Novel late-stage colorectal cancer treatment proves effective in preclinical models

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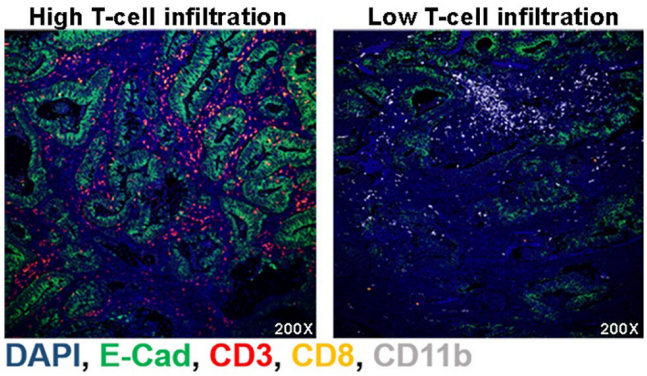

The low T cells are due to exosomal, immunosuppressive miRNAs that disrupt T cell function and loss of T cells in the tumor environment. Credit: University of Minnesota Medical School

In a recent discovery by University of Minnesota Medical School, researchers uncovered a new way to potentially target and treat late-stage colorectal cancer—a disease that kills more than 50,000 people each year in the United States. The team identified a novel mechanism by which colorectal cancer cells evade an anti-tumor immune response, which helped them develop an exosome-based therapeutic strategy to potentially treat the disease.

"Late-stage colorectal cancer patients face enormous challenges with current treatment options. Most of the time, the patient's immune system cannot efficiently fight against tumors, even with the help of the FDA-approved cancer immunotherapies," said Subree Subramanian, Ph.D., an associate professor in the U of M Medical School's Department of Surgery, and a senior author of the study.

In partnership with Xianda Zhao, MD, Ph.D., a postdoctoral fellow in Subramanian's laboratory, the duo set out to investigate how colorectal cancer becomes resistant to available immunotherapies. What they found was recently published in *Gastroenterology*, including:

- Colorectal cancer cells secrete exosomes that carry immunosuppressive microRNAs (miR-424) that actually prevent T cell and dendritic cell function because they block key proteins (CD28 and CD80) on these immune cell types, respectively. In the absence of these proteins, the T cells, which would normally kill the cancer cells, become ineffective and are eliminated from tumors, allowing tumors to grow.
- By blocking these immunosuppressive microRNAs in cancer cells, the team observed an enhanced anti-tumor immune response and discovered that cancer cell-secreted exosomes also contain tumor-specific antigens that can stimulate the tumor-specific T cell response.
- The researchers tested tumor-secreted exosomes without immunosuppressive microRNAs, in combination with immune checkpoint inhibitors, as a novel combination therapy in preclinical models with advanced-stage colorectal cancer, which proved effective.

"Our studies indicate that disrupting specific immunosuppressive factors in tumor cells helps unleash the immune system to effectively control tumor growth and metastasis in preclinical models with late-stage colorectal cancer," said Subramanian, who is also a member of the Masonic Cancer Center. "Eliminating the immune suppressive effects of those exosomes is now the focus of a new treatment option for patients with this deadly disease."

The intellectual property behind the modified exosome technology has been protected with assistance from the U of M Technology Commercialization. The team is currently

developing clinical-grade exosomes that can be tested in clinical trials for patients with colorectal cancer.

More information: Xianda Zhao et al, Tumor secreted extracellular vesicles regulate T-cell costimulation and can be manipulated to induce tumor specific T-cell responses, *Gastroenterology* (2021). DOI: 10.1053/j.gastro.2021.04.036

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