KNOWLEDGE

Peptide uses Achilles heel of the Zika virus

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Scientists at Nanyang Technological University, Singapore (NTU Singapore) have developed an antiviral peptide that utilizes the Zika virus on its Achilles heel - the viral membrane - thus stopping viruses from causing serious infections.

This new method of attacking the viral membrane directly stops Zika virus particles, rather than preventing the replication of new virus particles at the center and can potentially work against a broad spectrum of membrane-enveloped viruses.

When administered peptide-drug developed in Zika-infected mice in the laboratory (a compound consisting of amino acids) reduces the symptoms of the disease and the number of deaths. Importantly, the peptide was able to close almost impenetrable blood-brain barrier to fight viral infections in mouse brains and protect Zika from injury, an important function since Zika aims to cross the brain and central nervous system.

The research team headed by NTU Singapore's associate professor Nam-Joon Cho published their findings in the journal *Nature Materials* on October 22, 2018.

The study, conducted in collaboration with the Federal University of Minas Gerais (UFMG) in Brazil and the University of Ghent in Belgium, spanned six years and combined materials engineering, antiviral drug development and pharmacology.

"There are currently no vaccines for the Zika virus while available medications only relieve symptoms such as fever and pain," said associate professor Cho of the NTU School of Materials Science and Engineering. "The newly created peptide holds great promise of a future antiviral drug that can directly affect viral infections in the brain."

The Zika virus is transmitted by aedes mosquitoes and infections during pregnancy are related to birth defects such as microcephaly, a condition in which a baby is born with an unusually small head and brain. The World Health Organization declared the Zika disease an international emergency in 2016, and it remains a major threat worldwide today.

How does the modified antiviral peptide work?

In 2004, Associate Professor Cho developed the first antiviral peptide that works against viral membranes in laboratory experiments. Since then, NTU scientists have investigated how antiviral peptides can create pores of this form in membranes consisting of two layers of lipids (a component of fats).

Over the years, the team is studying the peptide interactions with lipid membranes and developing new peptides with more potency and improved pharmacological properties. These results led them to test a particularly promising peptide in the Zika-infected mice and also showed that it ruptured other similarly sized enveloped viruses in the lab, such as dengue fever and chikungunya.

"The peptide distinguishes between Zika viral membranes and mammalian cell membranes because the virus particles are much smaller and more curved, while the mammalian cells are larger and flatter. Like a pin stinging a balloon, the peptide pierces a hole in the viral membrane. Sufficient holes will sting and the virus will be broken, "said associate professor Cho.

Laboratory tests showed that the peptide was administered, 10 out of 12 mice survived infected. In comparison, the mice in the control group died within one week of infection. In addition, therapeutic concentrations of the peptide were able to cross the blood-brain barrier, allowing it to inhibit viral infection in the brain.

"The exciting antiviral findings confirm the potential of this innovative therapeutic strategy and are compounded by the peptide's ability to cross the blood-brain barrier," said Jeffrey S. Glenn, professor of medicine, microbiology and immunology at Stanford University, the not part of the study. Professor Glenn is also a former member of the US FDA Antiviral Drugs Advisory Committee.

New approach to virus targeting

In general, most antiviral drugs in replication are targeted by viruses. However, viruses often mutate rapidly and antiviral drugs that can become obsolete on viral replication. Attacking the physical structure of the enveloped virus is a new approach to the development of antiviral drugs. Look for promises for the peptide to be effective, even if the Zika virus is trying to mutate.

Associate Professor Cho said, "There are cases where a virus mutation can lead to an epidemic in a short period of time, leaving communities unprepared. By aligning the lipid membrane of the virus particles, scientists can develop robust and effective ways to stop viruses. "

The Zika virus belongs to the family Flaviviridae and refers to other mosquito-borne viruses such as dengue fever, Chikungunya fever and yellow fever. Like all flavivirus virus particles, which are around 40-55 nanometers in diameter and surrounded by a lipid membrane, the peptide developed by the scientists at NTU Singapore has the potential to work against these viruses.

Laboratory studies in this study confirm this potential and the research team intends to study in the future the effects of the peptide on diseases caused by these other viruses in more detail. The team will also conduct studies in larger animals and subsequently will initiate human clinical trials as soon as relevant preclinical studies are completed and regulatory approvals are obtained.

"This work represents a paradigm shift breakthrough in the field of antiviral drug design," commented Professor William C. Wimley, antimicrobial peptide expert at Tulane University in the United States, who is not part of the study.

"It shows how the viral envelope, a novel target in antiviral drug design, can be targeted by a peptide." It also shows that a peptide alignment of the viral envelope can effectively inhibit viruses in the body and also in the brain, an organ that has many Therapeutics actively closes. Given the enormous potential of peptides as antibacterial and antifungal agents, this may be a revolutionary discovery that broadly applies to the design of antiinfective drugs against many types of pathogens. "

Further information:
Joshua A. Jackman et al. therapeutic treatment of Zika virus infection with a brain invading antiviral peptide, *Nature Materials* (2018). DOI: 10.1038 / s41563-018-0194-2