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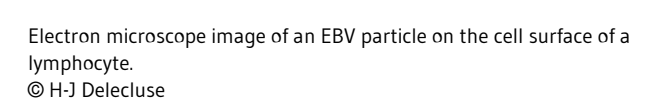
Vaccination against oncogenic Epstein-Barr viruses

Almost all humans are infected with Epstein-Barr viruses (EBV), which are linked to the development of benign diseases such as infectious mononucleosis as well as several cancers. Scientists from the German Cancer Research Center have developed a new strategy for creating a vaccine that targets different EBV virus life phases and has the potential to provide effective protection against EBV infection.



Electron microscope image of an EBV particle on the cell surface of a lymphocyte.
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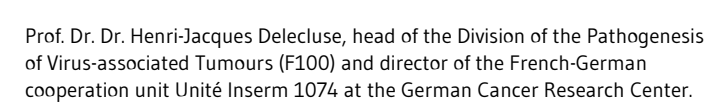
The Epstein-Barr virus, discovered in Burkitt lymphoma cells in 1964 by the English pathologists Michael Epstein and Yvonne Barr after whom it is named, was the first oncogenic (cancer-causing) virus to be identified in humans. Epstein-Barr virus (EBV) not only causes Burkitt's lymphoma (a highly aggressive form of cancer that is common in tropical Africa), but is also associated with various other, sometimes very different, tumours including nasopharyngeal carcinoma that is widespread in Southeast Asia, some Hodgkin's and non-Hodgkin's lymphomas as well as over ten percent of all gastric cancers. In addition, EBV triggers Pfeiffer's glandular fever (infectious mononucleosis), a benign infectious lymphoid gland disease that is transmitted through saliva and has become known as the "kissing" or "college" disease due to its frequent occurrence in young adults. EBV infections also play a role in the development of autoimmune diseases such as multiple sclerosis.

Numerous different EBV strains have since been identified. They belong to the family of herpes viruses. Their genome consists of a double helix of DNA which contains between 168,000 and 184,000 base pairs and overlapping DNA sequences coding for around 85 genes. The DNA is surrounded by a protein nucleocapsid, which, as electron microscope images show, is itself surrounded by a so-called tegument made of protein and by an outer envelope containing receptors.

Latent and infectious EBV development phases



Prof. Dr. Dr. Henri-Jacques Delecluse, head of the Division of the Pathogenesis of Virus-associated Tumours (F100) and director of the French-German cooperation unit Unité Inserm 1074 at the German Cancer Research Center.
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More than 90 percent of the global adult population is infected with Epstein-Barr virus - in most cases this passes completely unnoticed. Directly after infection, the virus usually (and often permanently) remains in the latent phase where it stays silent in infected B lymphocytes of the immune system. The virus replicates together with the infected B lymphocytes when they divide. When the virus reactivates from the latent phase, it progresses into the so-called lytic phase where new viral particles are formed and released.

Professor Henri-Jacques Delecluse of the German Cancer Research Center (DKFZ) in Heidelberg, one of the world's leading EBV and cancer researchers, believes that any infection with the virus constitutes a potential cancer risk. He estimates that the virus is responsible for over 200,000 cancer cases each year. He comments: "We urgently need a vaccine against EBV," further highlighting that shortly after EBV was discovered, vaccines were discussed as means to combat EBV-associated diseases. Despite decades of research, no licensed EBV vaccine is yet available. The majority of attempts targeted a major capsid glycoprotein (gp350), which induces a strong immune response in EBV-infected individuals for EBV in its lytic phase. This means that an immune response that targets the capsid protein can only be successful if free virus particles are present in the body. Vaccines that targeted the capsid provided no protection against subsequent infection with EBV. Research into vaccines directed exclusively against EBV proteins of the lytic or latent states were equally unsuccessful.

Test systems for a new vaccination strategy

Delecluse and his team - in cooperation with Josef Mautner from the Munich Helmholtz Center in Munich - are pursuing a new strategy for developing a vaccine directed against the complex life cycle of herpes viruses. With regard to the many antigens

expressed by EBV during its life cycle (i.e. different gene products for primary infection, latency phases and reactivation), it comes as no surprise that healthy EBV-infected individuals can mount effective immune responses against proteins of both lytic and latent life cycle phases. These immune responses occur both at the humoral (antibody production by B lymphocytes) and the cellular (by T lymphocytes) level.

The researchers' vaccine was based on virus-like particles (VLPs), which had also been used in previously developed vaccines. VLPs are empty virus shells that do not contain viral DNA and are therefore non-infective; they contain several dozen lytic-phase proteins but no latent-phase proteins. The researchers then constructed fusion proteins equipped with immunogenic fragments of proteins from the latent phase and BNRF1, the predominant virus tegument protein. This component caused the fusion proteins to become incorporated into the tegument of the VLPs. In addition, an inhibitory viral membrane glycoprotein was also removed from the modified VLPs.

Artist's impression of Epstein-Barr viruses in blood vessels.

The researchers tested the efficacy of their VLP-derived vaccine prototype in isolated cell systems ("ex vivo") and live animals. The prototype had an enlarged antigenic spectrum that included lytic and latent phase components. They showed that EBV-specific T lymphocytes that could recognize lytic and latent proteins were stimulated by modified VLPs. In addition, VLPs caused "ex vivo" expansion (i.e. clonal cell division) of EBV-specific cytolytic T lymphocytes (formerly referred to as "killer" cells) and prevented EBV-infected B lymphocytes from multiplying. For the animal experiments, the researchers used a "humanized" mouse model (transgenic mice with an immune system that is largely identical to that of humans). The animals developed a T cell-specific immune response against the modified VLPs and were protected against EBV infection.

"We have demonstrated the feasibility of our approach," said Henri-Jacques Delecluse. "The next step is to further develop this EBV vaccine prototype and test it step by step for possible application in humans."

References:

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- A novel mechanism of cancer development

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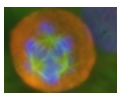

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