Microbiologists identify two molecules that kill lymphoma cells in mice

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Researchers at the University of Southern California have identified two molecules that may be more effective cancer killers than are currently available on the market.

The peptides, molecules derived from a cancer-causing virus, target an enzyme in cancerous cells that regulates a widely researched tumor suppressor protein known as p53. The peptides inhibit the enzyme, causing p53 levels in cancer cells to rise, which leads to cell death. Lymphoma tumors in mice injected with the two peptides showed marked regression with no significant weight-loss or gross abnormalities.

The discovery is detailed in the journal *Nature Structural & Molecular Biology*, which posts online on Sunday, Nov. 6.

HAUSP, or herpesvirus-associated ubiquitin specific protease, is an enzyme that cleaves the normally occurring protein ubiquitin from substrates like p53. In a healthy environment, ubiquitin binds to a substrate, causing it to degrade and die.

"Given the mounting evidence that HAUSP serves as a pivotal component regulating p53 protein levels, the inhibition of HAUSP should have the benefit to fully activate p53," said Hye-Ra Lee, Ph.D., the study's first author and a research fellow in the Department of Molecular Microbiology & Immunology at the Keck School of Medicine of USC.

Using co-crystal structural analysis, Lee and her colleagues found a tight, "belt-type" interaction between HAUSP and a viral protein that causes Kaposi's sarcoma and lymphoma. The peptides derived from this viral protein bind 200 times more strongly to HAUSP than p53, making them ideal HAUSP inhibitors. The researchers found that the peptides comprehensively prevented HAUSP from cleaving ubiquitin, allowing p53 levels to rise — thereby representing potential new chemotherapeutic molecules that can be used for anti-cancer therapies.

New research is under way with Nouri Neamati, Ph.D., associate professor of pharmacology and pharmaceutical sciences in the USC School of Pharmacy, to find small molecules that mimic the peptides. The peptides and other small molecules are being tested on different cancers.

"Significant advances in scientific understanding often come at the intersection of independent lines of research from different disciplines, for instance, structure and virus study. Time after time, viruses are teaching us," said Jae Jung, Ph.D., the study's principal investigator and chairman of the Department of Molecular Microbiology & Immunology at the Keck School of Medicine.

Provided by University of Southern California

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