Researchers identify key component of cellular malfunction leading to cancer

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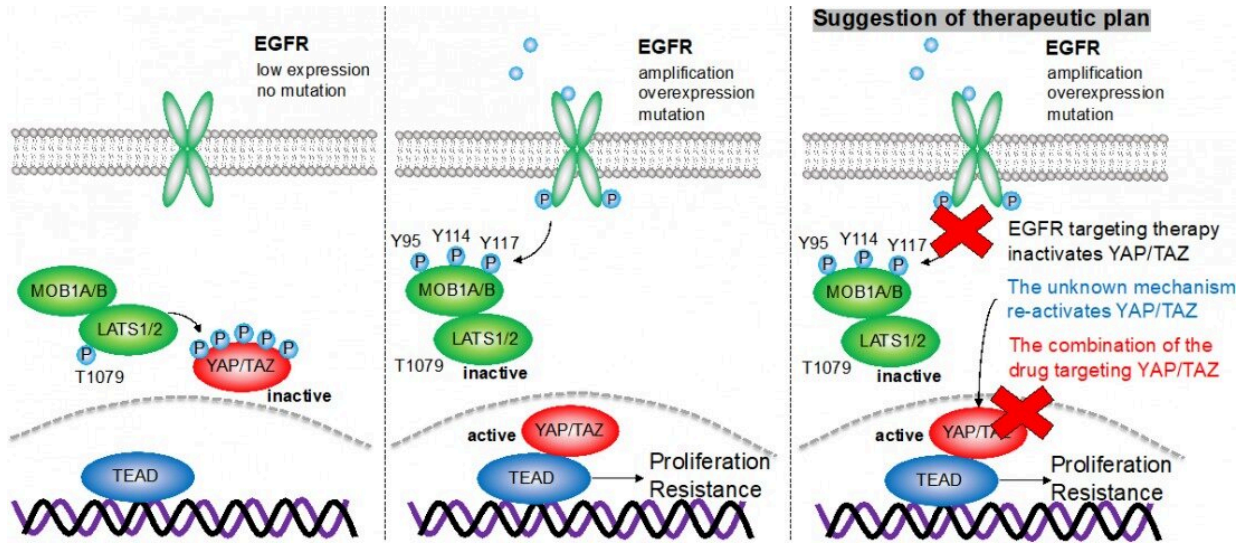

Scientists from Hiroshima University and University of California, San Diego have discovered the mechanism by which EGFR activates YAP/TAZ. Their results suggest that the combination of the drug targeting YAP/TAZ with EGFR targeting therapy may be beneficial for preventing cancer recurrence and progression acquired by YAP/TAZ re-activation through unknown mechanism. Credit: Toshinori Ando, Hiroshima University and J. Silvio Gutkind, University of California, San Diego

Malfunctioning of the so-called Hippo signaling pathway within animal cells leads to irregular activity of proteins that regulate genes involved in cell proliferation. Researchers have identified a key step in the process

of this aberration, opening the door to new therapeutics for cancers such as head-and-neck squamous cell carcinoma and lung adenocarcinoma.

Scientists have homed in on a crucial step within the sequence of chemical reactions that govern regulation of cell division, proliferation and death, and whose malfunction contributes to the growth of tumors.

The research appears in the journal *Communications Biology* on Nov. 1, 2021.

Within biology, the term signaling pathways describes the cascade of chemical reactions whereby particular molecules work to govern a cell's function. The "Hippo" signaling pathway in animals is one of these and controls organ size via the regulation of cell division, proliferation and death (apoptosis). It takes its name from one of its main components, the Hpo or "hippo" kinase. A kinase is a type of protein that adds or removes phosphate groups to other molecules, a process known as phosphorylation. Phosphorylation works as a sort of biological on/off switch and plays a critical role in the regulation of many cellular processes including cell cycle, growth, and apoptosis.

As many cancers are the product of uncontrolled cell division, researchers have increasingly focused a lot of attention on the hippo pathway, which when malfunctioning results in irregular activity of a pair of its downstream targets, the Yes-associated protein (YAP) and transcriptional co-activator with PDZ binding motif (TAZ). YAP/TAZ act to regulate the transcription of genes (copying their information from DNA form to RNA form) that are involved in cell proliferation. When the Hippo signaling pathway is active, YAP is inhibited, thus playing a role in control of tumor suppression. On the other hand, when Hippo signaling is inactive, YAP becomes persistently active and promotes cell proliferation.

But the precise mechanisms of YAP/TAZ activation remains poorly understood. It is known that the gene that encodes epidermal growth factor receptor (EGFR), a protein that helps cells grow, is often over-activated, especially in head and neck squamous cell carcinoma (HNSCC), and EGFR is often mutated and activated in lung adenocarcinoma (LUAC).

As a result, EGFR is a common target of anti-cancer therapies, either using kinase inhibitor drugs, or blocking antibodies. Yet here too, whether EGFR controls YAP/TAZ activation has been an open question.

"EGFR fails to reduce phosphorylation of YAP in some cellular systems, but inhibits the Hippo pathway to activate YAP in others," said Toshinori Ando, a main researcher working on the study and Assistant Professor at the Center of Oral Clinical Examination at Hiroshima University Hospital (with a cross-appointment as a post-doctoral scientist in the University of California, San Diego). "If EGFR is being targeted by therapeutics, we really should know a bit more about why we're doing this."

So the researchers carried out a series of investigations of Hippo pathway mechanisms, including via comparisons of EGFR gene activation (expression) and activation of YAP in a series of HNSCC cancer cells; cells that showed the most expression of EGFR amongst HNSCC cells; an analysis of all cancer types; and gene set enrichment analysis (GSEA)—a technique of identifying groups of genes that are over-represented within a large set and may be associated with certain diseases.

They found that EGFR activation promotes tyrosine phosphorylation of one of the core Hippo pathway components, called MOB1. This is a gene that directs activation of particular kinases, LATS1 and LATS2, which modulate the function of the YAP/TAZ. The EGFR-promoted

MOB1 tyrosine phosphorylation followed by LATS1/2 inactivation leads to aberrant YAP/TAZ activation in many cancers harboring EGFR alterations such as HNSCC and LUAC.

"Emerging evidence have shown that YAP is overexpressed and contributes to cancer growth, poor prognosis, and acquired resistance to EGFR-targeted drugs in HNSCC and LUAC, although the mechanism of YAP re-activation is unclear," added J. Silvio Gutkind, lead researcher of this project and Professor at the University of California, San Diego.

This EGFR-MOB1-YAP/TAZ signaling axis may represent a novel target for cancer therapies. In addition, a combination of EGFR targeting therapy and YAP/TAZ targeting therapy could prevent cancer cells from acquiring resistance that might have occurred if just one or the other therapies were used on their own.

A drug targeting YAP/TAZ has yet to be approved for the treatment of cancer patients. The researchers consider the development of such a drug to be an urgent priority as well as to clarify the unknown mechanism of YAP re-activation.

More information: Toshinori Ando et al, EGFR Regulates the Hippo pathway by promoting the tyrosine phosphorylation of MOB1, *Communications Biology* (2021). DOI: 10.1038/s42003-021-02744-4

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