Interspecies Cooperation to Fight Cancer

Microbes in the gut may be helping a variety of cancer therapies.

Bacteria were here first, colonizing everything in sight with a two billion-year head start over eukaryotes. In hindsight, it is not surprising, therefore, that bacteria would colonize us, too, as we evolved on the planet. But we have only recently become aware that we share our bodies with a microbial population that outnumbers our own cells by a factor of 10.

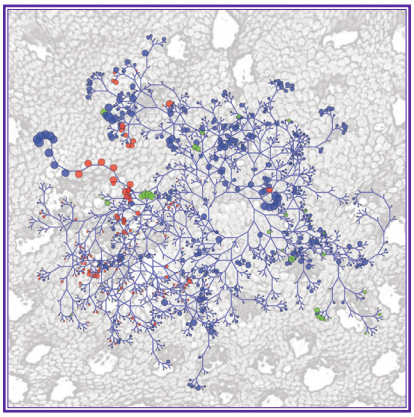
We are beginning to understand that our immune system is profoundly shaped by these unseen fellow travelers. Microbes in the gut, which include bacteria, archaea, fungi, viruses, protozoans, and even multicellular helminthes, affect inflammation and immunity systemically as well as locally, leading Giorgio Trinchieri, M.D., Chief of CCR's Laboratory of Experimental Immunology, to wonder whether they might affect inflammatory processes associated with cancer and its therapy.

To model this question, Trinchieri and Staff Scientist Romina Goldszmid, Ph.D., led their colleagues in a study of three different cancer types—lymphoma, colon, and melanoma—that could be injected under the skin of mice. The cell lines were chosen for their sensitivity to specific therapies. Preceding the tumor initiation, mice were either treated with a cocktail of antibiotics (vancomycin, imipenem, and neomycin in drinking water) to deplete their gut microbes or they were raised from birth in a germ-free environment. Then, once the tumors reached a certain size, the mice were challenged with an immunotherapy regime (intratumoral injection of CpG oligonucleotide, a TLR9 ligand, and systemic anti-interleukin-10 receptor) or a conventional platinum-based chemotherapy.

Regardless of the tumor type or treatment examined, mice depleted of their gut microbes responded less well to therapy than controls, as measured by reduction in tumor volume and long-term survival. Moreover, the response of myeloid-derived cells that normally infiltrate the tumors after therapy was reduced. Mice treated with immunotherapy had reduced tumor necrosis factor (TNF) expression and those treated with chemotherapy showed reduced reactive oxygen species (ROS) production. The findings were reported in the November 22, 2013, issue of *Science*.

Tumor-bearing mice that lacked the *tnf* gene did not respond to immunotherapy, regardless of the presence or absence of gut microbes. The researchers found that administration of bacterial products could restore TNF production by tumor myeloid cells in animals depleted of their gut microbiota. Allowing microbial colonies to reestablish after antibiotic treatment, they further determined that bacterial composition—not just abundance—was important for restoring the TNF response.

"The use of antibiotics should be considered as an important element affecting microbiota composition. After antibiotic treatment the bacterial composition in the gut never returns to its initial composition," said Trinchieri. "Our findings raise the possibility that the frequent use of antibiotics during a patient's lifetime or to treat infections related to cancer may affect the success of anticancer therapy."



(*Image: A. Dzutsev, CCR*)

Mouse gut bacteria phylogenetic tree superimposed over a microphotograph of colonic tissue, showing the abundance of bacteria by the size of the circles. Red circles indicate bacteria that primes the mice for a response to immunotherapy, while the green circles show bacteria that suppress antitumor response to the drug.

The researchers plan to continue their work in mice to fully understand the signaling between gut microbes and tumors in distant organ sites. However, the commensal microbial ecosystem is enormously complex and the extent to which results can be directly translated into humans is still unclear. Thus, important future directions for the team include studying the role of gut bacteria (and antibiotic interventions) in the human inflammatory response and tumor response to therapy.

To learn more about Dr. Trinchieri's research, please visit his CCR website at http://ccr.cancer.gov/staff/staff.asp?name=gtrinchieri.