

Beta-HPV Can Directly Cause Skin Cancer in Immunocompromised People

NIH case study finds a type of human papillomavirus virus drives creation of cancer cells in the context of defective T cells.

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Researchers at the National Institutes of Health (NIH) have shown for the first time that a type of human papillomavirus (HPV) commonly found on the skin can directly cause a form of skin cancer called cutaneous squamous cell carcinoma (cSCC) when certain immune cells malfunction. cSCC is one of the most common cancers in the United States and worldwide. Previously, scientists believed HPV merely facilitated the accumulation of DNA mutations caused by ultraviolet (UV) radiation, usually the primary driver of cSCC. The findings were published today in [The New England Journal of Medicine](#).

“This discovery could completely change how we think about the development, and consequently the treatment, of cSCC in people who have a health condition that compromises immune function,” said Andrea Lisco, MD, PhD, of NIH’s National Institute of Allergy and Infectious Diseases (NIAID). “It suggests that there may be more people out there with aggressive forms of cSCC who have an underlying immune defect and could benefit from treatments targeting the immune system.”

There are many different types of HPV, each tending to infect cells in a particular tissue and part of the body. The types of HPV found mostly on the skin—beta-HPV—are considered benign members of the skin [microbiome](#) that typically do not integrate into the DNA of skin cells. This contrasts with the alpha types of HPV, known to integrate into the DNA of mucous membrane cells and directly cause cancer of the genitals, anus, head and neck.

The NIH researchers made their discovery in a 34-year-old woman who came to the NIH Clinical Center for evaluation and treatment of recurrent cSCC on her forehead. She had undergone multiple surgeries and a round of immunotherapy to try to remove or kill the tumor, but it repeatedly grew back. Her local doctors thought this was due to an inherited inability to repair DNA damaged by UV radiation plus an impairment in immune cells called T cells. The tumor was one of many progressively worsening HPV-related diseases the woman was experiencing.

Through a sophisticated genetic analysis, the NIH researchers discovered that a beta-HPV had integrated into the cellular DNA of the woman’s well-established tumor and was extensively

producing viral proteins there. This contradicted the prevailing theory that beta-HPV only facilitates the establishment of cSCC without integrating into cellular DNA and plays no role in maintaining the cancer. Further genetic analysis of the woman's cells showed they were fully capable of repairing DNA damage from UV radiation, suggesting the virus alone had caused cSCC.

To understand how beta-HPV could take the unusual steps of integrating into the woman's skin-cell DNA and multiplying there unchecked, the investigators studied the woman's inherited immune disorder. They found that her genetic mutations greatly hampered T cells from activating in response to skin-cell infection by beta-HPV. This suggested that the immune disorder itself was responsible for the woman's worsening HPV-related diseases, including the beta-HPV cSCC on her forehead, and that treating this disorder might cure all of them.

Accordingly, NIH investigators developed a personalized plan to give the woman a [stem cell transplant](#) to replace her defective T cells with healthy ones. The process required extreme care because she was immunocompromised even before treatment began. The transplant proceeded without complications. Afterward, all her HPV-related diseases including the recurrent, aggressive cSCC resolved and have not recurred during the more than three years since the transplant. This confirms that the woman's inherited disorder had prevented her T cells from keeping beta-HPV in check, allowing the virus to directly cause and sustain cSCC.

"This discovery and successful outcome would not have been possible without the combined expertise of virologists, immunologists, oncologists and transplant specialists, all working under the same roof of the [NIH Clinical Center](#)," said Dr. Lisco.

According to the study authors, their finding suggests that other people with defective T-cell responses may also be susceptible to cancer caused directly by beta-HPV.

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