

An AIDS-related virus reveals more ways to cause cancer

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Researchers at the University of Pennsylvania School of Medicine have shed new light on how Kaposi's Sarcoma-associated Herpes Virus (KSHV) subverts normal cell machinery to cause cancer. A KSHV protein called latency-associated nuclear antigen, LANA for short, helps the virus hide out from the immune system in infected cells. When LANA takes the place of other proteins that control cell growth, it can cause uncontrolled cell replication.

The findings appear in a recent issue of the *Proceedings of the National Academy of Sciences*.

"This is the first report of LANA interfering with the crucial cellular protein called intracellular Notch," says lead author Erle Robertson, PhD, Professor of Microbiology and the Program Leader of Tumor Virology at Penn's Abramson Cancer Center. Notch is a signaling molecule that triggers cell development and maintains the stability of cells in many organs, such as the brain, heart, blood, and muscle.

"Intracellular notch, or ICN, promotes cell growth and proliferation, therefore it must be regulated so that these processes do not lead to cancer," says Robertson. "We found that regulation of ICN through binding to another protein called Sel10, a cell-cycle regulatory protein, is derailed. The large complex of ICN, Sel10, and other factors is marked for degradation by a process called ubiquitination," says Robertson. In normal uninfected cells, the level of ICN, and thus cell growth and proliferation, is fine-tuned by regulating ICN degradation.



LANA interferes with the degradation of ICN because it competes with ICN for the same binding site on Sel10. If LANA sits on Sel10, ICN cannot be degraded and cell growth and proliferation are no longer controlled. Kaposi's sarcoma and primary effusion lymphoma are two of the viral-associated cancers that are common in immune-compromised patients.

This is the second mechanism discovered by Robertson and his associates by which KSHV subverts control of normal cell growth. Robertson's group previously found that LANA marks tumor suppressors, such as p53 and VHL, for degradation.

Other herpes viruses, such as the one that causes cold sores and Epstein-Barr virus, which causes mononucleosis, are able to hide out in cells as well. "Whether these latent herpes viruses use some of the same strategies that we have found for LANA in KSHV has not been determined," says Robertson.

This new role for LANA was discovered using specific human cell lines. The next step is to test whether LANA works the same way in animals infected with KSHV. "We have completed some studies in mice that indicate that LANA can contribute to tumor development in an animal in ways similar to what we have observed in cell culture," says Robertson. The animal models will be useful for testing new drug therapies that may inhibit the activity of LANA and eventually prevent the growth of viralassociated cancers.

Source: University of Pennsylvania School of Medicine

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