Cells adapt to the loss of genes previously thought vital for survival

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A*STAR scientists have found that yeast cells lacking an ‘essential’ gene can survive through adaptive evolution. Credit: Realite Design

Yeast cells can survive even when missing certain 'essential' genes, A*STAR researchers have found. This surprising discovery has major

ramifications for understanding how cells adapt to challenging situations and for overcoming the problem of drug resistance.

Until now, an essential gene has been defined as one that is critical for a cell's survival. Knock out an essential gene in a cell and the cell will die. This textbook definition underpins many treatments: drugs are developed to block essential genes in cancer cells and pathogenic microbes, thereby killing these dangerous cells.

Now, Giulia Rancati, Norman Pavelka and co-workers at the A*STAR Institute of Medical Biology and Singapore Immunology Network have shown that the picture is not as clear cut. They found that, given time, yeast cells can undergo evolutionary processes that allow them to adapt to the absence of certain genes previously considered essential.

This means that there are three categories of genes: non evolvable essential genes, non essential genes and a sliding scale of genes lying between these two extremes, which the team dubbed evolvable essential genes. "Our study shows that some essential genes are more essential than others," explains Rancati.

The researchers performed a multistage investigation on yeast cells from which they had knocked out one of about 1,000 genes that were considered essential. During these experiments, cells were cultured for several days to give them time to evolve to the loss of the gene. Of the about 1,000 genes investigated, 88 were identified as being evolvable essential.

The discovery has evoked a wide range of reactions from the genetics community. "So far we've faced responses spanning the whole spectrum from 'Of course, we see that happening all the time!' to 'That can't be right. You must have made a mistake!'" says Rancati.

It also has profound implications for drug discovery and development. Drug companies frequently sink billions of dollars into developing a promising drug candidate, only to discover several years later that it is useless because resistance can occur. But now, by targeting true essential genes rather than evolvable essential genes, they face much greater chances of finding a drug for which resistance does not develop.

The team intends to bring these results progressively closer to home. "The next big thing will be to bring these studies to mammalian systems," says Rancati. "We are already planning to do a genome-wide screen to test the evolvability of human cells from which essential genes have been deleted."

More information: Gaowen Liu et al. Gene Essentiality Is a Quantitative Property Linked to Cellular Evolvability, *Cell* (2015). DOI: 10.1016/j.cell.2015.10.069

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