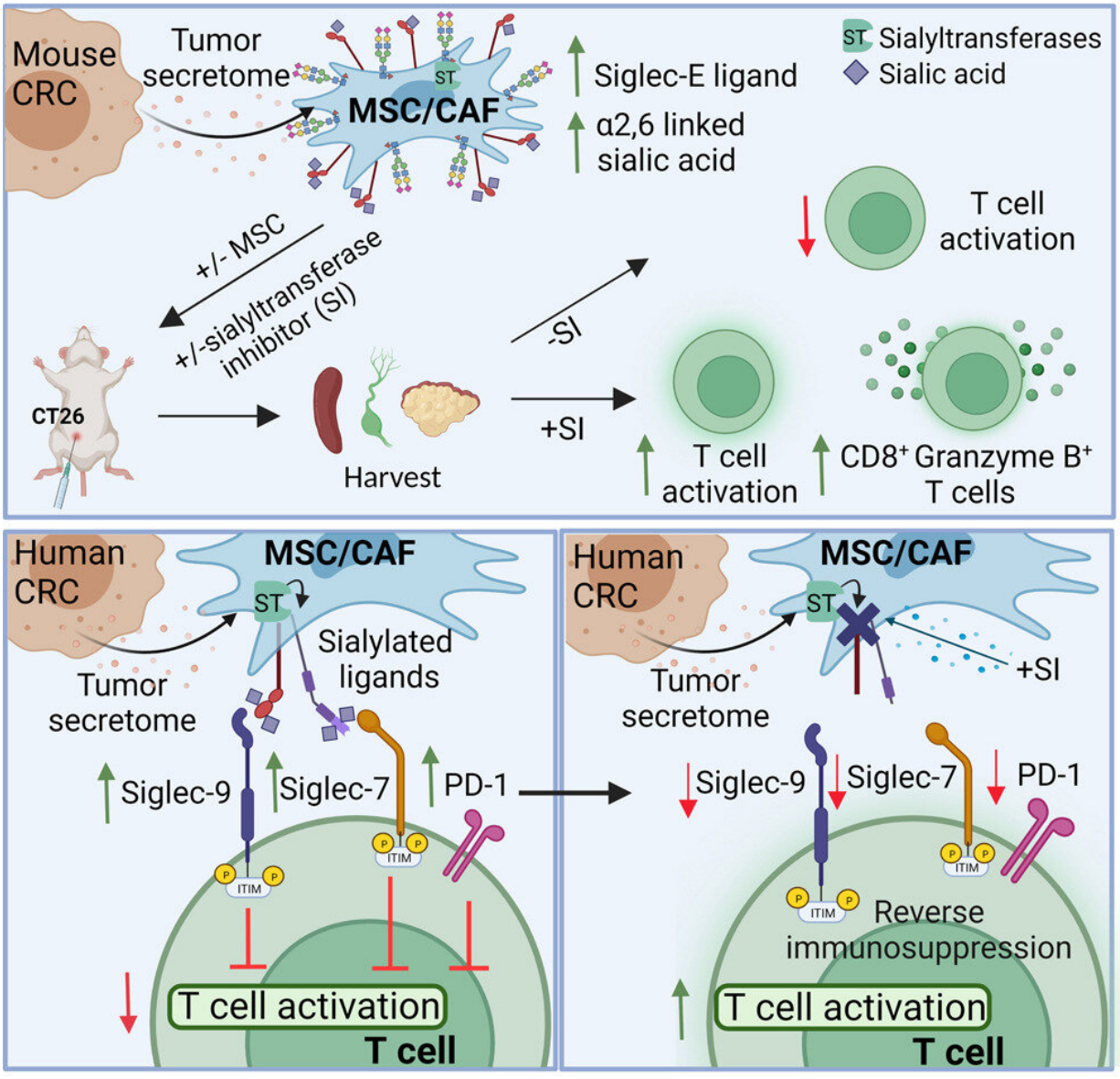
Researchers identify innovative strategy with potential to enhance bowel cancer treatment

May 11 2023



Graphical Abstract. Credit: *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.112475

Researchers at University of Galway studying cell interactions in bowel cancer have identified innovative strategies to enhance how the body and drug treatments fight the disease.

Colorectal, also known as bowel, cancer is a leading cause of death globally with increasing incidence in developing countries and in younger people. In Ireland alone, there are more than 2,500 newly diagnosed cases of bowel cancer every year, with limited treatment options for patients at advanced disease stage.

The findings of the research have been published in the journal *Cell Reports.*

Aideen Ryan, Associate Professor in Tumour Immunology at University of Galway's College of Medicine, Nursing and Health Sciences, said, "Unfortunately, a high proportion of colorectal cancer patients do not respond to immunotherapy. We have identified sugar coated molecules with sialic acid, called sialoglycans, that are present on cells in tumors, known as stromal cells. These are associated with poor responses to immunotherapy. Targeting these molecules enhances the immune response in tumors that have high levels of these cells."

The research was carried out by University of Galway in collaboration with VUB, Belgium; Palleon Pharmaceuticals, Boston, U.S.; CÚRAM, the SFI Research Centre based at University of Galway; Glasgow Beatson Institute for Cancer Research; Queen's University Belfast.

Approximately 25% of bowel cancer patients have a high density of

stromal cells, a type of cancer-supporting cell found in close proximity to cancer cells. These patients are the hardest to treat.

Stromal cells use a number of methods to inhibit or suppress immune cell responses, many of which are utilized by the cancer cells themselves, to promote tumor growth.

This leads to conventional anti-cancer therapies such as chemotherapy, radiotherapy and, more recently, immunotherapies, having less than favorable results.

The researchers studied a previously unknown mechanism of stromal cell immunosuppression. It occurs as sugar coated molecules expressed on the stromal cell surface binds to specific protein receptors expressed on the surface of immune T-cells.

The sugars—sialic acids (or sialoglycans)—bind to receptors called Siglecs. The Siglecs stop the cancer killing T cells from working.

The research showed that stromal cells, when exposed to inflammatory molecules released by bowel cancer cells, express increased amounts of the sialoglycans—on their surface.

It also showed that T cells could be re-activated by using specific drugs to disrupt the binding between the cells.

The researchers tested the findings using stromal cells isolated from bowel cancer patient biopsies and got the same results, confirming that targeting the binding of sialic acid/Siglecs may represent an innovative strategy to enhance anti-tumor immunity in immunosuppressive tumor microenvironments.

Dr. Ryan added, "Our plan now is to test the effects of combining this

new targeting approach with clinically approved immunotherapies in the hope that the combination will improve immune responses to cancer."

"We are fortunate to have access to drugs, called sialidases, that target sialoglycans through our collaborators Palleon Pharmaceuticals to test these new combinations in our laboratory. These sialidase molecules derived from Palleon's EAGLE glyco-immunology drug development platform has recent clinical proof of mechanism."

More information: Hannah Egan et al, Targeting stromal cell sialylation reverses T cell-mediated immunosuppression in the tumor microenvironment, *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.112475

Provided by University of Galway