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Stepping Off the Brake

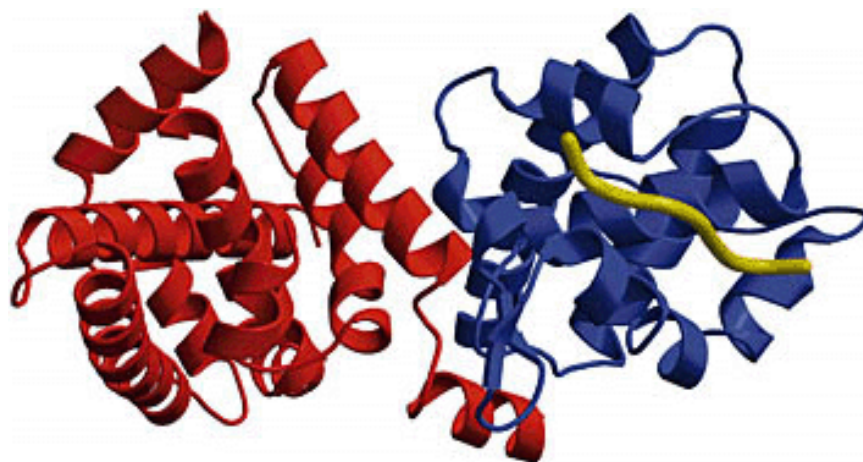


Image Title: The E7 peptide from human papilloma virus (yellow) reaches into the retinoblastoma pocket domain (red and blue) to shut down retinoblastoma's tumor-suppressing ability. - Jie-Oh Lee/Pavletich Laboratory

It's one thing to theorize how a virus knocks a tumor suppressor protein out of commission, but it's quite another to see inactivation in action. That's now possible for the intensely studied retinoblastoma (Rb) protein, the first tumor suppressor identified.

A Hughes research team at Memorial Sloan-Kettering Cancer Institute in New York has crystallized Rb protein just as it is being handcuffed by a fragment of the human papilloma virus (HPV) that is associated with 90 percent of all cervical cancers. The research is reported in the February 26 issue of *Nature*.

The business end of the Rb protein visualized by Hughes investigator Nikola Pavletich and colleagues contains the crucial "pocket domain." This is where viral proteins attach and where mutations can occur. "The pocket domain is at the center of a biochemical pathway that is altered in a majority of cancers," Pavletich said.

The three-dimensional view of the pocket domain now opens a window into how the alteration of Rb contributes to the development of many types of cancers, including lung, breast, and bladder carcinoma, Pavletich said.

Almost all of the body's cells express the Rb protein; it appears to act as one of the main brakes for the cell division cycle. When exposed to growth factors, the *Rb* gene is turned off by phosphorylation. The cell then enters a growth stage and begins to divide. Without the presence of such growth signals, *Rb* remains unphosphorylated and binds strongly to key regulatory proteins, preventing those proteins from promoting DNA replication in the nucleus.

For a tumor to grow, these regulatory proteins need to free themselves of Rb's restraint. Some cancer-promoting viruses do this by handcuffing Rb and preventing it from blocking cell division. The virus then commandeers the host cell's DNA synthesis machinery, causing the cell to divide recklessly, and possibly producing cancer.

HPV disarms Rb by inserting the E7 peptide from HPV into the pocket domain of Rb. This interference causes Rb to release the E2F transcription factors, which are required for the expression of genes involved in DNA replication.

Now that researchers can better visualize the union of Rb and E7, they may now be able to understand a more global problem: How does Rb inhibit E2F transcription factors?

Pavletich suggests that in the future, dysfunctional stages in this growth regulatory pathway may be fixed therapeutically to prevent the cancer from ever starting. "Each element of this regulatory pathway inhibits the next one, and if we truly understand the cascade of events, we may be able to restore normal function," he said.

Tyler Jacks, a Hughes investigator at the Massachusetts Institute of Technology, said that the structure of the Rb pocket domain will provide insights "related to basic questions about normal cellular regulation and tumorigenesis. It may also be possible to use this information in the future to design specific inhibitors of the viral oncoproteins for use in cancer treatment."