Common genetic alteration found in head and neck cancers may not be key to effective treatment

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Although a large majority of head and neck cancers have a deregulation of the PI3K/AKT/mTOR pathway, data recently published in *Cancer Research*, a journal of the American Association for Cancer Research, indicated that deregulation of this pathway does not necessarily signify that the tumor is dependent on it for survival and progression.

Cancer, particularly of the head and neck, is highly heterogeneous, with a large number of genetic alterations rendering it resistant to specific targeted treatments. Because cancer is linked to genetic abnormalities, genomic and proteomic biomarkers are currently being used to design targeted therapeutic intervention for a variety of cancer indications.

Research has shown the PI3K/AKT/mTOR pathway is deregulated in a large majority of solid tumors. Treatment with mTOR inhibitors results in robust activity in certain cancer cell lines, but they are not effective in all patients. Researchers are currently using biomarkers to try to stratify patients for response to mTOR inhibitors.

"However, these technologies have limited success due to their inherent limitations in lack of clarity in distinguishing driver mutations in pathways from those of passengers," said Pradip K. Majumder, Ph.D., of the division of cancer biology at Mitra Biotech, Bangalore, India.

Majumder and colleagues used a systems biology approach called tumor

explant model to distinguish driver mutations, or those that are critical for a tumor's survival, from passenger mutations. This distinction is important for stratifying patients for current treatments and for developing novel rational combinations of anticancer agents.

The researchers collected fresh tumor tissue from 22 patients with head and neck cancers and conducted ex-vivo explant experiments. They were able to identify responders to rapamycin, an mTOR inhibitor. However, a majority of the tumor samples did not have an antitumor effect after treatment with the mTOR inhibitor, possibly because rapamycin is known to activate the AKT pathway.

To combat the AKT pathway activation, Majumder and colleagues treated the tumor samples with rapamycin in combination with an AKT inhibitor. Rapamycin-induced AKT activation was reversed, but a subset of patients still failed to respond.

"While few tumors are dependent on only mTOR, others are dependent on both mTOR and AKT," Majumder said. "However, a majority of the mTOR pathway-activated tumors seemed to not be dependent on this axis for survival or maintenance."

Targeted phosphoproteomic characterization of tumors resistant to dual AKT/mTOR inhibitors showed that multiple pathways were supporting the tumors' proliferation and survival and likely responsible for treatment resistance. This approach of combining ex vivo functional analyses with molecular profiling could potentially be used to stratify patients for appropriate combination therapy, according to Majumder.

"A majority of anticancer drugs fail in the phase II efficacy stage of clinical development due to a lack of technologies to identify and appropriately stratify patients according to their tumor pathway dependence," Majumder said. "Using this approach, researchers may be

able to develop a translational tool for further clinical development of novel anticancer drugs."

Provided by American Association for Cancer Research

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