

From Dr. Jekyll to Mr. Hyde of cancer immunotherapy

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Novel immunotherapies can strengthen the body's own defenses against cancer cells. Treatment of patients with advanced disease can promote partial and complete tumor regressions. However, such strategies also frequently fail. The underlying mechanisms are incompletely understood. An international research team led by the University Hospitals of Magdeburg and Bonn has now discovered a previously unrecognized braking mechanism that limits the efficacy of cancer immunotherapies. The results are published in the renowned journal *Immunity* and provide a scientific basis to further develop cancer immunotherapy.

Specialized cells of the immune system, called T lymphocytes, normally detect and destroy viruses and bacteria but they can also eliminate mutated [cancer cells](#). Novel therapies with "immune checkpoint inhibitors" modulate the regulation of cellular immunity and thereby boost cancer cell recognition and killing. This new treatment approach was originally developed for patients with malignant melanoma. More recently it was also applied to other cancer entities with considerable success. However, in many cancer patients, immunotherapy shows no or only temporary effects. Researchers around the world are currently trying to understand the underlying mechanisms.

An international research team from Germany, Australia, and Belgium led by Prof. Michael Hölzel (Institute for Clinical Chemistry and Clinical Pharmacology at the University Hospital Bonn) and Prof. Thomas Tüting (Department of Dermatology at the University Hospital

Magdeburg) has now discovered a novel mechanism that limits the efficacy of [cancer immunotherapy](#). The researchers observed an important role for neutrophil granulocytes, a type of immune cell that is very common in the blood. "Neutrophils represent the front line of defense against invading bacteria, but they can also attack [cancer cells](#)" explains Prof. Hölzel. "However, in our mouse cancer models we observed that neutrophils inhibited the activity of T lymphocytes and thereby weakened the effect of immunotherapy" adds Prof. Tüting.

Neutrophils unexpectedly change their nature

"We found that soluble mediators, which are released by cancer tissues in response to attacking T lymphocytes, can cause the unexpected switch in the nature of the neutrophils," explain Dr. Nicole Glodde and Dr. Tobias Bald, first authors of the study. It is as though these mediators reveal an evil alter ego of neutrophils. "Similar to the famous fictional character of the kind-hearted Dr. Jekyll, who transforms into the heartless murderer Mr. Hyde due to a mysterious potion," notices Prof. Hölzel with surprise. The researchers assume that this mechanism normally protects our body against excessive inflammation. "However, in the case of immunotherapy, this is rather unfortunate," adds Prof. Tüting.

The research team also discovered how to prevent the unfortunate transition of [neutrophils](#) from Dr. Jekyll to Mr. Hyde. The researchers are confident that their results provide a rationale for further investigations and clinical trials that will lead to more effective cancer immunotherapies in the future.

More information: Nicole Glodde et al, Reactive Neutrophil Responses Dependent on the Receptor Tyrosine Kinase c-MET Limit Cancer Immunotherapy, *Immunity* (2017). [DOI: 10.1016/j.immuni.2017.09.012](#)

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