent EBV infection. It is still not clear whether EBV neutralizing antibody is a significant correlate of protection against IM. If neutralizing antibody does not correlate with protection, it is necessary to look for alternative correlates of protection. The low level of virus in the blood after virus infection (also known as viral set point) might reduce the risk of EBV-associated malignancies. Therefore, EBV DNA load in the blood of vaccine recipients should also be measured in the clinical trials. Moreover, it is not certain whether a gp350 vaccine with additional EBV antigens is more effective than gp350 alone. The vaccine efficacy of a mixture of EBV antigens should be evaluated in future clinical trials. For example, other EBV antigens such as EBNAs [19] and LMPs [20] could induce antigen-specific T-cell responses and were promising vaccine candidates against EBV-associated malignancies. Furthermore, to avoid possible side effects caused by EBV vaccines, the optimum vaccine formulation, including both the antigen and adjuvant, needs to be determined in the following trials.

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