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メトホルミンによる腫瘍局所免疫疲弊解除に基づく癌免疫治療

Cancer Immunotherapy by metformin-induced reversion of exhausted T cells in tumor microenvironment

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Abstract

Recent advances in immunotherapy have changed the landscape of cancer therapy. Immune checkpoint inhibitors have shown improved patient survival rates over traditional chemotherapy. Tumor-infiltrating CD8 T lymphocytes often undergo loss of function, referred to as immune exhaustion, which facilitates tumor growth *in vivo*. Immune checkpoint inhibitors prevent this inhibition of effector CD8 T cells, resulting in their reactivation and subsequent inhibition of tumor growth. However, this treatment is effective in less than 20% of patients with non-small cell lung carcinoma, as well as other cancers. It remains unknown why the remaining 80% patients with cancer do not respond to the same inhibitors. Although combination therapy with different checkpoint inhibitors has demonstrated greater success rates than monotherapy, its very high cost creates financial challenges. To overcome these problems, low molecular weight compounds having similar effects as checkpoint inhibitors are currently being explored. Metformin, a drug commonly prescribed for the treatment of type 2 diabetes (T2DM), is a potential candidate for this purpose.

Metformin is currently prescribed as a first-line therapy for T2DM because of its glucose-lowering effects, as well as its safety and low cost. T2DM patients receiving metformin have a lower incidence of cancer and mortality compared with those receiving other anti-diabetes drugs, though the reasons for this remain unclear. Direct inhibition of cancer and the reduction of insulin and insulin-like growth factors have been proposed as the reason for the observed cancer prevention effect. Conversely, we found that metformin induced the reversal of immune exhaustion in tumor-infiltrating CD8 T cells, resulting in tumor regression in mice tumor models. These surprising findings are now being confirmed by other studies worldwide.

Recent studies revealed that the function of immune cell subsets is tightly coupled to their energy metabolism. Effector T cells and M1-like macrophages depend on glycolysis to exert their functions, whereas immune-suppressive cells involved in wound healing and tolerance depend on oxidative phosphorylation (OxPhos) following fatty acid oxidation (FAO). In the tumor microenvironment, Treg, MDSCs, and M2-like macrophages undergo expansion, while effector and memory CD8 T cells and M1-like macrophages are very rare. This suggests that the immune cells that undergo expansion in tumors are dependent on OxPhos following FAO, whereas tumor cells uptake most of the glucose and are dependent on glycolysis (Warburg effect). Metformin appears to improve the metabolic imbalance in the tumor-infiltrating cells, but not in peripheral blood lymphocytes. Metformin-induced metabolic reprogramming causes CD8 T cells to increase the Glut1 expression (hence, elevate their levels of glycolysis), resulting in greater anti-tumor activity. Metformin-mediated complex I inhibition induces the production of ROS. ROS then activate Nrf2, which in turn activates mTORC1, resulting in cell proliferation.

Metformin acts synergistically with anti-PD-1 Ab blockade through the overlap of certain signal cascades. It is possible that artificial manipulation of the metabolism of tumor-infiltrating immune cells improves immune tolerance against tumors. In fact, metformin activates glycolysis, leading to the inhibition of Treg and MDSCs in tumors. Based on this evidence, we have begun an intervention trial for patients with cancer using Nivolumab and metformin. The knowledge that immune cell function is closely associated with cellular metabolism may offer additional possibilities in the advancement of cancer immunotherapy.