Peptide targets latent papilloma virus infections

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While a newly marketed vaccine promises to drastically reduce human papilloma virus (HPV) infections, the major cause of cervical cancer, a new discovery by University of California, Berkeley, researchers could some day help the millions of people already infected and at constant risk of genital warts and cancer.

One study found that 75 percent of sexually active men and women under 50 have, or have had, an HPV infection, while 10,000 women annually develop cervical cancer, more than 90 percent of which is caused by HPV. Four thousand women die of cervical cancer each year.

Once infected, it's difficult to rid oneself of the virus because it hides as a latent DNA in cells of the epithelial tissue, such as skin and the lining of the vagina and cervix, and spreads as these cells divide.

The UC Berkeley team created a protein fragment, or peptide, that successfully prevents the virus from hitching a ride on a cell's chromosomes as the cell divides. If such a peptide - or more likely, a drug that mimics the action of the peptide - works in the body, it would effectively stop the virus from spreading or generating warts, which can progress to cancer.

"We're optimistic that this will work generally for many different genetic variants of human papilloma virus, though it's too early to say how many of the genotypes of this virus will respond," said Michael Botchan, professor of molecular and cell biology and a faculty affiliate

of the UC Berkeley branch of the California Institute for Quantitative Biology (QB3). "The hope is to have one drug that works for all different human virus types."

"The second most preventable cancer in the world, after lung cancer, is cervical cancer, the result of high HPV infection rates in the developing world, in Asia and South America and Africa," he added. "If we can get something to stop HPV replication, it would have a big health impact."

Botchan, post-doctoral fellow Eric A. Abbate and researcher Christian Voitenleitner reported their results in the Dec. 28 issue of the journal *Molecular Cell*.

Many of the 90-plus known genetic variants or strains of HPV cause warts in surface tissues, including the penis, vagina and cervix, but three variants - HPV-16, 18 and 31 - are notorious as the primary causes of cervical cancer in the world. The virus hides out in epithelial stem cells, which are naïve cells at the base of the skin that can turn into many of the various types of cells that make up the skin. As these cells divide and differentiate into skin cells, the viruses hitch a ride on the cells' chromosomes but do not become part of the chromosomes, as do other known pathogens, such as HIV in blood cells.

The virus can transform infected cells and make them proliferate into nipple-like warts. Unlike unsightly warts on the skin, tongue or penis, warts in the cervix are often flat and easily overlooked unless laboratory staining is used to find signs of pathology, as in Pap screening. If untreated or left to flare up repeatedly, the warts can progress to cancer.

Earlier work by Botchan and numerous other researchers on the human and cow (bovine) papilloma virus has shown how the virus moves into new cells. It carries its genes in the form of a circular DNA plasmid that nestles in the nucleus of the cell and makes use of the cellular machinery

to generate more copies of itself. Each cell can house hundreds of plasmids.

When the cell divides into two daughter cells, the plasmids glom onto the chromosomes so as not be left behind, and are copied and delivered along with the duplicate chromosomes into the daughter cells, where they again take up residence in the nucleus as latent viral DNA. The viral plasmids turn into infectious viruses only in the top, differentiated layers of tissue.

Previous work showed that the bovine papilloma virus hitchhikes by throwing out a thumb - in actuality, a protein called E2 - that latches onto a cellular protein that, in turn, attaches to histone proteins that envelop the chromosome, tethering the plasmid to the chromosomes.

The new research by Botchan and his colleagues shows that HPV works the same way. The UC Berkeley team created a short peptide that binds to E2 in hopes that this synthetic peptide would prevent E2, and thus the viral plasmid, from successfully tethering to the chromosomes.

By tracking the plasmid DNA in dividing cultured cells, the researchers showed that the synthetic peptide did indeed prevent HPV from following the chromosomes into daughter cells. The plasmids were left behind.

Because they built the peptide to enter cells easily, the peptide has potential as a topical treatment for the viral infection.

"We didn't start out looking for a way to develop a drug, but we stumbled across a way to get the peptide taken up by the cell, and it works," said Voitenleitner. "So far, though, we've only shown that it has a short term effect of releasing the DNA from chromosomes, and this is a long way from curing cells in people."

The researchers hope to partner with a biotechnology company to improve the peptide or develop better drug candidates, and ideally to find a formulation that can be taken orally rather than applied topically.

Botchan, Voitenleitner and Abbate obtained the crystal structure of the site where E2 binds to the chromosomal proteins, which are called Brd4. This not only allowed for the development of the peptide, but should make it easier for drug developers to design a molecule that can nudge Brd4 aside so as to bind and block the action of E2.

Botchan, who has studied DNA replication in viruses for 30 years to understand similar processes in higher organisms, says that such a drug might work against all strains of HPV because the E2 tethering protein is similar in all the viruses. And because the E2 protein is found only in papilloma viruses, a drug that blocks it shouldn't have side effects in humans.

The strategy the researchers used to block HPV spread might also prove useful against other infectious viruses, such as the related Epstein-Barr virus, the cause of mononucleosis and an aggressive form of lymphocytic leukemia called Burkitt's leukemia, and the Kaposi's sarcoma virus, which can develop to cancer in those with AIDS.

Source: UC Berkeley