Disruption of a crucial cellular machine may kill the engine of deadly cancers

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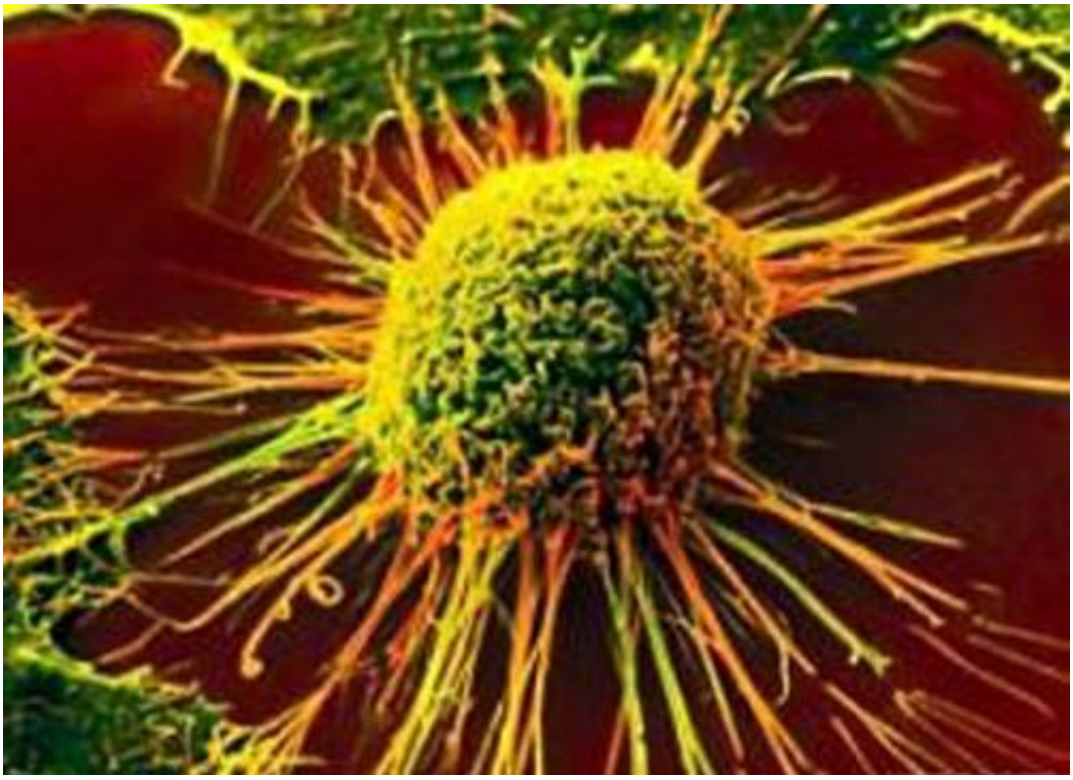

In a way, cancer resembles a runaway car with a gas pedal stuck to the floor, hurling out of control. Most new targeted cancer therapies seek to fix the gas pedal itself, and thus thwart the aggressive behavior of the tumor. But for many types of cancers, the pedal simply cannot be repaired, so new alternatives are desperately needed. A team at Baylor

College of Medicine has discovered a way to step on the brakes of some of the deadliest cancers.

"Almost thirty percent of all malignancies are driven by the cancer gene MYC. No one has been able to turn this gene off, and thus patients with MYC-driven cancers often lack effective therapies," said Dr. Thomas (Trey) F. Westbrook, associate professor in the department of biochemistry and molecular biology and molecular and human genetics at Baylor. "Like killing the engine of a runaway car, we have found a new way to kill cancers driven by MYC. We can do this by inhibiting a molecular machine within the cancer cell called the spliceosome." A report on their work appears online in the journal *Nature*.

Westbrook and colleagues have discovered that MYC-driven cancers depend on the spliceosome to survive.

"The spliceosome is a complex machine composed of many proteins," said Tiffany Hsu, an M.D./Ph.D student in the Medical Scientist Training Program and lead author of the study. "This machine helps cancers 'read' their instruction manual by deleting unnecessary steps. When we inhibit the spliceosome, cancers can no longer understand their instructions for growth and survival."

In their study, Westbrook, Hsu and colleagues found that inhibition of the spliceosome using a new drug kills tumor cells but leaves noncancerous tissues unaffected in mouse models.

"This study is a promising step towards helping patients with deadly cancers driven by MYC. We're also excited to discover a new side to the MYC oncogene, which is one of the most intensely studied but enigmatic cancer genes," said Hsu.

MYC rewires the cancer cell, and changes many things like production

of the building blocks that every tumor cell needs. But this rewiring also confers new stresses and new vulnerabilities in cancer cells. "If we could learn how to exacerbate those stresses, we could kill the cancer cell without harming normal tissues," said Westbrook, also a member of the Dan L. Duncan Cancer Center, an NCI-Designated Comprehensive Cancer Center, at Baylor. "The spliceosome may be a critical piece of the puzzle."

While spliceosome inhibitors are unlikely to provide an answer to all cancers, they are promising candidates for some aggressive malignancies like triple negative breast cancer, a common and particularly virulent form of the disease.

More information: The spliceosome is a therapeutic vulnerability in MYC-driven cancer, DOI: 10.1038/nature14985

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