Gut microbes may promote immune responses against colorectal cancer

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Bacteria in the gut could stimulate tumor cells to produce factors that regulate cell mobility called chemokines that recruit T cells to the tumor, which is linked to improved outcomes, according to data presented at the Third CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival, held Sept. 6-9.

"In the last decade it has become clear that the presence of certain types of immune cells, T cells in particular, within the tumor is associated with prolonged survival in patients with colorectal cancer," said Eleonora Cremonesi, PhD, a postdoctoral fellow in the group of Dr. G. Iezzi, at University of Basel, in Switzerland. "The factors promoting the recruitment of these immune cells and the mechanisms underlying their beneficial effect remain to be understood."

Cremonesi and team aimed to study the interaction between the gut microbiota and chemokines in promoting immune-cell infiltration into colorectal cancer and how this influences the clinical course of the disease.

First, the team evaluated the expression of a series of genes encoding chemokines in a cohort of 62 freshly excised human colorectal cancers and adjacent healthy colonic tissue and identified gene signatures associated with the infiltration of immune cells into the colorectal cancers. They also evaluated the bacterial load in these tissues by assessing the expression of gene sequences exclusively expressed by bacteria.

Next, they analyzed the recruitment of immune cells in tumor tissues by injecting human colorectal cancer cells into the peritoneal cavity (etherotopic model) or in the gut (orthotopic model) of mice. While tumors developing in the peritoneal cavity are not exposed to the gut flora, those developing in the gut wall are, explained Cremonesi.

"We observed that in mice with orthotopic tumors exposed to the gut flora, the production of chemokines as well as the migration ability of human T lymphocytes derived from colorectal cancer specimens was significantly increased, compared with mice with etherotopic tumors that are not exposed to gut flora," she said. "These data suggest that the presence of the gut microbes promote cytotoxic T-cell infiltration in tumors."

To further confirm their findings, the researchers treated the mice bearing orthotopic tumors with antibiotics and showed that it dramatically reduced the bacterial load. They also observed that the expression of genes encoding the chemokines involved in the recruitment of beneficial T-cell subset was significantly reduced. "These findings pave the way for additional studies aimed at the identification of bacterial strains of particular relevance in the induction of the production of these chemokines," Cremonesi said.

"That gut microbes play a role in colorectal cancer progression might appear like the Columbus egg. However, mechanisms involved in the generation of the peculiar microenvironment of colorectal cancer and in the interaction between cancer and immune cells are still largely unclear," she added. "Our findings may open the way toward the development of new treatments aimed at modifying the gut flora to promote the infiltration of colorectal cancers by lymphocytes displaying anti-tumor effects."

A limitation of the study is that the researchers could not assess the

potential impact of the identified chemokines on patients' survival in their cohort, which is usually evaluated after five years, Cremonesi said. She expects this analysis to be part of follow-up studies.

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