Biological computer destroys cancer cells

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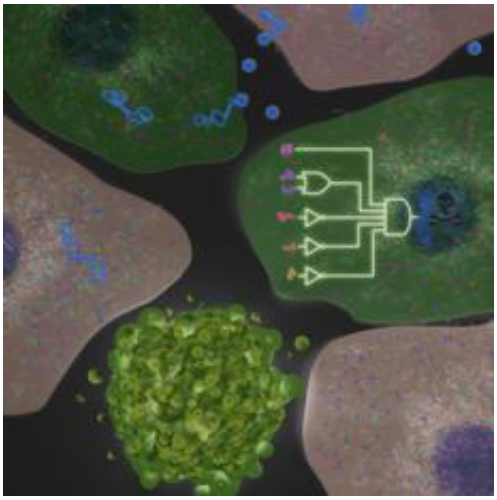


The wiring diagram of the cellular computer: all five factors must be in their correct state in order to trigger cell death. (Illustration: Benenson Y. & R. Weiss)

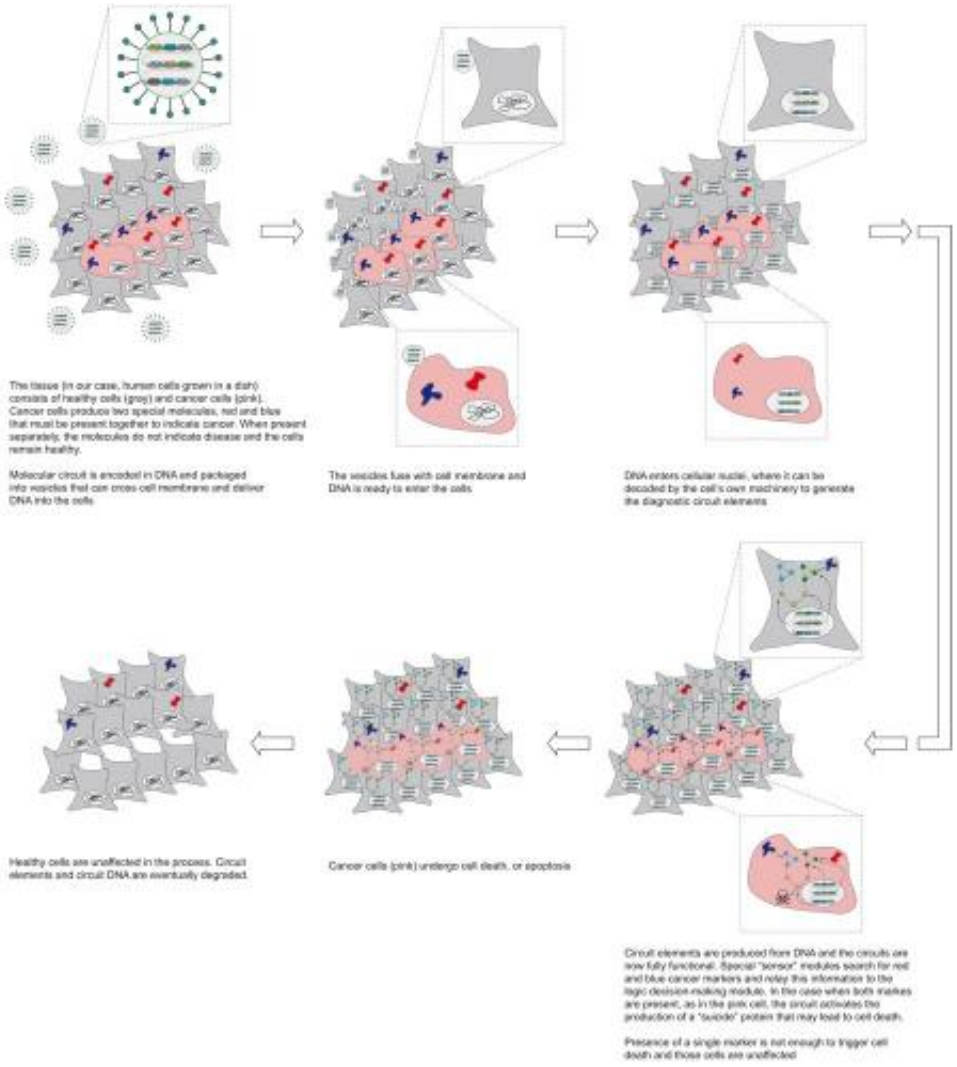
Researchers led by ETH professor Yaakov Benenson and MIT professor Ron Weiss have successfully incorporated a diagnostic biological "computer" network in human cells. This network recognizes certain cancer cells using logic combinations of five cancer-specific molecular factors, triggering cancer cells destruction.

Yaakov (Kobi) Benenson, Professor of Synthetic Biology at ETH Zurich, has spent a large part of his career developing biological computers that operate in living cells. His goal is to construct biocomputers that detect molecules carrying important information about cell wellbeing and process this information to direct appropriate

therapeutic response if the cell is found to be abnormal.

Now, together with MIT professor Ron Weiss and a team of scientists including post-doctoral scholars Zhen Xie and Liliana Wroblewska, and a doctoral student Laura Prochazka, they made a major step towards reaching this goal. In a study that has just been published in *Science*, they describe a multi-gene synthetic "circuit" whose task is to distinguish between cancer and healthy cells and subsequently target cancer cells for destruction. This circuit works by sampling and integrating five intracellular cancer-specific molecular factors and their concentration. The circuit makes a positive identification only when all factors are present in the cell, resulting in a highly precise cancer detection. Researchers hope that it can serve a basis for very specific anti-cancer treatments.

The scientists tested the gene network in two types of cultured human cells: cervical cancer cells, called HeLa cells, and normal cells. When the genetic bio-computer was introduced into the different cell types, only HeLa cells, but not the healthy ones, were destroyed.



Extensive groundwork was required to achieve this result. Benenson and his team had to first find out which combinations of molecules are unique to HeLa cells. They looked among the molecules that belong to the class of compounds known as microRNA (miRNA) and identified one miRNA combination, or profile, that was typical of a HeLa cell but not any other healthy cell type.

Finding the profile was a challenging task. In the human body there are

about 250 different healthy cell types. In addition, there are numerous variants of cancer cells, of which hundreds can be grown in the laboratory. Still greater is the diversity of miRNA: between 500 to 1000 different species have been described in human cells. "Each cell type, healthy or diseased, has different miRNA molecules switched on or off," says Benenson.

Creating a miRNA "profile" is not unlike finding a set of symptoms to reliably diagnose a disease: "One symptom alone, such as fever, can never characterize a disease. The more information is available to a doctor, the more reliable becomes his diagnosis," explains the professor, who came to ETH from Harvard University a year and a half ago. The researchers have therefore sought after several factors that reliably distinguish HeLa cancer cells from all other healthy cells. It turned out that a combination of only five specific miRNAs, some present at high levels and some present at very low levels, is enough to identify a HeLa cell among all healthy cells.

"The miRNA factors are subjected to Boolean calculations in the very cell in which they are detected. The biocomputer combines the factors using logic operations such as AND and NOT, and only generates the required outcome, namely cell death, when the entire calculation with all the factors results in a logical TRUE value," says Benenson. Indeed, the researchers were able to demonstrate that the network works very reliably in living cells, correctly combining all the intracellular factors and giving the right diagnosis. This, according to Benenson, represents a significant achievement in the field.

In a next step, the team wants to test this cellular computation in an appropriate animal model, with the aim to build diagnostic and therapeutic tools in the future. This may sound like science fiction, but Benenson believes that this is feasible. However, there are still difficult problems to solve, for example the delivery of foreign genes into a cell

efficiently and safely. Such DNA delivery is currently quite challenging. In particular this approach requires temporary rather than permanent introduction of foreign genes into the cells, but the currently available methods, both viral and chemical, are not fully developed and need to be improved.

"We are still very far from a fully functional treatment method for humans. This work, however, is an important first step that demonstrates feasibility of such a selective diagnostic method at a single cell level," said Benenson.

More information: "Multi-Input RNAi-Based Logic Circuit for Identification of Specific Cancer Cells," by Z. Xie et al. *Science* (2011). dx.doi.org/10.1126/science.1205527

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