Scientists identify new paradigm in genetics, paving way for development of better drug targets to save lives

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Agency for Science, Technology and Research (A*STAR)'s Institute of Medical Biology (IMB) and Singapore Immunology Network (SIgN) have identified a new paradigm for the identification and evaluation of genes for cell survival. By challenging long-held notions on gene essentiality and drug development, the study holds great potential to predict future drug resistance, thereby saving lives and optimising the use of resources. The study was published on 25 November 2015 in the online issue of Cell.

Traditionally, basic and applied genetics have relied on the core concept of gene essentiality, which states that certain genes are essential for a cell's survival. When the cells in question are cancer cells or pathogenic microbes, drugs can be developed to block these essential genes, so as to eradicate these harmful cells.

Yet, drug resistance, in which cells mutate and render the drug ineffective, is on the rise. According to a recent World Health Organization (WHO) report, "antibiotic resistance is happening right now, across the world." Other examples include chemotherapy resistance, which is a leading cause of cancer treatment failure, or the recent spread of antifungal drug-resistant fungi. The rising trend of drug resistance suggests that cells can in fact adapt to the inactivation of some of these seemingly essential genes.

Drug discovery is a long-drawn process that takes many years from development stage to first-in-man clinical trials. Currently, there is no way to predict future drug resistance at the early stages of drug development. Very often, companies spend billions on developing a single drug candidate, only to discover several years later during clinical trials or even after approval, that that resistance can occur. In fact, the success rate of clinical trials globally is estimated to be as low as 25 per cent, partially due to the high number of drug candidates found to be resistible only during trial stage. This represents the loss of time and resources which could otherwise have been used to develop more effective drugs and therapies.

Now, A*STAR scientists have redefined the underlying concept of gene essentiality by putting forth a new genetic paradigm. Previously, genes were divided into non-essential ones that are dispensable for cell viability, and essential genes that are required for cell survival. The new study found that essential genes can be further split into two kinds - one being the kind that cells need for survival, known as 'non-evolvable' essential genes, and the other being those that cells can find ways to survive without, by an evolutionary process of mutation and selection. Genes belonging to this latter class were termed 'evolvable' essential genes.

Cells knocked-out of one of these 'evolvable' essential genes need to adapt very quickly so as to survive. Through examining approximately 1,000 essential genes in yeast, the team found that cells were able to adapt so quickly because they mutate to change their number of chromosomes. In so doing, they change the relative balance of genes in their genome and use alternative pathways to perform the original function carried out by the missing gene. This also explains why the presence of extra chromosomes has been reported commonly in chemotherapy-resistant cancer cells and drug-resistant fungi and parasites.

This study holds great potential to improve the current drug discovery and development process, with applications for illnesses varying from cancer to infectious diseases. Drug candidates can be tested to see if they are in fact targeting 'non-evolvable' essential genes. This would then suggest a lower possibility of drug resistance since cells would not be able to adapt to the loss of these genes. With this new paradigm, drug resistance can be predicted at the discovery stage and resources can be optimised to develop more effective drugs that can save lives.

Dr Giulia Rancati, Principal Investigator at IMB and corresponding author of the paper, said, "We are thrilled to challenge a longstanding paradigm in genetics, especially one with such clinical implications. The next step will be to translate these findings in pathogenic fungi and human cells, and to find non-evolvable essential genes as novel antifungal and chemotherapy targets, respectively."

Professor Rong Li, Bloomberg Distinguished Professor of Cell Biology and Chemical & Biomolecular Engineering at Johns Hopkins University (JHU), and a world renowned expert in cellular asymmetry, division and evolution commented, "This is a fantastic study that takes a systematic approach to re-define the essentiality of gene function, taking into account the cell's adaptive potential. The findings demonstrate high-level plasticity across the genome-wide molecular network toward a range of genetic perturbations."

Both corresponding authors of the study, Dr Giulia Rancati and Dr Norman Pavelka, Principal Investigator at SIgN, are recipients of the A*STAR Investigatorship, a prestigious research award designed to attract the most promising young researchers around the world to do independent research at A*STAR. This breakthrough therefore attests to the world-class quality of R&D by researchers under the programme, and the strength of the award in nurturing leading scientific innovators.