Cell's fight against cancer revealed

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If anything in cancer biology can be likened to a cage match, this is it: the battle inside the cell walls between LTag, "The Most Amazing Molecule in the Universe," and p53, "The Guardian of the Genome."

By the painstaking use of X-ray crystallography to track motion in very large molecules, a University of Southern California-led research group has taken a first look at the life-or-death struggle of a cancer-causing protein – LTag – and a key tumor suppressor – p53.

Each villainous LTag (short for large T antigen) single-handedly ties up a tag-team of six p53 molecules, inhibiting their tumor-suppressant role, the researchers report in the Sept. 1 issue of *Genes & Development*.

Undeterred, the p53 fight back by preventing replication of the virus that produces LTag, known as an oncoprotein for its function in cancer growth.

The champion depends on which side is stronger and healthier.

"If you have a lot of functional p53, you can override large T antigen," said lead researcher Xiaojiang Chen, professor in molecular and computational biology in the USC College of Letters, Arts and Sciences.

Sometimes called the "Guardian of the Genome," a damaged p53 can leave a cell almost defenseless.

"p53 is a very important tumor suppressor that's mutated in a vast

majority of all cancers," said James Pipas, professor of biological sciences at the University of Pittsburgh.

It was Pipas who, after studying LTag for many years and marveling at its varied biological functions – including highly efficient tumor promotion – named it "The Most Amazing Molecule in the Universe" in one of his presentations.

Pipas called Chen's new study "a very important piece of work" that shows how a healthy cell's tumor defenses break down.

"Understanding exactly how this works is going to be a critical step toward our understanding of tumor genesis," he said.

This, in turn, may lead to new techniques for designing tumor-fighting drugs, Pipas added.

Chen's team was able to describe the interplay between LTag and p53 by crystallizing the complex of one LTag and six p53 molecules, totaling more than 50,000 atoms between them.

"It's quite a technical achievement, because these are fairly large proteins," Pipas said.

Chen said his study gave him new respect for LTag and its parent, Simian Virus 40. SV40 has long been used as a research tool to induce cancers in cell cultures.

"Somehow this virus knows how important p53 is, and has this oncoprotein (LTag) to target it by physically interacting with it and changing its conformation," Chen said.

If the virus succeeds, the result is a new tumor.

Source: University of Southern California