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Press release
For immediate release

How our body's macrophages adapt to low-nutrient tumor environments New insight into immune cell behavior in cancer

Graz, 30/10/2025: Macrophages—immune cells involved in inflammatory reactions and tumor processes—can adapt their metabolism to a low-nutrient environment with astonishing flexibility. This is demonstrated in a new Medical University of Graz study appearing in the current issue of the journal PNAS (Proceedings of the National Academy of Sciences). The international research team led by Katharina Leithner of the Otto Loewi Research Center and first author Katharina Schindlmaier was able to prove that macrophages also remain active despite glucose deficiency by "reversing" parts of the insulin pathway.

Macrophages exhibit astonishing metabolic flexibility

Macrophages are white blood cells that play an important role in the immune system. They detect, engulf and destroy pathogens and damaged cells. In the body, they fulfill a variety of functions including the elimination of infection and the regulation of inflammatory response. They also promote tumor growth by suppressing other immune cells. The microenvironment of tumors, for example lung tumors, is frequently deficient in certain nutrients like glucose. This represents a great challenge for macrophage metabolism. Using stable isotope labeling and metabolic analysis, the Med Uni Graz research team along with its cooperation partners in Austria and Spain demonstrated that macrophages activate certain steps in the gluconeogenesis pathway in response to glucose deficiency. The research group also established proof that this metabolic pathway, which normally serves to create glucose in the liver, was present in lung cancer cells as well. This adaptation was mediated by the enzyme phosphoenolpyruvate carboxykinase 2 (PCK2). At the same time, the cells increased their use of glutamine as an alternative source of carbon and fuel. "This finding takes our research to a new level. It shows how adaptable the immune system is—even under circumstances in which hardly any glucose is available," explains first author Katharina Schindlmaier of the Division of Pharmacology.

Focus on immune cell behavior in cancer

In addition, the research team discovered that this alternative metabolic program is activated in macrophages from lung tissue and lung cancer specimens. The study shows that immune cells in the tumor environment possess high metabolic adaptability—an important factor for their behavior in inflammation and cancer. "Our findings clearly indicate that macrophages do not have to rely on glucose alone but have many different pathways for ensuring their supply," explain the researchers. "This improves our understanding of how immune cells function in the tumor environment and might open up new therapeutic approaches in the long term." Interestingly, the

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main functions of macrophages remained uninfluenced by glucose deficiency, yet certain molecules that regulate macrophages for other immune cells were significantly changed by depriving them of glucose. The research group continues to investigate the significance of these adaptations.

Potential for new therapies

In the future, knowledge of these adaptive mechanisms may help develop targeted strategies for influencing the immune system during cancer treatment. If the targeted modulation of macrophage metabolism is successful, their proinflammatory or anti-inflammatory activity may be therapeutically regulated—for example, to improve the effectiveness of immunotherapies.

The new findings broaden the understanding of how immune cells adapt their metabolism to challenging conditions and might be an important piece of the puzzle of how to improve immunotherapy. "When we understand how different types of cells behave in the tumor environment, we may be able to learn how to influence this environment directly—to create conditions favorable for the patient and unfavorable for the tumor," says Schindlmaier about the future of research.

The project was supported by the Austrian Science Fund (FWF) and the professional organization EMBO.

Link:

"Metabolic adaptation of glucose-deprived macrophages involves partial gluconeogenesis"
<https://www.pnas.org/doi/10.1073/pnas.2419568122>

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Katharina Leithner is in charge of the Lung Cancer Metabolism and Microenvironment research unit at the Division of Pharmacology of the Medical University of Graz. Its goal is to understand the influence of cellular metabolism on the interaction between tumor cells and immune cells and to identify potential targets in the metabolism of tumor cells. In her research, she focuses on lung cancer, which frequently has a poor prognosis despite the number of new therapeutic options. Of particular interest are metabolic pathways that are activated under unfavorable nutrient conditions in tumor cells and certain immune cells like those that may exist in lung cancer.