Braking Mechanism Identified for Cell Growth Pathway Linked to Several Cancers

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Researchers at University of California, San Diego School of Medicine have discovered a self-regulating loop in the Hippo pathway, a signaling channel garnering increased attention from cancer researchers due to its role in controlling organ size, cell proliferation and cell death.

The finding, published June 26 online in the journal *Genes & Development*, provides new insights about how the Hippo pathway maintains cellular balance, a subject of growing interest since its malfunction can lead to uncontrolled cell growth and inhibition of cell death – two hallmarks of cancer.

"Since cancer has been associated with overgrowth of cells, dysfunctions in this pathway are being explored in several types of tumors," said Kun-Liang Guan, PhD, professor of pharmacology at UC San Diego School of Medicine and Moores Cancer Center and senior author of the study. Thus far, Guan said the clearest connections have been established in mesothelioma, a type of cancer developed in the protective lining that covers many internal organs of the body, and uveal melanoma, a cancer in the eye – a finding published by Guan's lab in 2014. The Hippo pathway's involvement is also suspected in other cancers.

Guan says the Hippo pathway exists in most body tissues and organs, where it controls the size of organs and tissues by keeping cell growth in check and promoting cell death as needed. For instance, signals transmitted through the Hippo pathway tell the heart to stop growing once it has reached appropriate size. The pathway was first discovered by researchers working in fruit flies in the 1990s. The researchers observed that, when the pathway was removed, the fruit fly grew a large head with skin folds around the neck, reminiscent of a hippopotamus.

While researchers found the pathway interesting from a mechanistic approach, it has only been in recent years that its role and therapeutic potential in cancer began to be explored, said Guan. "A lot of biological pathways have been studied in cancer, but this one is relatively new," he said. "It gained momentum around 2005 when people realized it was also present in the mammalian system. This meant that it's important not only in basic biology, but also in disease pathology."

Guan's lab and others have previously established the key signaling components of the pathway, but its control or braking mechanism – how the pathway shuts off at the proper time – had not been identified until now. "It was already known that YAP and TAZ, two transcription co-activators, work in the Hippo pathway to promote cell growth by inducing certain genes to express," said Guan. In this study, Guan and his team discovered that the two co-activators also have a built-in self-control mechanism that keeps cell growth from getting out of hand. "They have a negative feedback regulation loop that puts the brakes on cell growth."

Specifically, the researchers found that, in addition to promoting genes for cell growth, YAP and TAZ also induce expression of inhibitor genes, such as NF2, that dampen the cell growth signal. "This is important because without this braking mechanism you would get uncontrolled cell growth, which can lead to cancer," Guan said.

The findings, which were made in both cultured cells and mouse tissues, are in keeping with previous studies showing that knocking out the NF2 gene in mice produces uncontrolled cell growth. "Several biotech and pharmaceutical companies are looking at targeting the Hippo pathway for cancer therapy," he said.

Guan said their finding provides "a better picture of how these pathways keep balance, which is important to avoid unchecked signaling that could lead to disease."

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