Published in final edited form as:
Nat Med. 2014 February ; 20(2): 126–127. doi:10.1038/nm.3473.

Chemotherapy, immunity and microbiota—a new triumvirate?

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Abstract

The growing relevance of the gut microbiota to various human diseases may also directly impinge on the efficacy of chemotherapeutics. A recent study shows that subcutaneous tumors fail to respond to immunotherapy and platinum chemotherapy after antibiotic treatment[1], whereas another study reports that the effect of cyclophosphamide on the antitumor immune response relies on the presence of a 'healthy' gut microbiota[2]. The mechanisms mediating the role of the microbiota in the immune system during chemotherapy seem to involve the innate and adaptive immune arms. The unexpected influence of commensal intestinal bacteria in the outcome of cancer treatment and the function of anticancer immunity poses new questions from a preclinical and clinical standpoint in the cancer field.

Michael Karin

The gut microbiome affects many physiological processes, and intestinal dysbiosis, in which the microbiome composition is grossly perturbed, is thought to be responsible for a number of pathologies. Two recent *Science* papers show that the gut microbiome also influences the outcome of cancer therapy by modulating the host inflammatory response[1,2]. Basically, both papers conclude that an intact microbiome is required for successful tumor control in response to genotoxic as well as immunomodulatory therapies and that tumor-bearing germ-free mice or mice that have been treated with a concoction of antibiotics that eliminate most of the commensal microbiota hardly respond to anticancer therapy. Although the results obtained in mice are clear, it is rather unlikely that most patients with cancer will have a grossly depleted gut microbiome, so it is debatable whether these studies would alter the future practice of cancer treatment. Many genotoxic cancer drugs lead to an inflammatory condition known as mucositis, which is associated with gut barrier deterioration and bacterial translocation. As these drugs also cause neutropenia, bacterial translocation across the gut mucosa can cause severe systemic infections that will require antibiotics. However,

Competing Financial Interests: The author declares no competing financial interests.

antibiotic use in humans rarely leads to nearly complete depletion of the gut microflora, and any dysbiosis that ensues is usually transient. The two papers suggest that the inflammatory response that follows cancer therapy, which is strongly enhanced by the translocating commensals, contributes to tumor eradication through the upregulation of interleukin-17 (IL-17)[2] or tumor necrosis factor (TNF)[1]. So should oncologists make an effort to maintain IL-17 and TNF expression in patients with cancer treated with antibiotics?

Although both groups convincingly show that both inflammatory cytokines enhance the efficacy of cancer therapy in their particular model systems, a considerable body of data suggests the opposite in both mouse models and humans. Elevated production of IL-17, in response to translocating commensal bacteria or their disintegration products, promotes the progression of colorectal tumors[3], and in human patients it was linked to rapid progression from a controllable stage of colorectal cancer to metastatic disease[4]. Elevated IL-17 production has also been linked to therapy failure and most recently shown to antagonize anti-angiogenic treatment[5]. TNF, also a potent tumorpromoting cytokine[6], stimulates the metastatic spread of ectopic colorectal tumors[7]. Whereas Iida *et al.*[1] deliberately induced TNF expression by treating

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mice with CpG-oligonucleotide, TNF induction in response to bacterial endotoxin introduced during cancer surgery has been proposed to contribute to tumor recurrence and metastatic spread[7,8]. Another cytokine, IL-10, shown by Iida *et al.*[1] to counteract cancer therapy, has been shown to induce tumor regression by stimulating immune surveillance[9]. It seems that the cytokines modulated by the gut microbiome can have opposing effects on tumor growth and the outcome of cancer therapy, all of which need to be carefully considered when moving from mouse models to patients with cancer.

Christian Jobin

In little over 5 years, microbiome research has moved from simple, yet technically challenging, cartographic projects to stunning functional research linking commensal microbes to various important host biological functions such as nutrition, obesity, cancer and neurological processes. Two recent studies published in *Science* have pushed the growing field of microbiome research even further by showing that the efficacy of chemotherapeutic agents might also depend on microbiota-mediated innate and adaptive immune responses[1,2]. Two important concepts are highlighted: a complex interplay between the microbiota, the immune system and cancer drug treatment response and the negative effect of disrupting intestinal eubiosis on a drug's function at distant sites. Both studies showed that microbial disturbance by means of antibiotic exposure severely compromised efficacy of both immunostimulatory (CpG, cyclophosphamide) and platinum-based chemotherapeutics. Although these findings were mostly generated using mouse xenograft cancer models and as such may have limited relevance to human cancer, the studies raised a number of intriguing questions. A fundamental one is whether the prophylactic antibiotic

treatment that patients with cancer undertake before receiving chemotherapy interferes with the efficacy of the chemotherapeutics. Finding the answer would help assess the physiological relevance of these new studies and determine whether the microbiota should be farmed for cancer therapeutic purposes. For example, Iida *et al.*[1] observed that the presence of the commensals *Alistipes* and *Ruminococcus* positively correlate with the capacity of tumor-associated myeloid cells to secrete TNF-α, thereby enhancing anticancer effect. This observation raises the possibility that 'immunostimulatory microorganisms' could be used to alleviate the deleterious effect of microbiota depletion in patients or even to optimize anticancer drug response. It is still too early to include the microbiome as part of the decision-making process regarding cancer therapeutic options for patients; however, modulating microbial activities may boost drug efficacy or alleviate toxicity, two key aspects of chemotherapeutic treatment. Already, targeting microbial activities has been shown to attenuate irinotecan-associated gastrointestinal toxicity in mice[10]. Undeniably, microbiome research keeps pushing the boundary of medical research further, and this new knowledge has opened a vast and fascinating array of possibilities regarding prevention and treatment of various pathologies.

Frances Balkwill

Major advances in our understanding of the interactions between the immune system and cancers[11] have resulted in more effective immunotherapies and the appreciation that the actions of many chemo- and radiotherapies involve stimulation of the host immune response[12]. Given that 90% of the cells in our bodies are commensal bacteria and other organisms, our nonhuman cells may influence our response to cancer and cancer treatments.

Two recent papers in *Science*[1,2] report that prophylactic antibiotics inhibited the actions of cyclophosphamide and platinum-based chemotherapies or CpG-oligonucleotide immunotherapy—gut bacteria seem to prime the tumor-associated leukocytes to a more effective immune response after therapy. These experiments, which were conducted in subcutaneous transplanted tumors in mice, have implications for cancer treatment and maybe even cancer prevention, although similar experiments in genetic models of slowly evolving human cancer should be conducted because the influence of the microbiota may be different when malignant tissues have grown and evolved over months or years.

In the clinical setting, antibiotics are used prophylactically in some treatment regimens, particularly in patients with acute leukemia and lymphoma, where the drugs are myeloablative. Is there any evidence that this therapy has influenced response to treatment? Other chemotherapies, such a 5FU, cause major gastrointestinal side effects; however, it remains unknown whether this tempers their activity in patients. Could patient response be enhanced by judicious supplementation of 'good' bacteria during treatment?

Because antibiotic treatment decreased the number of potentially antitumor $Ly6C^+$ MHC class II major histocompatibility complex–positive myeloid cells in the lymphoma and colon carcinoma models[1], one might speculate that the mammalian gut microbiota could also influence cancer susceptibility and recurrence. A recent study in mice gave us a new perspective on recurrence of dormant cancers[13] by showing that the transition from minimal

residual disease to a recurrent tumor led to a host innate acute phase protein response triggered by proliferation of malignant cells and their release of inflammatory signals. Would this also occur in antibiotic-treated or germ-free mice? Would long-term antibiotic treatment in mouse or humans enhance cancer development or spread? In 2004, a study showed that increasing cumulative days of antibiotic use are associated with increased risk of incident breast cancer[14]. Although further studies have not fully supported this finding, the data so far seem to suggest a small increase in risk of cancer with antibiotic use.

Perhaps tumor immunology researchers should start considering the microbiota composition of experimental animals and patients with cancer and the antibiotic regimens that patients receive during cancer treatments.

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