Researchers study the cancer cell genes that resist drugs

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Researchers from the People's Friendship University of Russia (RUDN University) have studied the mechanism of drug resistance for ovarian and breast cancer cells. They discovered that these cancer cells have a redox-dependent mechanism which is tasked with sustaining their drug resistance. The results have been published in two articles in the journal of *Free Radical Biology and Medicine*.

Researchers from the RUDN University have reported one of the reasons that chemotherapy (in particular, cisplatin) gradually stops affecting the cells of ovarian and breast tumors.

The authors studied the biochemical mechanisms that allow tumor cells to develop resistance to antitumor drugs. During chemotherapy, certain drugs cause toxic and oxidative stress to cancer cells and stop their functioning. Sometime later, however, the cells adapt to the drug action, which necessitates using stronger doses, which, in turn, negatively affects the patient's health due to its toxic effect.

To stop the development of drug resistance, researchers need to learn how to control the expression of genes responsible for cell viability. Redox processes regulate cell antioxidant defense, which protects the cell against oxidative stress so that it can function properly. Without those "defender genes," it would be far easier for drugs to kill cancer cells. The researchers hope that the process could eventually be controlled.

Some of these changes in gene expression happen when human ovarian cancer (SKOV-3) cells and human breast cancer (MCF-7) cells develop resistance to an antitumor drug, cisplatin. The antitumor action of cisplatin is achieved in no small part by its pro-oxidant effect, meaning that it uses oxidative stress to destroy cells.

"As a result of development of the drug resistance in cancer cells, we observed an increase in the gene expression encoding isoforms of thioredoxin and peroxiredoxin, which play an important role in the antioxidant defense system and redox-dependent signaling. Significant increase in expression of such genes substantially contributes to a high level of antioxidant defense and therefore cancer cell resistance to the pro-oxidant action of cisplatin. Thus, the growth of expression of the Prx6 gene was observed in the resistant cells. The data also points to a significant role of Prx1, Prx2 and Prx3 isoforms in the redox-dependent mechanisms of the resistance development of the cell lines," says Elena Kalinina, one of the authors.

The increase in gene expression points to the fact that isoforms of thioredoxin and peroxiredoxin participate in the development of cancer cell drug resistance. The researchers note that this effect can also be considered as a part of a redox-dependent adaptive antioxidant response to the oxidative stress caused by cisplatin's pro-oxidant action.

"The results obtained significantly expand our fundamental knowledge of the sum total of molecular events in the mechanisms of death and formation of drug resistance for cancer cells and of the role redox-dependent systems in these processes," says Kalinina. These results could enable researchers to improve the drug treatment programs for oncology patients.

More information: Elena Kalinina et al, Thioredoxins, glutaredoxins and peroxiredoxins in redox-dependent formation of cancer cell

resistance, *Free Radical Biology and Medicine* (2017). DOI: 10.1016/j.freeradbiomed.2017.04.137