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**Paradigm Shift: Switch for Programmed Cell Death Promotes Spread of Glioblastoma**

**The protein CD95 is known to act as a molecular switch that triggers the apoptosis death program in cells. Scientists at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now shown that activation of this switch in glioblastoma has a totally unexpected effect. Instead of forcing the cancer cells to commit suicide, their spread is even promoted. Activation of CD95 was found to increase the tumor's ability to invade surrounding brain tissue. This finding necessitates a new approach in the development of novel treatment methods and, at the same time, reveals an unexpected target for new therapies.**

Malignant tumors have usually lost their ability to destroy themselves by programmed cell death, or apoptosis. Therefore, tumors are often resistant to chemotherapy or radiation therapy, whose effect is based on forcing tumor cells to commit suicide.

This resistance to apoptosis is caused by defects in one of the numerous molecular switches regulating the self-destruction process. This is why scientists have been trying for a long time to restore the formation of these switches in cancer cells and, thereby, to restore their apoptotic ability. Among the key molecular switches is cell surface protein CD95, which is activated by the binding of its partner, CD95L. This triggers a whole cascade of biochemical signals leading to the death of the cell.

At the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), **Dr. Ana Martin-Villalba** and her team have been studying the function of CD95 on glioblastoma cells. Glioblastoma is an extremely aggressive malignant brain tumor that resists all treatments. The cancer grows like a coral and invades surrounding brain tissue with very fine protrusions. Individual, isolated tumor cells can penetrate even further. Thus, surgeons have no chance to completely remove the tumor tissue. In addition, glioblastoma is highly resistant to both chemotherapy and radiotherapy.

Martin-Villalba's team found large amounts of CD95 on glioblastoma cells, while CD95L was localized primarily at the so-called invasive front – the border between tumor tissue and healthy brain tissue. Despite the presence of both molecules, the cells are resistant to programmed cell death. But this is not all: If CD95 on the surface of glioblastoma cells is activated by CD95L, this leads to the production of a protein called MMP9, which is known to be a molecular scissors. MMP9 cuts through the network of interwoven protein fibers that separate different tissue layers of the body from each other. With the aid of these protein scissors, tumor cells invade healthy tissue and form the dangerous protrusions that penetrate deep into the brain tissue.

The result showed the scientists a way how to stop the invasion of glioblastoma: They treated mice that had been transplanted glioblastoma with an antibody that blocks CD95. As a result, the migration of cancer cells ceded.

"This is almost a paradigm shift," says Ana Martin-Villalba. "Up to now, the goal has been to promote formation of CD95 and CD95L in tumor cells. In the case of glioblastoma, we now have to warn against this approach: This would only additionally support the spread of the tumor. The goal is rather to block activation of CD95." However, it is currently not possible to investigate this treatment approach in humans, because a useable antibody against human CD95 protein is not yet available.

Susanne Kleber, Ignacio Sancho-Martinez, Benedict Wiestler, Alexandra Beisel, Christian Gieffers, Oliver Hill, Meinolf Thiemann, Wolf Müller, Jaromir Sykora, Nina Schreglmann, Elisabeth Letellier, Cecilia Zuliani, Stefan Klussmann, Marcin Teodorczyk, Hermann-Josef Gröne, Tom M. Ganten, Holger Sültmann, Jochen Tüttenberg, Andreas von Deimling, Anne Regnier-Vigouroux, Christel Herold-Mende and Ana Martin-Villalba: Yes and PI3K bind CD95 to signal invasion of glioblastoma. Molecular Cell, 11 March 2008