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"Murder on Demand": TAp63α to Induce Death of Cancer Cells

Heidelberg scientists find an approach to overcome chemoresistance

The desired goal of successful chemotherapy is the sure death of cancer cells. The administered cytotoxins ("cell-stopping agents") are designed to cause a cell to commit suicide. However, tumor cells often turn out to be resistant. Scientists of the Heidelberg University Medical Hospital and the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now identified a cellular protein named TAp63α which mediates a death signal.

As discussed in the latest issue of *EMBO Journal**, the investigators have identified molecular mechanisms by which TAp63α triggers programmed cell death (apoptosis). The protein, a member of the p53 familiy, thus makes a cell more receptive to chemotherapy and opens up new possibilities for researchers to overcome resistance to medicinal treatment.

To preserve an organism, old or damaged cells are "sentenced to death". Cellular control molecules, most notably p53, induce programmed cell death and make sure that the cell is no longer able to multiply. Failure of this mechamism can lead to unrestricted cell division and, thus, in the worst case, to cancer. Chemotherapy makes use of a cell's suicide mechanism by signaling from outside that it is time to die. In cancer cells, the control molecules involved in the death program are often transformed in such a way that they are no longer able to fulfill their function properly. If cytotoxins have no "accomplice" in the cell interior, chemotherapy is usually destined to fail – chemoresistance is the result.

In her ongoing research, **PD Dr. Martina Müller-Schilling**, consultant at the University Medical Hospital in Heidelberg, found elevated levels of the control molecule TAp63α in cancer cells which had been treated with various cytotoxins. Like p53, TAp63α is a molecule that decides over life or death. In collaboration with **Professor Peter H. Krammer** of the German Cancer Research Center and scientists from Israel, Italy and the United Kingdom, Martina Müller-Schilling found out that TAp63α is able to reinforce the production of various so-called "death receptors" such as CD95, TNF-R and TRAIL-R both in liver and bone cancer cells. These are cell surface sensors whose job it is to mediate death signals from the cell surroundings into the cell interior. Moreover, TAp63α activates cellular proteins, e.g. members of the Bcl-2 family, which also start the self-destruction program via the cell's power plants, or mitochondria. In this way, the cell is made receptive to chemotherapy. In the reverse experiment, cells whose TAp63α gene was switched off developed a resistance to the administered drugs.

By searching for further molecules that induce cell death, scientists hope to find new insights and approaches that will make it possible to treat cancer more specifically in the future.

*Olav Gressner et al.: "TAp63α induces apoptosis by activating signaling via death receptors and mitochondria", EMBO Journal, June 15, 2005, Vol. 24 No. 12, doi: 10.1038/sj.emboj.7600708

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