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A cell-surface protein overexpressed in liver cancer offers a promising target for therapy

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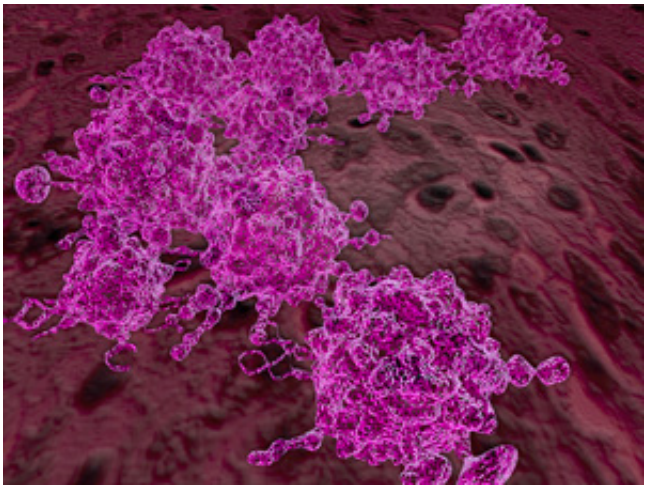

Blocking the activity of an abundant protein found on the surface of liver cancer cells could lead to new therapies for one of the most common and deadly cancers in the world. Credit: Purestock/Thinkstock

Patients with cancer of the liver express elevated levels of Agrin, a specific protein which aids the growth and spread of the cancer, according to new research from A*STAR scientists. The protein could be an attractive target for treating the liver cancer known as hepatocellular carcinoma, one of the most common and deadly cancers in the world.

"Current therapies such as sorafenibs and sunitinibs have been restricted to targeting kinase receptors, with modest effects on patient survival,"

says Sayan Chakraborty, who led the investigation with Wanjin Hong and colleagues from the A*STAR Institute of Molecular and Cell Biology. "Our study shows that there is immense potential to combine anti-Agrin agents with the already available enzyme inhibitors for effective and improved treatment."

Agrin is best known for its role as a signaling protein in junctions where muscle tissue connects with neural tissue. Using biochemical approaches and large-scale quantitative studies, the researchers identified high numbers of the molecule on the surfaces of liver cancer cells, suggesting a role in promoting tumor growth. Further clinical analysis of liver tissue samples from patients with hepatocellular carcinoma showed three to four times higher Agrin levels than samples from healthy patients.

When the researchers blocked Agrin expression in liver cancer cells, they observed a 42 per cent reduction in the rate of cellular proliferation and a more than 50 per cent increase in programmed cell death. The Agrin-depleted cells were also less likely to form free-floating colonies, migrate and invade noncancerous tissue. The shape of the cells changed from looking like prickly splinters to rounded cobblestones forming successive layers of cells. Mice injected with Agrin-depleted cancer cells developed tumors that were nearly 20 times smaller than those injected with the regular cancer cells.

The researchers were able to reverse these in vitro and in vivo effects, however, by reintroducing Agrin to the mutant cells.

To narrow in on the molecular mechanism of Agrin's cancer-provoking activity, the researchers conducted a series of experiments that ruled out all but one target protein. "Agrin is well reported to induce acetylcholine receptors in neuromuscular junctions," says Chakraborty. "To our surprise, we observed that Agrin hijacks the same receptor and downstream signaling repertoire in the liver to induce cell proliferation,

invasion and tumorigenesis."

The study provides solid support for the development of antibody therapies that inhibit Agrin activity, says Chakraborty. Furthermore, "the presence of Agrin in the plasma of hepatocellular carcinoma patients can also serve as an important diagnostic strategy," he adds.

More information: Chakraborty, S., Lakshmanan, M., Swa, H. L. F., Chen, J., Zhang, X. et al. "An oncogenic role of Agrin in regulating focal adhesion integrity in hepatocellular carcinoma." *Nature Communications* 6, 6184 (2015). dx.doi.org/10.1038/ncomms7184

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