Cellular metabolism self-adapts to protect against free radicals

September 7 2011

Oxygen-consuming organisms obtain energy through cellular respiration, which is the transformation of carbohydrates and oxygen into carbon dioxide and water. This process also produces toxic oxygen radicals which must be decomposed immediately, as they would otherwise cause damage to cells. Scientists from the Max Planck Institute for Molecular Genetics in Berlin have now discovered a mechanism, with whose help cells can coordinate respiratory activity and the degradation of free radicals. Thus, the cells prepare their metabolism for free radicals before they even arise.

Cellular respiration is a very efficient process through which a lot of energy is generated from a few sugar molecules and oxygen. However, up to two percent of the oxygen used in this process is transformed into superoxide, a free radical that is toxic to cells. A considerable proportion of this superoxide evades the respiratory chain of the mitochondria and poses a threat to biological macromolecules like DNA, RNA, proteins and fatty acids. However, evolution has equipped eukaryotic cells with comprehensive mechanisms that can decompose free radicals which arise in the cell and therefore prevent damage to the cell. These mechanisms work extremely efficiently and are well coordinated so that, contrary to popular belief, the treatment of healthy tissue with natural or synthetic antioxidants can disrupt the natural balance and, at worst, damage cells and accelerate the aging process.

Researchers at the Max Planck Institute for Molecular Genetics compared respiring and non-respiring yeast cells. When respiration was

activated, there was a direct increase in the cells' tolerance to oxidised substances; however, contrary to expectation, this was not accompanied by a rise in the concentration of free radicals. This proved that respiring cells are entirely capable of dealing with the increased formation of free radicals and keeping them at the level of the non-respiring cells.

According to the researchers, a hitherto undiscovered feedback mechanism located within a central metabolic pathway is responsible for this process. The carbohydrate-degrading enzyme pyruvate kinase regulates the respiratory activity of yeast cells. It is less active in respiring cells and this leads to the accumulation of its substrate phosphoenolpyruvate. The accumulation of this substance inhibits another glycolytic enzyme, triosephosphate isomerase. The researchers were already very familiar with this enzyme: they had previously discovered that a low level of activity of this enzyme provides protection against free radicals. "If we block this feedback mechanism artificially while activating respiration, the free radical concentration increased significantly and damaged proteins and mitochondria. This tells us that cells can predict when the radical production will rise and adapt their metabolism before the free radicals are even produced," explains Markus Ralser, researcher at the Max Planck Institute for Molecular Genetics and the University of Cambridge.

This discovery may prove to be of particular significance for cancer research. The enzyme pyruvate kinase is partly responsible for the fact that tumour cells usually respire less and thus have a higher rate of sugar metabolism than healthy tissue. This effect is named after Otto Warburg, who was the first scientist to demonstrate this higher rate of sugar metabolism in cancer cells in the 1920s. The Max Planck researchers hope that it will be possible to use this newly discovered feedback mechanism to cause targeted nutrition deficiency in tumour cells and render them more vulnerable in this way.

More information: Nana-Maria Grüning, Mark Rinnerthaler, Katharina Bluemlein, Michael Mülleder, Mirjam MC Wamelink, Hans Lehrach, Cornelis Jakobs, Michael Breitenbach and Markus Ralser, Pyruvate kinase triggers a metabolic feedback loop that controls redox metabolism in respiring cells, *Cell Metabolism*, September 7, 2011

Provided by Max-Planck-Gesellschaft