Infection Research

The Genome Editing Tool CRISPR Inactivates HIV-1 Proviruses in Brain Cells

Scientists at the Helmholtz Zentrum München have developed a vector that efficiently transfers the genome editing tool CRISPR/Cas9 into cultured brain cells (astrocytes). Delivery of CRISPR/CAS9 programmed to snip away key HIV segments resulted in inactivation of HIV proviruses in latent astrocyte reservoirs. The results of the study have now been published in the journal 'Glia'.

Currently, around 37 million people worldwide are living with the human immunodeficiency virus (HIV). Antiviral drugs can reduce the amount of virus circulating in the body, but they cannot cure virus infection. Chronic infection is caused by latent viral genomes that hide in long-lived cells of the host, but may be activated by various factors. "These cells also include astrocytes, the most abundant cells in the human brain," said Professor Ruth Brack-Werner of the Institute of Virology at Helmholtz Zentrum München. To address the question whether HIV can be activated in astrocytes she set up a multidisciplinary collaboration with researchers at the University of Heidelberg (Professor Dirk Grimm) and other groups at Helmholtz Zentrum München.

The scientists first developed a vector – a kind of molecular shuttle based on adeno-associated viruses (AAV) for targeting astrocytes. This shuttle can dock specifically to the surface of human astrocytes. "We were able to show that this vector can selectively target cultured human astrocytes, even in brain organoids" said first author Christine Kunze, a scientist at the Institute of Virology. "In contrast, the vector hardly ever targeted neurons, which are also important brain cells but are not infected by HIV."

In the next step, the Helmholtz researchers packaged the information for the CRISPR-Cas9* system, a powerful tool used for genome editing in the astrocyte-selective AAV vector. In this case, the editing function was designed to specifically attack the HIV-1 provirus," said Kunze.

Reactivation of the proviruses was significantly inhibited in latently infected astrocytes exposed to these new vectors. Sequence analyses revealed that important sections of the genome of the HIV-1 proviruses were mutated or even completely deleted by the treatment.

"Latently infected astrocytes are a potential long-term reservoir for the HIV-1 provirus and can promote neurological disorders in patients," said Brack-Werner, who directed the study. "Our results show that the vector developed in this study is a promising tool for specifically inactivating the latent HIV-1 genomes in human astrocytes." In future studies, the authors plan to study to what extent these promising cell culture results can be translated to living organisms.

In 2015, the group led by Ruth Brack-Werner developed a model for research on latently infected astrocytes and demonstrated the use of this model for testing of the effects of various drugs on latent HIV in astrocytes. The current publication demonstrates the use of gene therapy approaches based on the CRISPR/CAS9 genome editing system for inactivation of HIV in astrocytes. This study is an important milestone for expansion of the arsenal of strategies for attack of HIV in the brain.

Further Information

* The CRISPR/Cas method enables editing of genetic material similar to the editing of a text with a word processing program. Both processes involve deletion, modification or insertion of information. Hence the term genome editing. The acronym CRISPR/Cas9 stand for Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9.

Original Publication:
Kunze, C. et al. (2017): Synthetic AAV/CRISPR vectors for blocking HIV-1 expression in persistently infected astrocytes. Glia, DOI: 10.1002/glia.23254

The Helmholtz Zentrum München, the German Research Center for Environmental Health, pursues the goal of developing personalized medical approaches for the prevention and therapy of major common diseases such as diabetes and lung diseases. To achieve this, it investigates the interaction of genetics, environmental factors and lifestyle. The Helmholtz Zentrum München is headquartered in Neuherberg in the north of Munich and has about 2,300 staff members. It is a member of the Helmholtz Association, a community of 18 scientific-technical and medical-biological research centers with a total of about 37,000 staff members. www.helmholtz-muenchen.de/en

The Institute of Virology (VIRO) investigates viruses that chronically infect humans and can cause life-threatening diseases. The research activities of the institute focus mainly on the HI virus which causes AIDS, on endogenous retroviruses, which are integrated into our germline, and hepatitis B and C viruses, which cause liver cirrhosis and hepatocellular carcinoma. Molecular studies identify new diagnostic and therapeutic concepts to prevent and treat these viral diseases or to prevent the formation of virus-induced tumors. www.helmholtz-muenchen.de/viro

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