Chance determines cell death or normal sugar consumption

January 17 2014

Some cells fail by chance, and not due to a genetic defect, to properly initiate the molecular processes for the breakdown of sugar. These cells are unable to grow and subsequently die. This discovery was done by a multidisciplinary team led by Bas Teusink, professor in Systems biology at VU University Amsterdam, the Netherlands. This discovery fundamentally changes our perceptions of such metabolic pathways and their regulation, and could potentially lead to novel ways of treating cancer cells. Einstein said: "God does not play dice". It appears, however, that cells do: the chance of a metabolic failure can be predicted and manipulated, but it is not possible to predict which individual cells will be affected. The results from this study were published in *Science* on 16 January.

Glycolysis is a metabolic pathway that is central to the energy generating activities inside cells: this route breaks glucose (sugar, a carbohydrate) down, step-by-step, to lactic acid (in humans) and alcohol (in yeast), and in this process generates the energy required for growth and survival. This pathway plays a key role in both disease (diabetes, cancer) and biotechnology (biofuels, food fermentation). Teusink: "One expects that when you offer sugar to cells, a chemical flux (movement of molecules) through the pathway follows."

Identical twins & coca-cola

In collaboration with other groups at VU University, and with scientists from the Kluyver Center in Delft, the systems biologists from VU University discovered that this is not always the case: sometimes the uptake and breakdown process fails to start properly, resulting in a metabolic 'traffic jam' that hampers the movement of molecules through the pathway; a state that leads to death. Which cells can cope with sugar and which cells end up with a 'traffic jam', is a matter of chance: small non-genetic differences between individual cells at the moment that sugar is given to them. This leads to two-types of cells, growing and non-growing, in population of genetically identical individuals. "It is like having a population of identical twins, you give them all a glass of coca-cola and a few become sick. Do this again, and by chance a different set of individuals get sick."

Computer simulations

The scientists made this discovery by combining biological knowledge and mathematics into a computer model of glycolysis; this allowed them to simulate the 'metabolic traffic' through the pathway. Predictions made by these simulations were then validated, experimentally, in the laboratory. With this systems biology approach, they discovered the mechanism by which yeast cells – champions of glycolysis in industry, e.g. beer, wine and biofuels – minimize the chances of a metabolic 'traffic jam' occurring. By understanding this mechanism, the fraction of cells that function properly can be enhanced to e.g. optimize biotechnological applications. On the other hand, the same insight can be exploited to reduce the number of cells that can cope with sugar and suggests potentially novel strategies for reducing the viability of unwanted (e.g. cancer) cells.

More information: "Lost In Transition: Startup Of Glycolysis Yields Subpopulations Of Nongrowing Cells." Bas Teusink, et al. *Science* 1245114. DOI: 10.1126/science.1245114

Provided by Vrije Universiteit Amsterdam