Why chemotherapy causes more infertility in women than in men

February 22 2011

For a long time a relationship between infertility and chemotherapeutic agents has been assumed. Now, the mechanism has been elucidated. Mainly women are affected because the quality control in the oocytes is different from male germ cells. As biosicentists from Goethe-University have found out, tetramer and dimer structures in the p53 protein family play a key role.

Chemotherapeutic agents, used in cancer treatment, destroy not only cancer cells but also healthy cells, thus affecting germ cells as well. Consequently, after surviving cancer many female patients are confronted with the diagnosis: infertility. For a long time a relationship between infertility and chemotherapeutic agents has been assumed, but until now, the exact mechanism was not known.

Scientists from the research group of Prof. Volker Dötsch (Institute of Biophysical Chemistry, Goethe University Frankfurt) in cooperation with international partners have now started to unveil the mechanism of cancer treatment related infertility. Their results are published in the internationally renowned journal *Cell*. Mainly women suffer from infertility because the quality control in the oocytes is different from male germ cells. Male germ cells are produced throughout the whole life span but the number of female germ cells is restricted and already fixed before birth. If the oocytes are damaged during cancer treatment, they are destroyed by the female quality control mechanism.

Essential for this process is the protein p63 which shows striking

similarity to another important protein of the same family: p53. p53 is also named "guardian of the genome" because of its regulatory function in cell division and cell death of damaged cells and, therefore, plays a key role in the suppression of genetic anomalies which could lead to cancer. In more than half of all human tumors p53 is altered and no longer functional.

For a long time the exact regulation of p53 and p63 and the similarities and differences between these two proteins have been the object of many international research projects. In the currently accepted model the concentration of p53 in healthy cells is relatively low. If genetic anomalies occur in a cell which could cause the transition to a cancer cell, the concentration of p53 increases and four p53 proteins form a tetramer. In this tetrameric state the tumor suppressor is active and initiates either repair of the damaged DNA or programmed cell death. Surprisingly, despite the fact that p53 and p63 show high similarity, the mechanism by which the activity of p63 is controlled in oocytes seemed to be different.

The research group of Prof. Volker Dötsch could show now that the two mechanisms that regulate the activity of p53 and of p63 are closely related, but distinct. The level of p63 in normal oocytes is high and the protein is kept in a closed dimeric and inactive state. If DNA double-strand breaks occur, for example caused by radioactive radiation, p63 becomes phosphorylated. As a result of this phosphorylation, the structure of the p63 dimer changes to an open state allowing the attachment of a second phosphorylated dimer. The resulting active p63 tetramer is similar to the active p53 tetramer and leads to the death of the damaged oocyte. Many of the chemotherapeutic agents cause DNA double-strand breaks which activate p63, finally leading to the cell death of the oocytes.

The related proteins of model organisms such as Caenorhabditis elegans

(nematode) are also investigated by the Dötsch group. Because of the short life span of this worm its p63 related protein does not act as a tumor suppressor but controls the genetic stability of the germ cells. The quality control of germ cells, thus, seems to be the original function of the p53 protein family and leads to the conclusion that p63 is the ancestor of the entire p53 family.

Interestingly, p63 shows an additional function: it is essential for the maintenance of stem cells in epithelial layers like skin. Because of the close similarity of stem and germ cells, this second function shows the evolutionary process of the p53 protein family from p63-like proteins, that in simple organisms are responsible for the genetic stability of germ cells, via controlling the maintenance of stem cells in organisms with renewal tissues, finally to p53-like tumor repressors in somatic cells. This demonstrates the outstanding importance of the p53 protein family for the development and health of human beings.

More information: Deutsch et al., DNA Damage in Oocytes Induces a Switch of the Quality Control Factor TAp63a from Dimer to Tetramer, Cell (2011), doi:10.1016/j.cell.2011.01.013

Provided by Goethe University Frankfurt