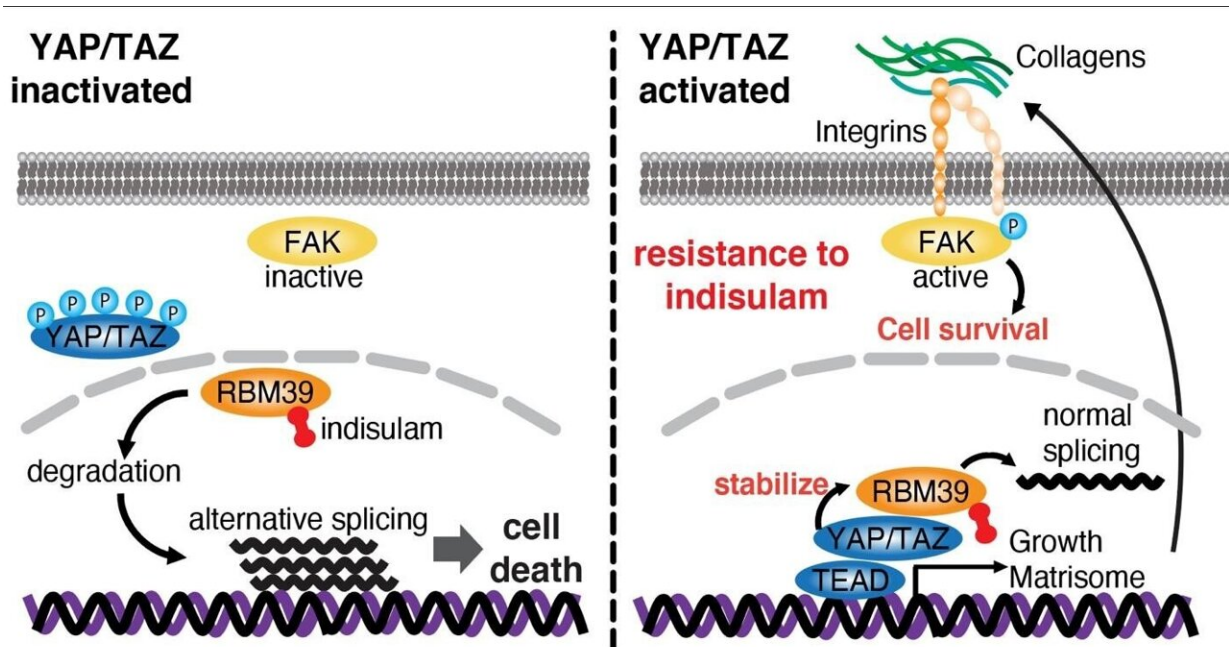


# YAP/TAZ interactions can confer resistance to anti-tumor drug indisulam

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Scientists from Hiroshima University Hospital clarified the mechanism by which YAP/TAZ confers resistance against indisulam. Indisulam induced degradation of RBM39 in YAP/TAZ inactivated cells, thereby inducing cell death (left). When RBM39 interacts with activated YAP/TAZ (right) it enhances transcription of growth and matrisome genes including collagens and integrins, which activates FAK which is important for cell survival. In addition, YAP/TAZ stabilizes RBM39 so as not to cause alternative splicing. Therefore, YAP/TAZ-activated cells are resistant to indisulam. Credit: Toshinori Ando, Center of Oral Clinical Examination, Hiroshima University Hospital

In a healthy human body, tissue growth and development are coordinated by many different mechanisms. Within our bodies, these mechanisms regulate the healthy growth of cells, limit their size and number, and control the timing of cell death through apoptosis. However, when these regulatory pathways are altered, or break down, cell growth and proliferation may increase beyond what is safe and this can lead to cancer.

One critical [cell growth](#) regulatory mechanism is the Hippo signaling pathway. This pathway regulates the expression of several genes that control cell proliferation and apoptosis via the transcription coactivators YAP/TAZ. Dysregulation of this pathway is commonly seen in several different cancers including head and neck [squamous cell carcinoma](#) (HNSCC).

One promising anti-tumor drug is indisulam, a cell cycle inhibitor that inhibits the expression of cell proliferation genes and triggers aberrant mRNA splicing by degrading the RNA-binding protein (RBM39) causing cell death. It has shown promise both in cell cultures and in animal studies. However, [clinical trials](#) have shown fewer clear-cut results. Scientists from Hiroshima University Hospital have been researching the reasons behind this resistance to indisulam.

"Clinical trials of indisulam failed to show good response in solid cancer patients but the mechanism of the resistance has not been solved. I wondered if YAP/RBM39 interaction may be involved in the resistance mechanism of indisulam," said Toshinori Ando, senior lecturer at the Center of Oral Clinical Examination, Hiroshima University Hospital.

In fact, they found "that YAP interacts with RBM39 and confers resistance against indisulam, which is the critical obstruction to be solved for future clinical usage of indisulam," Ando said. Their research was published on July 15 in [Oncogenesis](#).

A signaling pathway is a series of chemical reactions that are activated by a signal, often environmental. Once begun, each reaction within the pathway is activated in series ending up with the activation or inactivation of a specific cellular function. This allows the body to react to the presence or absence of specific chemicals, such as hormones, by activating or deactivating transcription of certain genes depending on what the cell needs at that moment. The Hippo [signaling pathway](#) is a critical pathway that can deactivate the transcription of genes that control cell proliferation by inactivating YAP/TAZ.

The anti-tumor drug indisulam acts by degrading RBM39, a protein that binds to [transcription factors](#), which enhances transcription as well as regulating the mRNA splicing that is integral to the process of gene transcription. By degrading RBM39, indisulam interferes with RBM39's normal function causing changes in splicing leading to cell death, thereby reducing the cell proliferation that can lead to tumor formation.

The Hiroshima University researchers focused on the reactions within the nucleus between the YAP/TAZ transcriptional coactivators and RBM39 to understand what exactly was occurring between them. They also investigated what happens when indisulam was added to determine what was causing the resistance to the anti-tumor drug.

Using proteome analysis, the group identified RBM39's interactions with YAP/TAZ. They also found evidence that it does promote YAP/TAZ's transcriptional activity. When indisulam was added, it inactivated a focal adhesion kinase (FAK), an enzyme which is very important for cell survival and which caused degradation in RBM39, thereby shutting down the transcription of the cell proliferation genes.

Interestingly, they discovered that the root of indisulam resistance was the activation of YAP/TAZ. When activated, it delayed indisulam's ability to induce the degradation of RBM39 and it reactivated the FAK,

thereby reducing the drug's effectiveness. Activation of YAP/TAZ conferred resistance both in vivo, in cell cultures and in vitro, in mice.

"In this study, we identified RBM39 as a novel YAP/TAZ interactor in the nucleus. Notably, we demonstrated that YAP/TAZ interacts with RBM39 to confer resistance to indisulam. Our findings decipher the resistance mechanism of indisulam, which may aid the development of a novel therapeutic approach for patients with solid cancers including HNSCC," Ando said.

Going forward, their research will be focusing on "further mechanism of interaction between RBM39 and YAP, thereby developing a new drug targeting the interaction for the patients with solid cancers including HNSCC," Ando said.

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**More information:** Toshinori Ando et al, YAP/TAZ interacts with RBM39 to confer resistance against indisulam, *Oncogenesis* (2024). [DOI: 10.1038/s41389-024-00527-0](https://doi.org/10.1038/s41389-024-00527-0)

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