

Study details how protein made by HPV teams up on and thwarts protective human protein

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Celestine Chi of Uppsala University is the first author of the *Journal of Biological Chemistry* paper “Biophysical characterization of the complex between human papillomavirus E6 protein and synapse associated protein 97.” Credit: Handout

An international team of researchers is reporting that it has uncovered new information about human papillomavirus that one day may aid in the development of drugs to eliminate the cervical-cancer-causing infection.

Led by researcher Per Jemth of Uppsala University in Sweden, the collaborators from four institutions detail in the [Journal of Biological Chemistry](#) how an offensive [protein](#) generated by the sexually transmitted virus handicaps a defensive protein made by the human body.

Co-author Neil Ferguson, a biophysicist at University College Dublin, says: "It has proved difficult to stem the proliferation of many viruses using conventional [drug discovery](#). Inhibitors of protein-protein interactions, as in HPV's case, are potentially potent ways to perturb viral infections."

There are almost 200 strains of HPV, dozens of which are transmitted through genital contact, and about half of sexually active people have had one or more infections.

The immune system eliminates the virus within two years in about 90 percent of cases, according to the Centers for Disease Control and Prevention in Atlanta, but it lingers for many years in a minority of cases. Some strains result in no visible symptoms, others cause [genital warts](#) and still others cause cancer.

"Infection by high-risk human papillomaviruses is causing as many as half a million cases of [cervical cancer](#) and more than 200,000 deaths among women per year, making it one of the most common forms of cancer," Jemth emphasized.

For the virus to replicate, it has to interfere with the body's natural inclination to kill infected cells.

What is known as "[programmed cell death](#)," or the destruction of sick cells, ordinarily is carried out by several human proteins. However, when HPV is present, the virus sends out two of its own assassin proteins, known as E6 and E7, to stop the defensive human proteins in their tracks.

"Why is the virus causing cancer? In rare cases, the HPV infection is not cleared by the immune system and persists for decades. The virus' release of E6 and E7 proteins then increases the risk of deterioration to

cancer by causing cell proliferation and preventing programmed cell death," explains Jemth. "If the cell dies, the virus will die along with it. So, the virus sends out these gunmen to assassinate proteins made by the body -- a hostile takeover, if you like."

In its study, Jemth's team offers a detailed look at how one human protein in particular, SAP97, is targeted by HPV assassin E6.

"To develop antivirals that prevent protein-protein interactions, in this case those of E6 and human proteins, it is necessary to first understand the biomolecular interactions required for virus viability and, where relevant, exploit these insights," says Ferguson.

So, the team used different techniques to visualize the attack – or, rather, how HPV's E6 and man's SAP97 bind to each other.

"We studied how fast E6 is latching onto SAP97, how fast it is coming off, how strongly it holds onto SAP97, and what happens to the shape of SAP97 as E6 is attached to it," says Celestine Chi, the first author of the paper.

It turns out that there are three places on SAP97 where HPV's E6 can latch on, he says, which bogs down the human protein so that it cannot carry out its normal function.

In fact, the team reports, three E6 molecules can attach to one SAP97 molecule simultaneously – essentially teaming up on the protein.

There currently are two vaccines that prevent [HPV infection](#) on the market, Cervarix and Gardasil, but they do nothing for those people who already are infected.

"Fundamental research on HPV is, therefore, still necessary to discover

new routes to cure infection," Jemth says, which is why the team intends to continue its investigation and now has its crosshairs on HPV's E7 protein.

Ferguson adds: "The team's work represents an important step forward in understanding HPV biology and has important implications for therapeutic strategies. What was nice about this collaboration is that multiple laboratories worked synergistically such that the scope of the research and strength of the conclusions were significantly increased."

More information: Read the paper "Biophysical characterization of the complex between human papillomavirus E6 protein and synapse associated protein 97" at www.jbc.org/content/early/2010/01/27/jbc.M110.190264

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