A novel therapeutic approach against Epstein-Barr-virus-associated tumors

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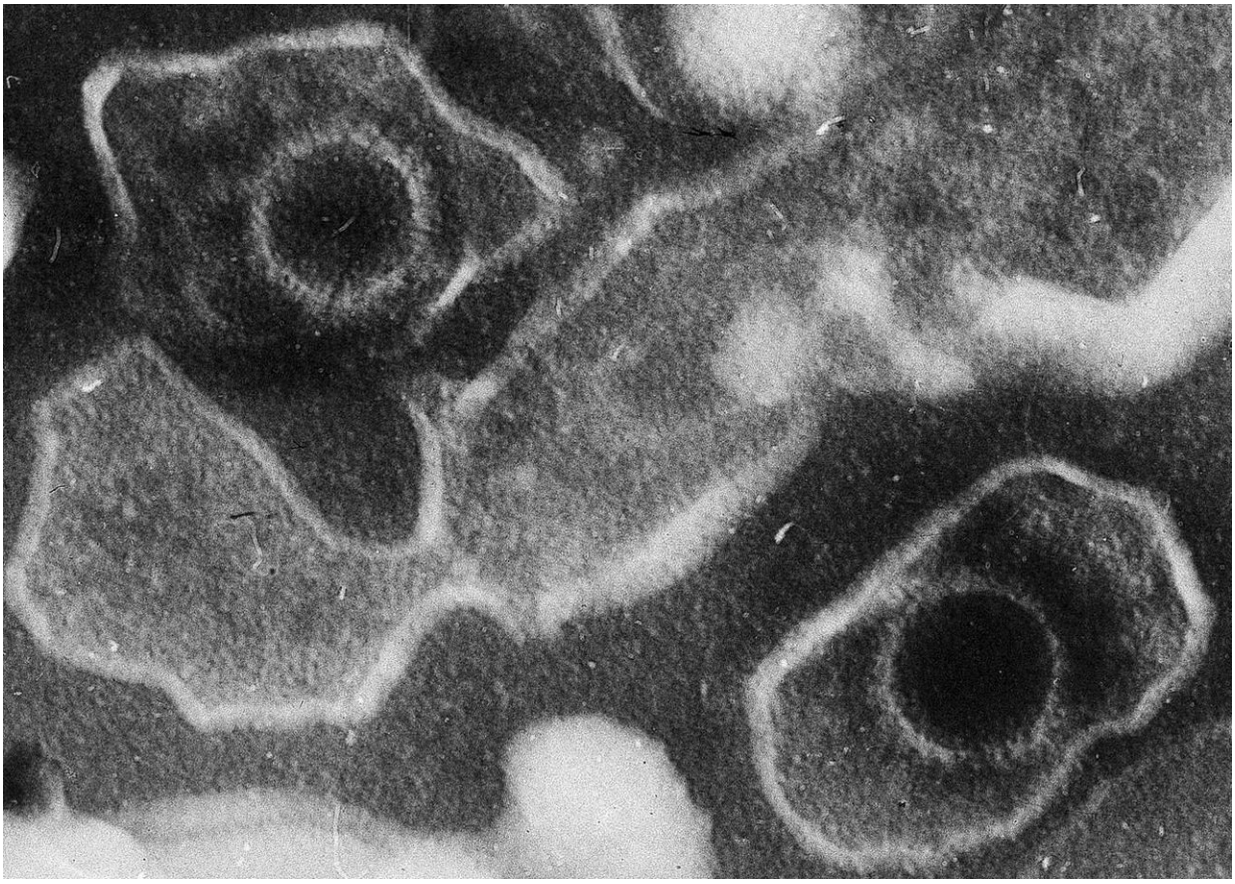

This electron microscopic image of two Epstein Barr Virus virions (viral particles) shows round capsids—protein-encased genetic material—loosely surrounded by the membrane envelope. Credit: DOI: 10.1371/journal.pbio.0030430.g001

A research team at LKS Faculty of Medicine, The University of Hong Kong (HKUMed) reports that exosomes derived from Vδ2-T cells (Vδ2-T-Exos) can effectively control Epstein-Barr-virus-associated tumors and induce T-cell anti-tumor immunity. The novel findings of Vδ2-T-Exos provide insights into a new therapeutic approach for Epstein-Barr virus (EBV)-associated tumors. The groundbreaking findings have been published in the leading academic journal *Science Translational Medicine*.

EBV infects about 95% of the human population and causes more than 200,000 cases of cancer each year, and that around 2% of all cancer deaths are due to EBV-attributable malignancies. EBV-associated tumors include Burkitt lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma, gastric tumors and post-transplant lymphoproliferative disease, etc.

Current treatment options for EBV-associated tumors are limited with considerably unwanted off-target toxicities and incomplete effectiveness for relapsed or refractory disease. Vδ2-T cells are innate-like T cells with anti-tumor potentials against EBV-associated tumors. Unfortunately, its clinical translation is limited because Vδ2-T cells from some cancer patients are difficult to expand. Exosomes are endosome-originated small extracellular vesicles that mediate intercellular communication. Compared with cell-based therapy, cell-free exosomes have advantages with higher safety, easier storage, and lower costs. However, the anti-tumor activity of exosomes derived from Vδ2-T cells (Vδ2-T-Exos) remains unknown.

The team found that Vδ2-T-Exos contained death-inducing ligands (FasL and TRAIL) and immunostimulatory molecules (CD80, CD86, MHC class I and II). Vδ2-T-Exos targeted and efficiently killed EBV-associated tumor cells through FasL and TRAIL pathways and promoted EBV antigen-specific CD4 and CD8 T cell expansion. Administration of

Vδ2-T-Exos effectively controlled EBV-associated tumors in immunodeficient and humanized mice.

Because expanding Vδ2-T cells and preparing autologous Vδ2-T-Exos from cancer patients ex vivo at a large scale is challenging, the team further explored the anti-tumor activity of allogeneic Vδ2-T-Exos in humanized mouse cancer models. Interestingly, the team found that allogeneic Vδ2-T-Exos had more effective anti-tumor activity than autologous Vδ2-T-Exos in humanized mice; the allogeneic Vδ2-T-Exos increased the infiltration of T cells into tumor tissues and induced more robust CD4 and CD8 T cells-mediated anti-tumor immunity. Compared with exosomes derived from NK cells with direct cytotoxic anti-tumor activity or dendritic cells that induced T-cell anti-tumor responses, Vδ2-T-Exos have dual anti-tumor activities by directly killing tumor cells and indirectly inducing T cell-mediated anti-tumor responses, thus resulting in more effective control of EBV-associated tumors.

"Our study provides the first evidence about the anti-tumor activities of Vδ2-T-Exos against EBV-associated tumors. These exosomes could effectively control EBV-associated cancers in multiple mouse models. More importantly, allogeneic Vδ2-T-Exos had higher therapeutic efficacy than autologous Vδ2-T-Exos to control EBV-associated tumors. Therefore, the Vδ2-T-Exos prepared from healthy donors can be used to treat patients with EBV-associated tumors, which is highly beneficial to the clinical application of this novel approach," said Professor Tu Wen-wei, Antony and Nina Chan professor in Pediatric Immunology, Department of Pediatrics and Adolescent Medicine, HKUMed, who led the research.

The findings of the study have significant implications in cancer immunotherapy. First, the fact that Vδ2-T-Exos has a potent immunostimulatory property suggests that it could be designed as a cancer vaccine by serving as immune adjuvant and delivering

immunogens. Secondly, the Vδ2-T-Exos has advantages over other exosome-based therapies (e.g., NK-Exos and DC-Exos) by displaying dual anti-tumor activities and is easier in preparation. Thirdly, the results that allogeneic Vδ2-T-Exos have higher anti-tumor efficacies than autologous Vδ2-T-Exos can greatly enhance the clinical feasibility of Vδ2-T-Exos, because the preparation of allogeneic exosomes does not require personalized procedures and is easier in quality control, standardization and centralization for clinical application.

More information: Xiwei Wang et al. Exosomes derived from Vδ2-T cells control Epstein-Barr virus–associated tumors and induce T cell antitumor immunity, *Science Translational Medicine* (2020). DOI: 10.1126/scitranslmed.aaz3426

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