Engineered molecule changes itself to detect and attack diseased cells

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(PhysOrg.com) -- Assistant Professor of Bioengineering Christina Smolke has engineered biological molecules that regulate a cell's behavior by adjusting their own forms and functions in response to the internal conditions of the cell. These tools can be used to facilitate medical research and biotechnology today and could one day be used as diagnostic and therapeutic aides.

Imagine if your doctor could look for cancer in your body just by checking for green glowing cells, alerting her to the presence of the disease. Imagine further that she could convince any cancerous cells in your body to commit suicide, while leaving your healthy cells unaffected.

In Friday's issue of *Science*, a Stanford researcher reported engineered biological "devices" that could one day offer these kinds of diagnostic and treatment options. The devices built by Assistant Professor of Bioengineering Christina Smolke, along with a graduate student and a postdoctoral researcher, can sense disease states in cultured human cells and fine-tune their own functions in response to a cell's internal signals.

These autonomous biological tools are called "sensor-actuator" devices because they sense what's happening in a cell and act upon what they detect.

The researchers built these devices by combining different pieces of DNA into one long stretch. The DNA is then put into cells that convert it

to RNA, a slightly different version of genetic material that is frequently made by cells. The RNA molecule can then be read like a recipe by the cell's protein-making molecular machinery.

The sensor-actuator devices are built with efficient redesign in mind. Each piece of the device, whether the sensor or the protein-recipe actuator, can be swapped out for another version. This way, researchers can conveniently build a device to fit their particular needs. "You can fan out with lots of different outputs and you have lots of different inputs you could potentially link into," said Smolke. The input could be any number of protein signals inside a cell and the output could be instructions for the cell to create a molecule that's easily detected by a researcher – as in the case of the green-glowing cancer cells.

Or the output could cause a diseased cell to kill itself.

The sensor part of the RNA molecule can detect whether a certain protein is present simply by binding to it. The proteins these devices detect are chemical messengers, communicating information gathered inside and outside of the cell into the nucleus, which acts like the cell's control center.

Smolke and her team used the molecular devices to sense disease-like states, such as inflammation and cancer, in cultured human cells. "We have a lot of these different signaling pathways in our cells and many diseases are associated with mistaken signaling through these pathways," said Smolke.

The RNA sensor-actuator devices can "listen in" on the messages communicated by the cell and act accordingly. Depending on whether or not the device binds to the input protein, the RNA molecule could keep its original structure, or cut out a piece of itself and thus change the genetic information it contains.

When the RNA is read by the cell's protein-making machinery, the final product will depend on the RNA's information content.

Powerful tool for cells

The process by which the RNA device can remove part of itself is called "alternative splicing." Alternative splicing is an everyday process for many cells and is a powerful way to generate a diverse array of proteins inside a cell.

In the sensor-actuator devices described in the study, the optional piece of the RNA that could be cut out contained a "stop" message that instructed cells to stop making a protein before it was complete. When this "stop"-containing piece was removed, the device produced instructions for a whole and functional protein, one that, for instance, could glow green. In this way, the device could alter its output based upon the state of the cell.

"This is the first time a sensor-actuation device has been developed to respond to protein inputs and control an alternative splicing event linked to gene expression," said Smolke.

"With the application of this device, you encode a certain level of intelligence that allows it to go into the cell and first assess whether the cell is diseased or not based upon disease markers. If yes, then it can then specifically activate therapeutic effects in that cell."

One such therapeutic effect is the ability to specifically kill diseased cells. The researchers engineered an actuator module with an output that converted an inactive drug into an active form that causes cells to die. The sensor-actuator device only made the drug-activating output protein when the cell was diseased. Otherwise, the "stop" signal was left in the device and acted like a safety trigger preventing the death of healthy

cells.

But the power of alternative splicing is not limited to just functional and non-functional outputs. "Instead of just yes/no, alternative splicing could modulate function," said Smolke. Proteins could be modified to have slightly different functions in response to different cell states. "There's a lot of richness in alternative splicing that could be used to develop more complex genetic circuits, beyond the demonstrated examples, that we might begin to implement in human cells," she said.

Smolke began the study at Caltech, where she was an assistant professor of chemical engineering. She moved to Stanford mid-project in 2009, where she completed much of the data analysis. Caltech student Stephanie Culler and postdoctoral researcher Kevin Hoff also contributed to the report.

More information: www.sciencemag.org/content/330/6008/1251.full

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