Ferroptosis Enables Immune Therapies to Fight Against Liver tumors and Liver Metastases.

Researchers from the Georg-Speyer-Haus in Frankfurt am Main and the University Hospital and Goethe University Frankfurt, identified a new combination therapy to boost anti-tumor immune therapy in liver cancer and liver metastasis.

Over the last decade, immune therapies have become part of the portfolio for the fight against cancers. For some tumors, immune checkpoint blockades are by now part of first–line treatment. Unfortunately, for other cancers, such as liver cancer, the response to immune checkpoint blockade is poor.

A research team led by Prof. Florian Greten has made a discovery that represents a step toward a solution for making liver cancer susceptible to immunotherapy. They found that in cancer cells, ferroptosis - an iron-dependent form of cell death - triggers activation of tumor-fighting T cells in preclinical models. However, tumor-fighting T cells are in turn inactivated in ferroptotic tumors by two independent mechanisms. On the one hand, cells called myeloid-derived suppressive cells suppress tumor-fighting T cells. On the other hand, the tumor cells shield themselves from the T cells with the immune checkpoint receptor PD-L1. Thus, the team succeeded in showing that in a preclinical model, a triple therapy consisting of a substance that induces ferroptosis combined with the simultaneous administration of an immune checkpoint blocker as well as an inhibitor that prevents the recruitment of myeloid suppressive cells significantly reduces the growth of hepatocellular carcinoma.

The authors went on to study if this combination therapy was also effective on other cancer types such as colorectal cancer. Even though, the combination therapy had no effect on colorectal cancer at the primary location, it reduced the number of metastases in the liver from colorectal cancer in preclinical models. Following-up on this observation, the researchers determined that the success of the combinatory therapy depends on the liver microenvironment and not on the origin of the cancer.

Dr. Claire Conche, one of the first authors of the now published study, explains: "With this new combination therapy, we attack the immune system from three sides. First, we make the tumor-fighting T cells reactive toward the tumor cells. Then we remove the obstacles the tumor-fighting T cells face, the suppression cells and the shielding by PD-L1." Prof. Fabian Finkelmeier, the second first author from University Hospital says, "The fact that the efficacy of the combination treatment depends on the liver microenvironment suggests that combination therapy may be effective for liver metastases of any cancer type."

Prof. Florian Greten, director of Georg-Speyer-Haus and spokesperson of the LOEWE Centre Frankfurt Cancer Institute explains: “The study highlights the crucial role of the tumor microenvironment in cancer therapy. It focuses on the immune compartment of the tumor microenvironment and how to modulate the immune system toward a potent anti-tumor response. Our data on preclinical models are encouraging for the improvement of immune therapy options for hepatocellular carcinoma and liver metastasis.”

Publication: Conche et. al. *Combining ferroptosis induction with MDSC blockade renders primary tumours and metastases in liver sensitive to immune checkpoint blockade*. Gut, 2023.

http://dx.doi.org/10.1136/gutjnl-2022-327909

Further information

Prof. Dr. Florian R. Greten

Georg-Speyer-Haus
Institut für Tumorbiologie und experimentelle Therapie / Goethe-Universität Frankfurt
Tel. +49 (0)69 63395-232

Greten@gsh.uni-frankfurt.de

Twitter: @FCI_health