Boosting immunotherapy in non-responsive cancer cells

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Avik Chattopadhyay working in the lab. Credit: Nikita Ramteke

Cancer immunotherapy primes a patient's immune system to better find and destroy cancer cells, improving upon the body's natural ability to fight tumors. Contemporary immunotherapy approaches aim to stimulate immune cells called T cells to target tumors.

In this process, the production and functioning of a cytokine (a small signaling protein) known as Interferon-gamma (IFN-γ) are essential for the immune system to eliminate tumors effectively. These approaches affect fewer normal cells when compared to chemotherapy or radiation. However, they are either very expensive or less efficient.

In a new study, researchers at the Indian Institute of Science (IISc) tried to understand how different types of cancer cells respond to IFN-γ activation. They found that only some types of cancer cells respond well to IFN-γ activation, while others don't. They also suggest some approaches that can be used to make these non-responsive cancer cells better respond to immunotherapy. The study was published in Frontiers in Immunology.

"IFN-γ is produced by immune cells such as T cells or natural killer cells . It binds to tumors, and induces apoptosis [cell death]," explains Avik Chattopadhyay, first author and Ph.D. student at the Department of Biochemistry, IISc. "Reports in the literature have shown earlier that if there are lower amounts of IFN-γ or defects in its signaling, then the tumors don't respond well to the immunotherapy processes."

In the current study, when the team first treated cancer cells in the lab with IFN-γ, they found that the color of the cell growth medium changed to yellow, indicating that the cells were releasing acidic byproducts such as lactic acid. This led the team to dig deeper into the role of these byproducts. They found that the higher amounts of lactic acid produced in the cell culture medium was due to increased glycolysis, a series of chemical reactions that extracts energy from glucose.

The team found that cancer cell lines derived from the liver and the kidney showed increased production of nitric oxide (NO) and lactic acid upon IFN-γ activation. This, in turn, increased the production of toxic reactive oxygen species (ROS) leading to oxidative damage, which eventually kills the cancer cells.

However, cancer cell lines derived from the colon and skin did not produce NO or lactic acid even after being treated with IFN-γ, indicating that they might respond poorly to immunotherapy.

The researchers then tried to see how these non-responsive cancer cells can also be tweaked to produce lactic acid and NO, and therefore respond better to immunotherapy. They tested different ways, including treating the cells with salts like potassium lactate and other molecules.

Such mechanisms—especially adding potassium lactate—reduced cancer cell growth drastically even in the initially non-responsive cancer cells. This observation—that lactic acid plays an important role in the cancer cells' response to immunotherapy—was surprising to the researchers as lactic acid is often thought of as a dead-end metabolic product.

"The study is really a proof-of-concept at this point," says Dipankar Nandi, Professor at the Department of Biochemistry, IISc, and corresponding author of the study. He adds that further experiments need to be carried out in animal models to see if certain compounds targeting metabolism can boost anti-tumor responses to hard-to-treat cancers, in synergy with IFN-γ activation during immunotherapy.

More information: Avik Chattopadhyay et al, IFN-γ lowers tumor growth by increasing glycolysis and lactate production in a nitric oxide-dependent manner: implications for cancer immunotherapy, *Frontiers in Immunology* (2023). DOI: 10.3389/fimmu.2023.1282653

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