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Advances and Challenges in the Development of an Epstein-Barr Virus Vaccine

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Abstract

The development of a vaccine against Epstein-Barr Virus (EBV) is crucial due to its association with various cancers and diseases such as Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal cancer, and multiple sclerosis. Despite the slow progress, significant strides have been made in identifying potential vaccine targets and adjuvants. Glycoprotein 350 (gp350) on the surface of EBV is a primary focus, with studies indicating that multimeric gp350 vaccines elicit stronger immune responses than monomeric versions. Human clinical trials have shown partial protection using gp350-based vaccines, but challenges remain in achieving long-lasting immunity and complete protection. Future vaccines may need to incorporate additional epitopes beyond gp350, such as gH/gL, gB, and gp42 glycoproteins. This article summarizes current research and highlights the ongoing efforts to develop an effective and safe EBV vaccine.

Keywords: Epstein-Barr; Virus; Vaccine; Advances; Challenges

Introduction

Epstein-Barr virus (EBV), a pervasive pathogen known for its association with a wide array of diseases, stands as a significant challenge in the field of infectious diseases and oncology. With its complex lifecycle and the diverse spectrum of illnesses it causes—from mononucleosis in the short term to cancers such as Burkitt lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma, as well as autoimmune conditions like multiple sclerosis in the long term—EBV presents a unique target for vaccine development. Despite the clear link between EBV and these severe health outcomes, progress toward an effective prophylactic vaccine has been slow and fraught with challenges. This article delves into the intricacies of EBV's impact on human health, the current state of vaccine research, and the innovative approaches being explored to overcome the hurdles in developing a vaccine capable of curtailing the virus's widespread impact. By focusing on key vaccine targets such as the glycoprotein 350 (GP350) and exploring the role of adjuvants in enhancing immune responses, researchers aim to pave the way for a vaccine that not only prevents EBV infection but also reduces the incidence of EBV-associated diseases. The quest for an EBV vaccine is a crucial endeavor in the fight against viral-induced cancers and autoimmune diseases, offering hope for a future where the burden of EBV is significantly diminished.

Description

There is a potential to make an Epstein-Barr virus (EBV) vaccine. This would greatly alleviate the large burden of disease that can manifest years later. EBV can result in patients later in life having cancer. Burkitt lymphoma is often caused by an EBV virus infection and is a common childhood cancer in Uganda [Balfour et al., 2019]. Around 40% of Hodgkin lymphoma cases are caused by EBV [Balfour et al., 2019]. Many nasopharyngeal cancers are caused by EBV as well [Balfour et al., 2019]. Not only does EBV often result in cancer, but it may also cause multiple sclerosis [Balfour et al., 2019]. EBV is also related in the pathophysiology of anemia, thrombocytopenia, hepatitis, myocarditis, upper respiratory infections, and mastoiditis EBV has a complicated lifecycle, which makes it hard to target. That's why there are so many different vaccine targets [Rühl et al., 2020].

Progress on a prophylactic EBV vaccine has been painstakingly slow [Balfour et al., 2019]. The target for many of the vaccines in progress is the glycoprotein 350 on the surface EBV [Balfour et al., 2019]. GP350 is the most abundant glycoprotein on the EBV

envelope [Zhong et al., 2022]. It's important to choose the correct adjuvant so as to elicit an effective and long-lasting immune response. These adjuvants include, but aren't limited to alum, Syntex adjuvant formulation [SAF-1], immune-stimulating complexes, Freund's adjuvant and glucopyranosyl lipid A [Zhong et al., 2022]. Alum as an adjuvant seems to have worked well in a number of animal studies [Emini et al., 1989]. Alum induced a more robust immune response in common marmosets than Freund's adjuvant [Emini et al., 1989]. In a subsequent study mono-gp350 with SAF-1 and ALUM as the investigational adjuvants yielded a result with equal efficacy in regards to antibody levels [Finerty et al., 1994]. SAF-1 seems to work better as an adjuvant than alum in a gp-350 vaccine [Finnerty et al., 1994]. A new unique based adjuvant called Matrix-M is made up of two saponin based components [Lövgren Bengtsson et al., 2011]. The two components increase the safety and efficacy of the vaccine [Lövgren Bengtsson et al., 2011]. Matrix-M in a recent clinical trial has shown safety and high efficacy [Lövgren Bengtsson et al., 2011]. Adjuvants will most likely be part of any EBV vaccine. A multimeric gp350 EBV vaccine trial in animals yielded a more robust immune response than a monomeric gp350 vaccine [Zhong et al., 2022]. Mice that were immunized with tetrameric gp350 vaccine resulted in a more immune response than mice that received a monomeric gp350 vaccine [Zhong et al., 2022]. Investigators aren't sure why a multimeric vaccine results in a more robust response. Better presentation and trapping by follicular dendritic cells or enhanced B cell receptor binding may be the reasons why multimeric EBV vaccines are more robust [Zhong et al., 2022].

Adjuvants are necessary to decrease the number of inoculations given, the frequency injected and dose administered [Zhong et al., 2022]. Some studies in animals have shown the level of antibodies from an EBV vaccine doesn't correlate with its efficacy [Zhong et al., 2022]. Neutralizing antibodies seem to be essential for protecting against tumor development in cottontop tamarins [Finerty et al., 1994]. It's likely that a person will need vaccines over time to prevent lymphoma [Zhong et al., 2022]. A novel approach is using an adenovirus or vaccinia virus as a viral vector to deliver the code for gp350 [Zhong et al., 2022]. A vaccinia viral vector was used in numerous animals to immunize against gp350 [Zhong et al., 2022]. A humoral response was elicited in the marmosets, tamarins and rabbits [Zhong et al., 2022]. The tamarins that were immunized with a vaccinia virus were protected 75% of the time from developing lymphoma after being given a large dose of EBV when compared to a placebo group [Morgan et al., 1970]. The EBV dose injected into the tamarins normally causes lymphoma 100% of the time [Morgan et al., 1970].

Another possibility in creating a proper immune response is eliciting CD8+ T cell immunity against Epstein-Barr virus nuclear antigen [Khanna et al., 1992]. A promising approach from the Cohen research group stated that a vaccine containing the glycoproteins gH/gL or gH/gL/gp42 induced a strong epithelial and B cell neutralizing antibody response in mice and nonhuman primates [Bu et al., 2019]. Glycoprotein 220 vaccines have been studied that try to prevent viral entry as well. Human clinical trials often use the gp350 protein as the antigen. Gu et al. used a recombinant vaccinia live virus that coded for the gp350 protein. Three of the nine infants in the intervention group did contract EBV later whereas all 10 of 10 contracted EBV in the placebo group. A trial in humans compared the use of gp350 alone, gp350 with alum, and gp 350 with AS04. The formulations were all tolerated and safe. The vaccine that only contained gp350 alone elicited the smallest immune response [Moutschen et al., 2007]. The vaccines only offered partial protection. Humans' studies seem to show that antibodies seem to quickly decrease after being vaccinated [Zhong et al., 2022]. Children who had chronic kidney disease were given two different doses of an EBV vaccine. Only 1/4 in the low dose group and 3/9 in the high dose group developed neutralizing antibodies [Rees et al., 2009]. There is still a lot of work to do to create an effective and safe EBV vaccine.

Previous human trials have not resulted in sterilizing immunity. Fortunately, a lot of data has been developed that will help in the future development of a potential vaccine. A future vaccine will most likely have to include more epitopes than just gp350 [Zhong et al, 2022]. The vaccine may also have to include gH/gL, gB, and gp42 glycoproteins [Zhong et al., 2022]. Anti-gHgL antibodies seem to be 18% more effective than antibodies against gp350 in preventing EBV from infecting B cells [Zhong et al., 2022].

A new vaccine trial initiated by the US National Institute of Allergy and Infectious Disease has started to investigate a preventative EBV vaccine. The vaccine is a gp-350 Ferritin nanoparticle vaccine with a saponin-based Matrix-M adjuvant [Rogers, 2022]. The vaccine targets the gp350 protein on the surface of the EBV virus and on the surface of virus-infected cells

[Rogers, 2022]. Ferritin is a natural iron storage protein located in the cells of all species. Ferritin is considered to be a promising vaccine platform as it has the ability to display proteins from the targeted virus on its surface [Rogers, 2022]. Further research and work need to be done to elucidate how to make a proper EBV vaccine. Various methods have been tried and few have yielded a proper vaccine candidate. Hopefully, future combinations of adjuvants and glycoproteins may yield a sterilizing vaccine and eliminate much morbidity and mortality.

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