

PRESS RELEASE

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NEW APPROACHES TO OVARIAN CANCER: THE TUMOR'S OWN IMMUNE CELLS HELP OVERCOME CHEMO-RESISTANCE

Date

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Ovarian cancer often responds well to chemotherapy at first, but usually returns in a chemoresistant form. A team led by Dr. Ricardo Coelho at the University Hospital Basel now shows that combining the investigational drug birinapant with standard chemotherapy kills significantly more cancer cells than chemotherapy alone. Surprisingly, this enhanced effect depends on immune cells within the tumor, known as macrophages, which send out a signal that further boosts the effect of the treatment. In the future, the findings could help predict which patients will benefit most from this therapy. The Wilhelm Sander Foundation supported the project with €134,000.

High-grade serous ovarian carcinoma is the most common and most aggressive form of ovarian cancer. Most patients initially respond well to standard treatment consisting of surgery and chemotherapy, but the disease almost always returns in a form that evades chemotherapy. Once this resistance has developed, treatment options are very limited. New combination therapies that can overcome this resistance are therefore urgently needed.

Restarting the cell's self-destruct program

Cells normally have a built-in "self-destruct program," known as programmed cell death, which they use to eliminate damaged or unwanted cells. Cancer cells also carry this program, but they often find ways to switch it off and thus survive treatment. A new class of drugs, known as SMAC mimetics, was developed to flip this switch back on.

The team led by Dr. Ricardo Coelho at the Department of Biomedicine at the University Hospital Basel investigated whether this "self-destruct program" can be reactivated in ovarian cancer cells when the SMAC mimetic birinapant is combined with common chemotherapy drugs (carboplatin or paclitaxel). Experiments on cancer cell lines and on tumor samples taken directly from patients showed that sequential treatment, meaning chemotherapy first and then the SMAC mimetic, killed significantly more cancer cells than chemotherapy alone.

An immunological alarm signal amplifies the effect

The researchers investigated why the combination works so well. They found that chemotherapy triggers a signaling cascade involving the molecule TNF-alpha, a kind

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of immunological alarm signal. This signal considerably enhances the cancer-killing effect of birinapant: it sets off a chain of molecular signals in the cancer cell that ultimately activates its "self-destruct program." Importantly, the alarm signal comes mainly from immune cells, the tumor-associated macrophages, which are normally found within the tumor. Not only a tumor's genetics but also its immunological makeup can therefore directly determine how well it responds to treatment.

Which patients could benefit?

The researchers also identified the protein mesothelin on the surface of cancer cells as a marker that predicts sensitivity to the new treatment: cancer cells with low mesothelin levels responded significantly more strongly to birinapant. Interestingly, chemotherapy itself lowers mesothelin levels and may thus prepare tumors to respond even better to subsequent birinapant treatment.

To test these findings under realistic conditions, the team developed DRUGSENS, a new laboratory method in which a patient's tumor tissue is kept alive together with its natural immune cells, so that drug combinations can be tested directly and in a personalized way within a few days. Together with experiments in mice and zebrafish, this confirmed that tumors with a higher proportion of these immune cells and a stronger alarm signal responded best to the combination therapy. This advantage disappeared as soon as the immune cells were removed.

"The tumor's immune environment is not a mere bystander. It can apparently play an active role in deciding whether a treatment succeeds," says project leader Dr. Ricardo Coelho. "By identifying the features associated with greater sensitivity to the combination therapy, we hope to be able to match each patient with the treatment combination most likely to help her in the future."

Toward personalized treatment of ovarian cancer

Taken together, the results provide a mechanistic explanation for why combining SMAC mimetics with chemotherapy is effective, and they identify two measurable tumor features: the level of immune cells and of mesothelin. Physicians could thus in future select those patients most likely to benefit from this approach. The team is now working to validate the findings in larger patient groups and to move toward early clinical testing of birinapant-based combination therapies in ovarian cancer. The underlying study is currently available as a preprint and is being revised for publication in *Cell Death & Differentiation*.

Wilhelm Sander Foundation: Research. Knowledge. Future.

The Wilhelm Sander Foundation has supported the research project with a total of around €134,000. The foundation's purpose is to promote medical research, in particular projects in the fight against cancer. Since its founding, more than €350 million has been approved for research funding in Germany and Switzerland, making the

Wilhelm Sander Foundation one of the most important private research foundations in the German-speaking world. It was established from the estate of the entrepreneur of the same name, who died in 1973.

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Original publications

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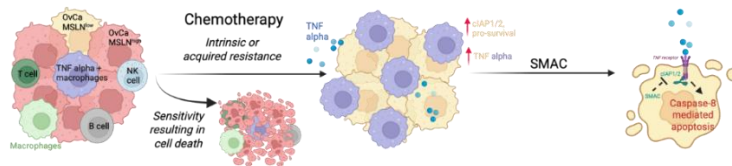
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Figures

For exclusive use in connection with reporting on this press release. We will gladly provide high-resolution image material upon request: info@sanst.de

Figure



Caption

In ovarian cancer tumors, cancer cells share space with immune cells (T cells, NK cells, B cells and macrophages), some of which secrete TNF-alpha, a signaling protein that can trigger cell death. Chemotherapy kills sensitive cancer cells, but some cells resist. These resistant cells respond by producing more TNF-alpha as well as a protein pair called cIAP1/2, which blocks the death signal of TNF-alpha and allows the cells to survive instead of dying. A class of drugs called SMAC mimetics removes this protection by degrading cIAP1/2. Without cIAP1/2 as an obstacle, TNF-alpha signaling is redirected through caspase-8, a protein that carries out cell death, so that the resistant cancer cells eventually die.

Image credit

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