Scientists genetically engineer yeast to improve understanding of how cells work

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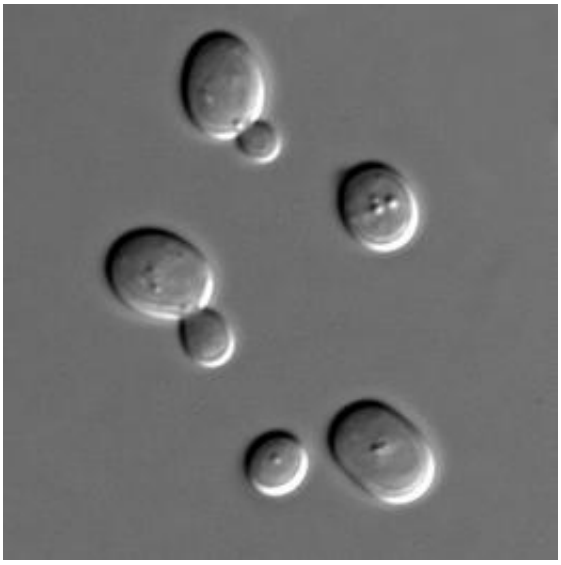

Sacharomyces cerevisiae cells in DIC microscopy. Credit: Wikipedia.

Researchers have 'fine-tuned' a major cell signalling mechanism by rewriting DNA inside yeast cells to control how they respond to their environment.

The study, which was published today by *Cell*, has immediate biotechnology uses but could also have wider implications for healthcare research. It is hoped being able to alter how cells react will help scientists understand how diseased cells function and lead to modified cells being used to treat patients.

Academics from the University of Cambridge and Imperial College London, in collaboration with AstraZeneca, used mathematical modelling and genome engineering to edit yeast cells to help scientists control not just what the cells sense but how they react to what they sense in a more desirable way.

Yeast was chosen because it shares key characteristics with human cells—most importantly that it can sense its environment using G protein-coupled receptors (GPCRs).

Dr. Graham Ladds, a lecturer in the Department of Pharmacology and a Fellow of St John's College, University of Cambridge, said: "Yeast was used as a mechanism to understand what happens in humans. We used mathematical modelling and genetic modification to edit the cell and retune what its response should be."

GPCRs are receptors which enable cells to sense chemical substances such as hormones, poisons, and drugs in their environment. The cells read their environment and sense the levels of hormones such as adrenalin, serotonin, histamine and dopamine. They can also act as light, smell and flavour receptors with some located on the tongue to give us our sense of taste.

There are around 800 different GPCRs in our bodies and around half of all medication acts using these receptors—including beta blockers, antihistamines and various kinds of psychiatric drugs. But not enough is known about how GPCR signalling works.

One of the difficulties for researchers is that DNA variations can have an impact on the signalling network and determining how parts of the DNA affect this is a major challenge.

The Cambridge team created a mathematical model of the yeast cell

with varied concentrations of different cell components and found the optimum levels for the most efficient signalling of each one. This knowledge was then used to genetically modify cells by a team of researchers at Imperial College London.

Dr. William Shaw, first author on the paper and researcher at the Bioengineering department of Imperial College London, explained: "It enabled us to understand exactly how we can genetically engineer a cell so it senses the desired amount of something for us in a way that we have control of.

"Guided by the computational findings, we created a highly-modified strain of yeast with all the non-essential interactions within the GPCR signalling pathway removed. By varying the levels key components identified in the model we were able to predictably alter the way the cells responded to their environment."

Dr. Tom Ellis, from the Bioengineering Department at Imperial College London and the paper's senior author, added: "We learned important principles about why cells will respond differently to the same molecules of the same concentrations. If there's a variation in the DNA sequence that determines key component levels, then this can change everything."

Dr. Mark Wigglesworth, Director of Hit Discovery at AstraZeneca, said: "GPCRs are fundamentally important to the function of healthy cell systems and they remain one of the most targeted proteins in human medicine. It is hoped that increasing our understanding of these proteins will lead to more innovative medicines in the future."

Provided by University of Cambridge

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