Treatment approaches that target tumor suppressors mutate

For all the differences documented between cancers, they share some striking similarities. Around 80% of detected cancer-related mutations are errors in so-called 'tumor suppressor genes', and more than half of all cancers have below-normal amounts of the tumor suppressor protein p53. This makes tumor suppressors—and p53 in particular—enticing targets for drug developers. Despite failed attempts in the past, researchers have hope for new variations on this cancer treatment approach.

"There has been a huge amount of interest in therapeutic targeting of p53 for over 15 years," says Alex Swarbrick at the Garvan Institute in Sydney. For example, in a small subset of cancer cases, the gene producing p53 is inhibited by the protein MDM2, murine double minute 2. A class of drugs called Nutlins, made by the Swiss pharma giant Roche, have shown promise for its ability to block MDM2 and are currently in clinical trials to treat people with tumors in their fat tissue. Meanwhile, several small molecules are being studied for their ability to restore mutant p53 proteins, but results have been mixed.

So far, there are no approved anticancer agents that target p53. One reason for the absence is that cancer cells sometimes completely lack that gene, and therefore there is nothing to target. Other times, p53 is present, but mutated, and restoring the function of a protein is inherently difficult.

The latest idea for targeting tumor suppressors is through microRNAs, small pieces of single-stranded, noncoding RNA that regulate an estimated 20% to 30% of all protein-coding genes, including both tumor suppressor genes and oncogenes (*Cancer Res.* **70**, 7027–7030, 2010).

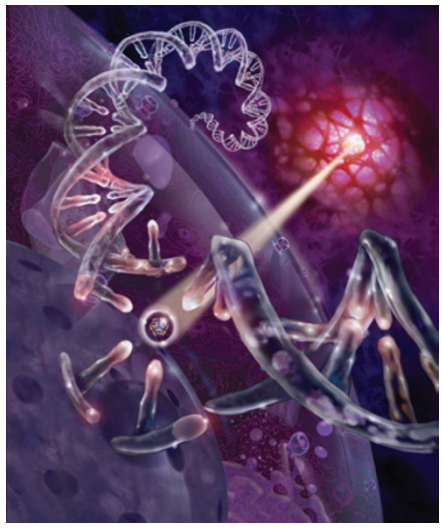
In the same way that tumor suppressor proteins are often absent or nonfunctional in cancer cells, so are certain microRNAs. A strategy known as microRNA replacement therapy aims to create the same sequence of missing RNA and restore it to the cancer cells. The approach could be more powerful than restoring the missing protein, because individual microRNAs regulate upwards of a hundred protein-coding genes at once, so "targeting microRNAs in cancer cells can have a very potent effect," says Joshua Mendell, of the Johns Hopkins University School of Medicine in Baltimore, whose group is studying these molecules in liver cancer.

Pathways to success?

Last year, for example, Mendell and his colleagues showed that introducing a microRNA called miR-26a could reduce the size of liver tumors in mice by about a third without any harmful effects on healthy tissue (*Cell* **137**, 1005–1017, 2009). More recently, scientists at Mirna Therapeutics, a biotech company in Austin, Texas, showed that another microRNA called miR-34a, which regulates the p53 pathway, blocks the growth of human lung tumors in mice (*Cancer Res.* **70**, 5923–5930, 2010) and inhibits prostate cancer stem cells and metastasis (*Nat. Med.* **17**, 211–215, 2011). According to Mirna's associate director of research Andreas Bader, the company intends to apply for human testing of their microRNA sometime next year.

Despite these recent advances, several hurdles remain. Because miRNAs regulate so many genes, researchers worry about how they will affect healthy tissue, even though no serious adverse events have been detected in any of the mice studied so far.

Even more challenging is the problem of designing an effective way to deliver microRNAs to the site of the tumor without the small strands of RNA getting degraded or filtered out of the body, notes Bader. "Delivery still remains the major hurdle to bringing this to the clinic," he says. Various strategies under development include encasing microRNAs in lipid membranes that can then be coated with tumor-specific peptides to act like homing agents, as well as using nanoparticles or viral vectors as delivery mechanisms.



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On target: microRNAs replace mutated genes.

Nevertheless, researchers are cautiously optimistic. "It would be circumspect to propose that microRNAs will be magically easier to work with than tumor suppressors," says Swarbrick, who is studying the role of microRNAs as both tumor suppressors and oncogenes. All the same, he adds, there's clear evidence that microRNAs will be important molecules to try and target in cancer. "The field is exploding."

Monica Heger

Historically, scientists have had a tough time finding viruses that attack cancer cells without harming healthy tissue. But researchers can now engineer oncolytic viruses that lack certain regulatory genes—such as the *E1A* or *E1B* genes—that they use to defeat the antiviral defense mechanisms possessed by normal cells, rendering the viruses harmless in healthy tissue. These defense systems are often switched off in cancer cells, making them vulnerable to the engineered infectious agents.

On top of this, genes coding for proteins that enhance the body's immune response, such as granulocyte-macrophage colony–stimulating factor, can be added to stimulate the expansion of white blood cells that enhance the immune response against tumors, as with BioVex's and Jennerex's products. So can genes coding for enzymes that turn a separately injected drug precursor into a toxic anticancer agent.

"The issue of targeting oncolytic viruses selectively to cancer cells is largely solved and not as much of a barrier anymore," says Timothy Cripe, a physician at Cincinnati Children's Hospital Medical Center who develops oncolytic viruses for treating pediatric cancers.

Other challenges still persist, though. The immune system, for example, can be a double-edged sword, prone to attacking the oncolytic viruses as well as the tumor. "The barriers now are getting the viruses to spread efficiently within a tumor microenvironment and to persist long enough to have their effect," says Cripe.

Scientists are continuing to evaluate how viruses might join chemotherapy and radiotherapy in the arsenal of cancer treatments. "What we're going to continue to see over the next couple of years is a careful assessment of safety and some glimpses of efficacy as an add-on to existing therapeutic regimens," predicts William Phelps, program director of preclinical and translational cancer research at the American Cancer Society in Atlanta.

Jon Evans