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Researchers confirm new cancer-causing virus

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An important new study from the Laboratory for Developmental Genetics at USC has confirmed cytomegalovirus (CMV) as a cause of the most common salivary gland cancers. CMV joins a group of fewer than 10 identified oncoviruses — cancer-causing viruses — including HPV.

The findings, published online in the journal *Experimental and Molecular Pathology* over the weekend, are the latest in a series of studies by USC researchers that together demonstrate CMV's role as an oncovirus, a virus that can either trigger cancer in healthy cells or exploit mutant cell weaknesses to enhance tumor formation.

Lead author Michael Melnick, professor of developmental genetics in the Ostrow School of Dentistry of USC and Co-Director of the Laboratory for Developmental Genetics, said the conclusion that CMV is an oncovirus came after rigorous study of both human salivary gland tumors and salivary glands of postnatal mice.

CMV's classification as an oncovirus has important implications for human health. The virus, which has an extremely high prevalence in humans, can cause severe illness and death in patients with compromised immune systems and can cause birth defects if a woman is exposed to CMV for the first time while pregnant. It may also be connected to other cancers besides salivary gland cancer, Melnick added.

"CMV is incredibly common; most of us likely carry it because of our

exposure to it," he said. "In healthy patients with normal immune systems, it becomes dormant and resides inactive in the salivary glands. No one knows what reactivates it."

This study illustrates not only that the CMV in the tumors is active but also that the amount of virus-created proteins found is positively correlated with the severity of the cancer, Melnick said.

Previous work with mice satisfied other important criteria needed to link CMV to cancer. After salivary glands obtained from newborn mice were exposed to purified CMV, cancer developed. In addition, efforts to stop the cancer's progression identified how the virus was acting upon the cells to spark the disease.

Thus, the team not only uncovered the connection between CMV and mucoepidermoid carcinoma, the most common type of salivary gland cancer, but also identified a specific molecular signaling pathway exploited by the virus to create tumors, being the same in humans and mice.

"Typically, this pathway is only active during embryonic growth and development," Melnick said, "but when CMV turns it back on, the resulting growth is a malignant tumor that supports production of more and more of the virus."

The study was conducted by Melnick with Ostrow School of Dentistry of USC colleagues Tina Jaskoll, professor of developmental genetics and co-director of the Laboratory for Developmental Genetics; Parish Sedghizadeh, director of the USC Center for Biofilms and associate professor of diagnostic sciences; and Carl Allen at The Ohio State University.

Jaskoll said salivary gland cancers can be particularly problematic

because they often go undiagnosed until they reach a late stage. And since the affected area is near the face, surgical treatment can be quite extensive and seriously detrimental to a patient's quality of life.

However, with the new information about CMV's connection to cancer comes hope for new prevention and treatment methods, perhaps akin to the development of measures to mitigate human papilloma virus (HPV) after its connection to cervical cancer was established. Jaskoll added that the mouse salivary gland model created to connect CMV to cancer might also be used to design more effective treatments.

"This could allow us to have more rational design of drugs used to treat these tumors," she said.

Melnick said that in the not too distant future, he expects much more information about viruses and their connections to cancer and other health issues seemingly unrelated to viral infection to emerge.

"This should be a most fruitful area of investigation for a long time to come," he said. "This is just the tip of the iceberg with viruses."

More information: "Human Cytomegalovirus and Mucoepidermoid Carcinoma of Salivary Glands: Cell-Specific Localization of Active Viral and Oncogenic Signaling Proteins is Confirmatory of a Causal Relationship," *Experimental and Molecular Pathology*.

Provided by University of Southern California