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Painting a 'bullseye' on cancer cells

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Scientists are constantly on the hunt for treatments that can selectively target cancer cells, leaving other cells in our bodies unharmed. Now, Prof. Eytan Ruppin of Tel Aviv University's Blavatnik School of Computer Science and Sackler Faculty of Medicine and his colleagues Prof. Eyal Gottlieb of the Beatson Institute for Cancer Research in Glasgow, UK, and Dr. Tomer Shlomi of the Technion in Haifa have taken a big step forward. They have successfully created the first computerized genome-scale model of cancer cell metabolism, which can be used to predict which drugs are lethal to the function of a cancer cell's metabolism.

By inhibiting their unique metabolic signatures, explains Prof. Ruppin, cancer cells can be killed off in a specific and selective manner. The efficacy of this method has been demonstrated in both computer and laboratory models pertaining to kidney cancer. Because the researchers' new approach is generic, it holds promise for future investigations aimed at effective drug therapies for other types of cancer as well.

The results were recently published in the journal *Nature*.

Lethal to cancer, safe for other cells

The ability to specifically target cancer cells is the holy grail of cancer research. Currently, many cancer drugs are designed to target any proliferating cells in the body — and while cancer cells certainly proliferate, so do healthy cells, such as hair and gut lining cells, the growth of which are essential to the body's overall health. This explains

why many cancer treatments, including chemotherapy, have adverse side effects like nausea and hair loss.

Targeting the metabolism of the cancer cell itself may be one of the most effective ways forward. Cancer cells have a special way of metabolizing nutrients for growth and for energy. This makes cancer cell metabolism essentially different from that of a normal cell.

The researchers' computer model is a reconstruction of the thousands of metabolic reactions that characterize cancer cells. By comparing it to a pre-existing model of a normal human cell's metabolism, they could distinguish the differences between the two. They could then identify drug targets with the potential to affect the specific, special characteristics of cancer metabolism.

To test their predictions, the researchers chose to target cells from a specific type of renal cancer. "In this type of renal cancer, we predicted that using a drug that would specifically inhibit the enzyme HMOX, involved in Heme metabolism, would selectively and efficiently kill cancer cells, leaving normal cells intact," explains Prof. Ruppin. Their computer model led them to hypothesize that the Heme pathway was essential for the cancer cell's metabolism.

In an experimental study led by Prof. Gottlieb's lab, the researchers were able to verify this prediction in both mouse and human cell models, and to study these metabolic alterations in depth.

An all-around treatment model

Metabolism is a large and complex network, built on thousands of reactions. It is beyond the human capability to fully understand, let alone predict how such a complicated system works, says Prof. Ruppin. Now, by allowing researchers to simulate the effects of a disorder, computer

models are helping researchers to predict the efficacy of potential drugs and treatments. Though the predictions should always be verified in a lab or clinic, this method is highly cost effective and leads to exciting opportunities for accelerating future drug developments.

While the first model was built to characterize a specific type of cancer, this approach can be applied in the future for creating models for other types of cancer. "This is the next big challenge for us," says Prof. Ruppin. "We are going to continue to build models for other types of cancer, and seek selective drug therapies to defeat them." Their multidisciplinary approach requires both the predictions of a computer model and the findings of experimental clinical trials, and may lead to the faster development of more selective and effective cancer treatments.

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