Kaposi Sarcoma Herpesvirus: targeting viral entry to prevent oncogenesis

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Structural biology, virology

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herpesviruses, immunogen design, translational medicine

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CONTEXT & OVERALL OBJECTIVE:

This project focuses on the oncogenic Kaposi's sarcoma-associated herpesvirus (KSHV), which belongs to the Herpesviridae family of DNA-based, membrane-enveloped viruses that establish latency in specific tissues, leading to life-long persistent infections. The objective of this project is to develop protein-based immunogens as candidates for KSHV prophylactic vaccine capable of eliciting humoral and cellular immune responses.

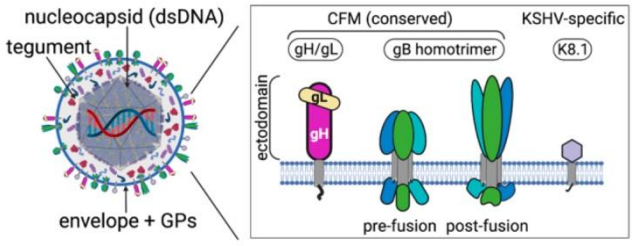

Figure 1. Representation of a herpesvirus particle (left) and GPs relevant to this project (right inlet). The nucleocapsid, tegument and envelope, from which multiple GPs project outwards, are indicated. GPs gB and gH/gL are conserved across the herpesvirus family, forming the Core Fusion Machinery (CFM). In KSHV they also play a role in binding to cellular receptors. K8.1 is specific for KSHV. GPs gp42 and gp350 (not shown on the figure) are specific for EBV.

Complexity of herpesvirus mediated entry: Herpesviruses share a common virion organization (Fig. 1). The surface is decorated with several to a dozen glycoproteins (GP), which play a role in the attachment to cells and/or inducing fusion of the viral and cellular membranes. The glycoproteins B, H, and L together form the "core fusion machinery" (CFM), a conserved structure across the herpesvirus family responsible for mediating membrane fusion (1). Both gB and gH are type I single-pass transmembrane glycoproteins with large ectodomains, while gL is a smaller glycoprotein lacking a transmembrane anchor. gL forms a tight heterodimeric complex by co-folding with the gH ectodomain. gB assembles as homotrimers that undergo a conformational change from the pre-fusion to post-fusion state, promoting the fusion of viral and cellular membranes in a mechanism similar to the coronavirus Spike protein. Additionally, each herpesvirus subfamily expresses a distinct set of glycoproteins that interact with cellular receptors, termed receptor-binding proteins (RBPs), which dictate the virus's tropism for specific host cells. Examples of such RBPs include K8.1 in KSHV, and gp42 and gp350 in EBV.

While daunting in terms of basic research endeavors, the complexity of herpesvirus entry confers multiple opportunities to interfere with the entry via multiple GP antigens that can be targeted. Numerous human neutralizing antibodies against EBV GPs have been reported (2, 3), implying that B-cell response plays an important role. The knowledge on the KSHV GPs is however limited to a couple of reports showing that the GPs elicit antibody response in mice(4) and rabbits (5). We are on a quest to identify neutralizing KSHV antibodies targeting its GPs in a separate project.

There has been a recent surge of interest in developing an Epstein-Barr virus (EBV) vaccine, spurred by evidence that EBV is a causative agent of multiple sclerosis. The latest study describes a protein-based EBV vaccine comprising the envelope glycoprotein gp350, a key target of the humoral immune response, along with several epitopes from latent-phase proteins, which have proven to be potent T-cell antigens (6). This vaccine elicited both B-cell and T-cell immune responses. The ideal KSHV vaccine should also induce humoral and cellular immunity, as was highlighted at a recent NIH-organized workshop for KSHV experts (7). Our collaborator, C. Munz, demonstrated that the chemokine-like protein K6 secreted by KSHV, along with LANA, ORF66, and ORF73, provide antigens capable of inducing CD8+ T-cell proliferation in their EBV-KSHV co-infection humanized mouse model (8), making these proteins attractive candidates for immunogen development.

PROJECT DESCRIPTION:

We had started this project by aiming to elicit a powerful antibody response targeting KSHV GPs. To do that we established protocols for expression and purification of I53-50 nanoparticles (NP) displaying KSHV K8.1, gH/gL or gB in post-fusion form. These synthetic NPs, designed in David Baker's lab (9), allow display of up to 60 copies of an antigen and have been used for RSV immunogens for example (10) (now in clinical trials). We are optimizing the protocol to increase the yields of gH/gL and gB carrying NPs, to have sufficient amounts to test them as immunogens in mice, and then in a marmoset KSHV infection model, developed by our collaborator Alex Hahn at the German Primate Center in Gottingen.

Next, we would next like to generate a KSHV multi -epitope vaccine, similar to the EBV vaccine mentioned above (6), that contains one or more GPs and a polyprotein made of epitopes from proteins shown to activate T-cells (LANA, ORF66, and ORF73). These candidates will be tested in collaboration with our collaborator, Prof. Christian Münz to determine if they simulate the B- and T-cell responses in normal mice, that resemble the ones they found in mice co-infected with KSHV and EBV and which develop KSHV-like malignancies (11, 12). If the results are positive, the best candidate(s) will be tested in the marmoset KSHV infection model to determine if they can prevent KSHV infection and if the immune priming may decrease the virus spread to the tissues where malignancies develop.

MEDICAL NEEDS / INDICATIONS:

There is currently no cure or vaccine against KSHV. In industrialized countries, KSHV-associated diseases pose a problem for high-risk groups and immunocompromised individuals such as transplant recipients and HIV positive individuals (reviewed in (13)). Kaposi sarcoma ranks among the most frequent types of cancer in sub-Saharan Africa, with seroprevalence exceeding 80% in some regions (13). Consequently, even low pathogenicity results in a substantial disease burden, and significant parts of the population cannot control the virus because of HIV infection. Even before the advent of HIV, KS has existed in Africa, frequently as a paediatric disease.

DEVELOPMENT STAGE: Emergence / Development

PRODUCT TYPE: Recombinant protein-based vaccines (displayed on nanoparticles or as multi-component vaccines)

PATENT / INVENTION DISCLOSURE (DI): None so far.

PUBLICATIONS RELATED TO THE PROJECT: None so far.

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