RNA nanoparticles fight cancer

Successful in mice and lab-grown human cells

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RNA nanoparticles have been built that can deliver drugs to specific cells and have already shown promise against cancer in mice and human cell cultures.

The nanoparticles are assembled from three short pieces of ribonucleic acid and resemble miniature triangles.

They have the right size to gain entry into cells and the right structure to carry other therapeutic strands of RNA inside them.

"RNA has immense promise as a therapeutic agent against cancer, but until now we lacked an efficient system to bring multiple therapeutic agents directly into specific cancer cells so they can perform different tasks," says research team leader Peixuan Guo of Purdue University. "Physicians have hoped that nanotechnology might provide a solution to the problem, but it is possible that the application of these tiny triangles could lead to the solution."

Using their nanoparticles, Guo and colleagues have delivered three different therapeutic agents into a cell at the same time, which is considered a major accomplishment that points to the particles' potential.

A news release describes the research:

RNA molecules come in many variant forms, and the sort that the team mimicked is called pRNA—also can be linked to other types of RNA to form longer, hybrid strands with properties the researchers could assign.

"We looked around for RNA strands that would behave in certain ways when they encounter a cancer cell because each of them needs to perform one step of therapy," Guo explained. "An effective agent against cancer needs to accomplish several tasks. It needs first to recognize the cancer cell and gain access to its interior, and then it needs to destroy it. But we'd also like the agent to leave a mark for us, to mark the path the molecule has taken somehow. That way, we can pinpoint the location of the cancer and trace the outcome after the treatment.
To accomplish these tasks, the team turned to other forms of RNA that can interact with the goings-on inside cells. The team sorted through a variety of RNA forms that have shown promise for disease treatment and found three that could perform the desired tasks. One example is "small interfering RNA," or siRNA, which deactivates certain genes in cells. The others are RNA aptamers, which bind to cancer cell surface markers, and ribozymes, which can be designed to degrade specific RNA in cancer cells or viruses.

"We linked each of the three therapeutic strands with a piece of pRNA, forming hybrid strands," Guo said. "Then, using techniques we learned from our earlier work, we were able to combine all three into triangles that are between 25 and 40 nanometers wide. This is the Goldilocks size for any nanoparticle that is too big, not too small, not too small.

Particles larger than about 100 nanometers are generally too large to pass through cell membranes into the cell's interior, Guo said, and the body has a hard time retaining particles smaller than 10 nanometers. But the tiny triangles fit, and worked well enough to interrupt the growth of human breast cancer cells and leukemia model lymphocytes in laboratory experiments.

"One characteristic of cancer cells is that they do not stop growing, which is one reason tumors develop," Guo said. "Once inside, the siRNA essentially instructs cells to 'stop not stopping.' The nanoparticles had done their work on the breast cancer cell cultures within a few days."

Additionally, the team found that the nanoparticles completely block cancer development in living mice. A group of mice that were in the process of developing cancer were tested with the nanoparticles, and they did not develop the disease. A second group that was tested with mutated inactive RNA all developed tumors.

There are several hurdles to go before the findings can be applied in people, such as ways to protect the RNA from degradation by enzymes in the body.

The research is reported in two related papers in the journals *Nano Letters* and *Human Therapy*.