Technology reveals 'lock and key' proteins behind diseases

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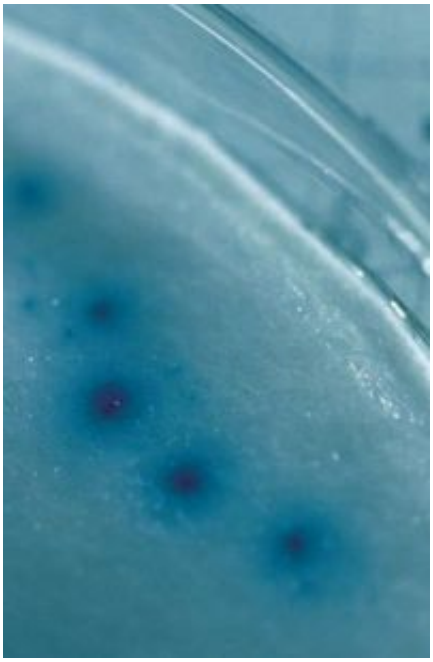

The "iMYTH-system" shows a positive readout of our iMYTH sytem. If two proteins interact in iMYTH system the yeast cell will stain blue. Credit: Staglar lab

A new technology developed at the University of Toronto is revealing biochemical processes responsible for diseases such as cystic fibrosis and could one day pave the way for pharmaceutical applications.

A study appearing in the April 13 issue of *Molecular Cell* describes how U of T and Johns Hopkins University researchers designed a device to

test for proteins that play an important role in human health and disease.

The technology, iMYTH (or integrated membrane yeast-two hybrid system), scans cells to detect proteins that interact with key proteins called ATP-binding cassette (ABC) transporters – proteins that, when impaired, can cause disease. One of the best known ABC transporters is the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), which, when disabled by mutation, causes cystic fibrosis, a hereditary disease that results in progressive disability and early death. Another important ABC protein is the Multidrug Resistance Protein (MRP), which normally removes drug metabolites and toxins from cells in our bodies but when overzealous can contribute to the drug resistance of tumours, thereby thwarting chemotherapy.

"All the cells in our bodies contain transporters that are poised in cellular membranes and act as ‘gatekeepers’ to allow the entry of certain substances, like nutrients, into the cell and promote the export of other substances, like toxins, out of the cell," says Professor Igor Stagljar, Department of Medical Genetics and Department of Biochemistry at the University of Toronto and lead author of the study. "When the function of these transporters is impaired, disease can result. This device gives us insights as to what proteins are interfering with this process."

iMYTH works by scanning cells to reveal proteins that fit with the transporters, the only screening system sophisticated enough to work with delicate membrane proteins. Simply, if two proteins interact in iMYTH, they will stain the yeast cell blue. "Like lock and key, if two proteins interact with one another, it is safe to assume they participate or regulate the same cellular process," explains Stagljar. "Identifying new interactors for ABC transporters may reveal unanticipated aspects of how these transporters function and help researchers gain clues for fighting disease and drug resistance."

Using iMYTH, the Stagljar lab identified six proteins that interact with and presumably communicate with the ABC transporter Ycf1p, a yeast version of the human proteins CFTR and MRP. These newly discovered protein interactors represent novel potential pharmaceutical targets. Through a series of biochemical and genetic tests, the researchers discovered that one of these interactors, Tus1p, regulates Ycf1p transporter function in a completely novel way to stimulate its ability to remove toxins from the cell.

"The more we learn about membrane proteins, the better we can use this knowledge for pharmacological and clinical applications," Stagljar says. "We work by putting together biochemical processes piece by piece like a puzzle. Hopefully soon we will have a complete picture of how many other diseases such as breast cancer, heart diseases, arthritis and schizophrenia are caused by mutations in various human membrane proteins."

Source: University of Toronto