New study reveals metformin-dependent antitumor immunity

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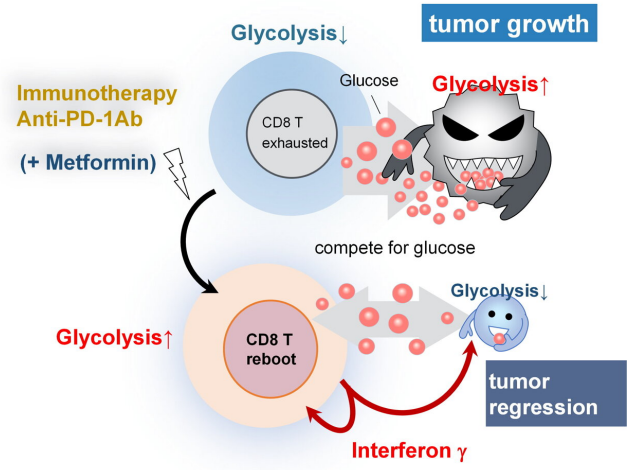

Scientists report that metformin, used to treat type 2 diabetes mellitus, induces activation and proliferation of tumor-targeting CD8+ T-lymphocytes (CD8TIL), via mechanisms that involve the generation of reactive oxygen species in mitochondria of CD8TIL and an increase in glycolysis. Credit: Heiichiro Udono, Okayama University

Modern medicine has made slow progress in combating the menace of cancer. With all the permutations and combinations of cancer affecting millions of people worldwide, a blanket, yet targeted therapy would be ideal. Recently, certain drugs like metformin, which is used to treat lifestyle diseases like type 2 diabetes mellitus, have been found to have anti-cancer effects. Use of metformin appears to bolster anti-tumor immunity. However, the underlying immunological mechanisms have eluded scientists till date.

Japanese scientists led by Professor Heiichiro Udono from Okayama University thus decided to address this oncological research question. In their recent study, they looked at how a specific subset of immune cells, called CD8+ infiltrating T-lymphocytes (CD8TIL), which specifically attack tumor cells, behaved in response to metformin. Their findings have been published in the *Journal for ImmunoTherapy of Cancer*.

Prof. Udono, who spearheaded the study, almost gave up on his anti-cancer pursuits when he lost his own father to cancer. However, inspiration came knocking at a conference, he says: "Nearly 10 years ago, a switch turned on in my head when I attended a Keystone Symposia discussing cancer and hypoxia, held in Banff, Alberta. I realized that we had missed addressing the Warburg effect, an effect that bolsters the growth of cancer, in our previous research. So reverting the Warburg effect to a normal metabolic profile in cancers became a topic that got me thinking. Surprisingly, I got a hint from the same conference that metformin may aid cancer immunity. So we got to work."

Prof. Udono and his team meticulously executed a series of experiments on cancer cell lines and a knock-out mouse model of possible biomolecules that result in metformin-dependent anti-tumor immunity. To arrive at their results, they probed the intracellular mechanisms in CD8TIL when exposed to metformin, and assessed different biomarkers for growth. Given that CD8TIL produces proteins called interferons to attack cancer cells, they also assessed corresponding levels.

Accordingly, the scientists found that metformin causes the generation of reactive oxygen species in the mitochondria of CD8TIL (mtROS) and increases glycolysis. Further, they found that mtROS activated growth pathways in CD8TIL, thus allowing proliferation of these immune cells. Notably, this is achieved through a transcription factor involved in anti-oxidative stress response, called Nrf. In addition, they also ruled out that metformin causes an anti-tumor effect through apoptosis. Also, they determined that metformin caused CD8TIL to robustly secrete interferon-? to

alter the tumor microenvironment to favor death of tumor cells.

Speaking about the findings, Prof. Udono exclaims, "More than anything else, our study provides the knowledge that we can ourselves protect our body from cancer. We hope that this understanding will result in not only the reduction of cancer incidence and improve treatment, but also will help prolong life." The researchers also add that these findings strongly suggest the possibility of using metformin as a drug to strengthen anti-tumor immunity in patients with cancer.

More information: Mikako Nishida et al, Mitochondrial reactive oxygen species trigger metformin-dependent antitumor immunity via activation of Nrf2/mTORC1/p62 axis in tumor-infiltrating CD8T lymphocytes, *Journal for ImmunoTherapy of Cancer* (2021). DOI: 10.1136/jitc-2021-002954

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