microRNA silencing provides a successful new model for cancer therapeutics

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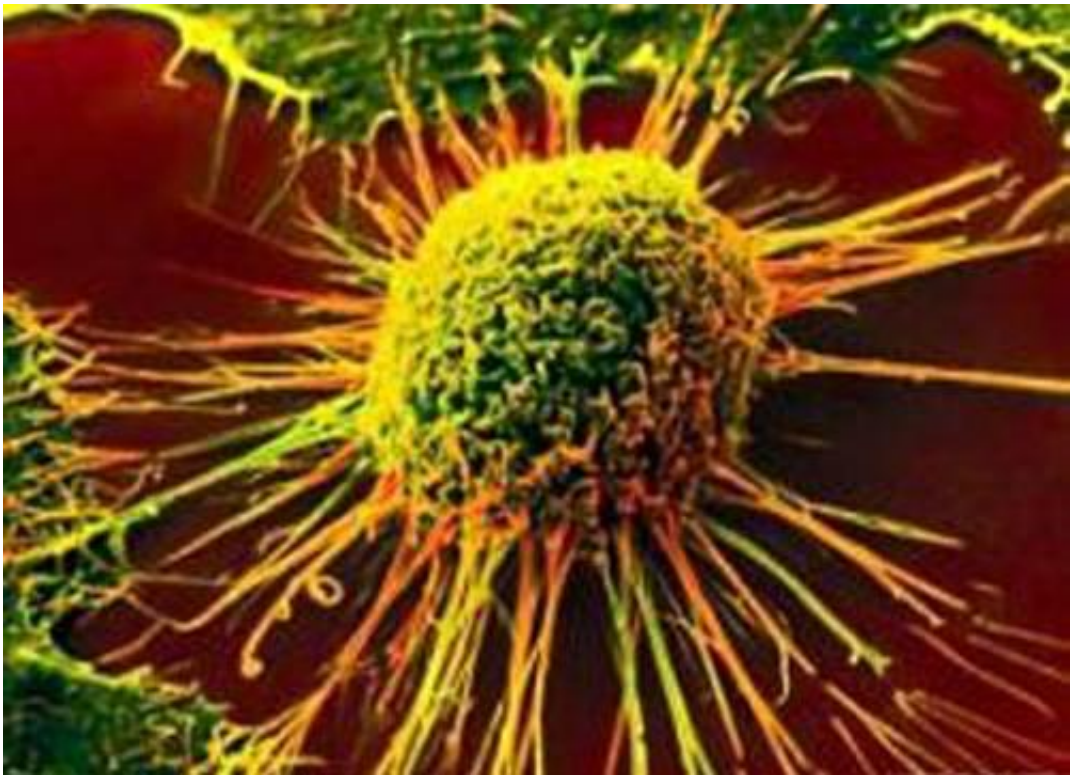

Since the discovery that microRNAs play key roles in regulating human disease, the hope has been that these short non-coding RNA molecules could be translated into a therapeutic strategy for the treatment of cancer. But this promising application has been significantly hampered by a number of physiological and cellular barriers that prevent

microRNA-based therapies from actually reaching tumor cells.

Now scientists have identified a novel delivery platform by which an antisense molecule - akin to the mirror image of the microRNA - can be used to exploit a unique feature of the tumor microenvironment and thereby gain access to cancer cells. Described online in the journal *Nature*, the promising findings suggest a new model for the development of microRNA-based anti-cancer drugs and targeted drug delivery.

"We have been building the case that there are certain, critical microRNAs that cause cancer when they are overexpressed in cells," explains senior author Frank Slack, PhD, Director of the Institute for RNA Medicine (iRM) in the Cancer Center at Beth Israel Deaconess Medical Center. "With this publication, we have now shown the applicability and the utility of a new therapeutic target for cancer."

For the past 10 years, Slack has investigated the roles of microRNAs as oncogenes and tumor suppressors, demonstrating how a number of microRNAs regulate processes important for cell growth, division, survival and migration, all of which can go awry in cancer. His work has revealed that microRNAs are both effective targets and therapeutics in cancer.

In this new work, conducted as part of an interdisciplinary team at Yale University, Slack and his coauthors created a mouse model to study miR-155, a microRNA that, when overexpressed, leads to the development of diffuse large B-cell lymphoma (DLBCL), a type of blood cancer that is difficult to treat. "We hypothesized that we could inhibit the function of miR-155 by way of an antisense molecule that would bind to miR-155," says Slack. An antisense molecule can shut down RNA activity when it binds to the original molecule. But first it has to get there.

"There are a number of significant obstacles to reaching the tumor cell target," explains Slack. "Some roadblocks are clearance through the kidneys and accumulation in the liver, which absorbs any systemically injected agent. Furthermore, even if you are able to reach your targeted cells, the molecules must cross cell membranes and escape degradation from a process known as endocytosis. If you can picture our antisense molecule being a warhead, we had to find the right 'rocket' to actually transport it to its target."

The "rocket" turned out to be a peptide with a low-pH induced transmembrane structure (pHLIP), meaning it inserts into cell membranes only in instances when cells are low in pH. And tumor cells provided the ideal environment.

"Unlike normal cells, which produce energy through glycolysis plus oxidative phosphorylation, cancer cells conduct a high rate of glycolysis followed by lactic acid production," says Slack. "This unique feature results in an acidic tumor microenvironment, and that proved to be the trick. When we attached our antisense warhead to the pHLIP peptide, not only did it successfully insert itself into the tumor cell, but it also dragged the antisense molecule itself into the cell. Now the 'warhead' could deploy and actually inhibit microRNA function - and control cancer growth."

The miR-155/DLBCL mouse models showed dramatic differences in tumor size, with slowed tumor growth and extended survival of the animals that were treated with the anti-microRNA therapy. The authors went on to further show that this particular treatment is less toxic than the existing treatment for human disease.

"With this delivery platform, we should also be able to transform other RNAs into druggable targets," says Slack, adding that low pH is also an issue in kidney disease, myocardial infarction, stroke and infection,

among other conditions.

"This advance shows tremendous efficacy with no short-term side effects," says Roy Herbst, MD, PhD, Chief of Medical Oncology in the Yale Cancer Center, where the work was conducted. "Under Frank Slack's leadership, this collaboration of biochemists, pathologists, biomedical engineers and basic scientists has demonstrated the enormous value of interdisciplinary translational research in moving biomedical discoveries toward patient care. The hope is that a variant of this therapeutic might soon be able to enter clinical trials."

Adds Pier Paolo Pandolfi, MD, PhD, Director of the BIDMC Cancer Center, "With this new work, Dr. Slack has made a critically important step in demonstrating how relevant it will be to effectively target microRNAs in the treatment of cancer in the years to come. MicroRNAs and other non-coding RNAs are among the most promising avenue in our pursuit of personalized cancer therapies, and with this novel delivery platform, we are poised to begin testing these agents in humans."

More information: MicroRNA silencing for cancer therapy targeted to the tumour microenvironment, *Nature*, DOI: 10.1038/nature13905

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