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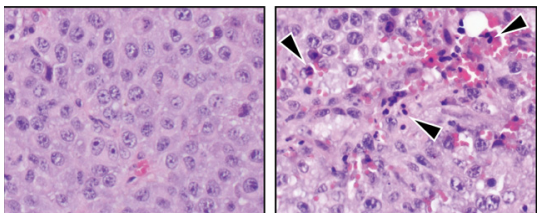
Study Reveals New Role for Hippo Pathway in Suppressing Cancer Immunity

Previous studies identified the Hippo pathway kinases LATS1/2 as a tumor suppressor, but new research led by University of California San Diego School of Medicine scientists reveals a surprising role for these enzymes in subduing cancer immunity. The findings, published in *Cell* on December 1, could have a clinical role in improving efficiency of immunotherapy drugs.



The image on the left is of melanoma cells growing in a mouse model. On the right, arrows point to immune cells infiltrating a tumor with LATS1/2 deleted.

"Before our study, no one knew that the Hippo pathway was regulating immunogenicity," said first author Toshiro Moroishi, MD, PhD, postdoctoral researcher at UC San Diego Moores Cancer Center. "LATS1/2 deletion in cancer cells improves tumor immunogenicity, leading to the destruction of cancerous cells by enhancing anti-tumor immune responses."

Hippo pathway signaling regulates organ size by moderating cell growth, apoptosis and stem cell renewal, but dysregulation contributes to cancer development. *In vitro* studies of Hippo pathway kinases LATS1/2 showed that the loss of these enzymes promoted cell proliferation and tumor survival. *In vivo* research using immune-compromised mouse models also supports a tumor suppressor function of the Hippo pathway.

However, when Moroishi and team deleted LATS1/2 from mouse cancer cells and examined tumor growth in models with healthy immune systems researchers found that immunogenicity — the ability to stimulate an immune response — improved, destroying cancer cells. Researchers caution that immune systems of mouse models are different from the human immune system so the response might be different and further studies are needed.

If the outcome proves to be the same, using a LATS1/2 inhibitor alone or in combination with an immune checkpoint inhibitor may stimulate the immune system of patients that previously did not respond to immunotherapy treatments.

Currently, most immunotherapy research focuses on targeting the immune system, but the new findings reveal that tumor cells may also be vulnerable to inhibitors.

“Inhibiting LATS1/2 could be an attractive approach to treat cancer,” said Kun-Liang Guan, PhD, Distinguished Professor of Pharmacology at Moores Cancer Center and senior author of the study. “LATS is an ideal target because there are many kinase inhibitors that have been successfully developed as cancer drugs.”

This study focused on breast cancer, melanoma and squamous cell carcinoma but the same could be applied to other cancers, said Moroishi.

Study co-authors include: Tomoko Hayashi, Yu Fujita, Dennis A. Carson, UC San Diego; Wei-Wei Pan, UC San Diego and Jiaxing University; Matthew V. Holt, and Jun Qin, Baylor College of Medicine.

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Disclosure: Kun-Liang Guan is co-founder of Vivace Therapeutics and holds equity interest.

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