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Small molecular bodyguards kill HPV-infected cancer cells by protecting tumor-suppressor

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Researchers at The Wistar Institute announce the discovery of small molecules that kill cancer cells caused by infection with human papillomavirus (HPV). Their results, in both cell and mouse models, demonstrate that the small molecule inhibitors protect a tumor-suppressing protein targeted by viral proteins, thus killing the infected tumor cells.

The Wistar scientists presented their findings in the April 20 issue of the journal *Chemistry & Biology*. The researchers believe that, with further testing and refinement, their inhibitors could provide a therapeutic for HPV-caused tumors, such as those seen in cervical cancer.

"While there is an effective vaccine for preventing HPV infection, there is currently no therapeutic that specifically targets cancers caused by the virus," said Ronen Marmorstein, Ph.D., senior author, Hilary Koprowski, M.D. Professor, and leader of The Wistar Institute Cancer Center's Gene Expression and Regulation program.

"HPV often turns cells cancerous for the virus's own reproductive advantage, and we have found a class of small molecules that effectively prevents a key HPV protein from allowing cells to become cancerous," Marmorstein said. "We think that this could be the start of an effective drug strategy for cancers caused by HPV."

HPV is one of the primary infectious causes of cancer, responsible for most cases of cervical cancer, nearly 20 percent of all head and neck cancers, and has been implicated in cancers of the vagina, penis, and anus. American Cancer Society statistics estimate that over 4,000 women will die this year from cervical cancer alone.

The US Centers for Disease Control estimates that about 50 percent of sexually active men and women will be infected with HPV at one point in their lives. While most infected people will naturally fight off the infection, the virus frequently becomes "latent," residing within the body for decades at a time. When HPV re-emerges from its latent state, it may cause host cells to become cancerous as the virus replicates.

According to Marmorstein, research has shown that the HPV protein, E7, targets an important tumor-suppressing protein called the retinoblastoma protein (pRb). When E7 binds to pRb, it disturbs the normal process of cell division, allowing the cells to grow out of control and unhindered and thus become cancerous.

In this latest study, the Wistar researchers describe the results of an exhaustive search for potential small molecule drug candidates to prevent E7 from binding to pRb. They screened a library of over 88,000 molecular compounds to find a class of small molecules that can prevent HPV-E7 from disabling pRb. Surprisingly, these inhibitors work by binding to pRb itself, yet do not seem to keep pRb from doing its normal job within the cell.

"Typically, you would think that an inhibitor would bind to the disease-causing 'bad' protein, in this case HPV-E7, but instead the inhibitor latches onto pRb itself," Marmorstein said. "In any event, these inhibitors bind to the same spot on pRb that E7 clamps onto in order to disable pRb."

Once attached to pRb, these inhibitors allow pRb to trigger the molecular mechanisms of normal cell division without the disruptive effect of E7 upon HPV infection.

In subsequent studies, conducted with Wistar Associate Professor Joseph Kissil, Ph.D., of Wistar's Molecular and Cellular Oncogenesis program, one of these small molecular bodyguards proved effective in killing HPV-positive cells in mice.

"With this new class of inhibitors, we have a promising scaffold on which we can build therapies to treat HPV-related diseases," Marmorstein said.

The Marmorstein laboratory is currently involved in additional research towards developing inhibitors that block the ability of another key HPV protein called E6 to inactivate another important tumor suppressor protein called p53, a protein that is inactivated in the majority of human cancers. In addition, refinement of the HPV-E7 inhibitors is continuing. Their work will involve gaining a better molecular understanding of how their HPV-E7 inhibitors bind to pRb, which will enable them to make more informed decisions on how to best refine the inhibitors so that they are both more effective and suitable for human use.

Provided by The Wistar Institute