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Short Communication

The Emerging Role of Microbiota in Modulating Cancer Therapy Outcomes

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DESCRIPTION

The human microbiota, a complex community of trillions of microorganisms residing primarily in the gut, has gained significant attention in recent years for its profound influence on health and disease. Beyond its established role in digestion, immunity, and metabolism, growing evidence suggests that the microbiota is a critical modulator of cancer development and response to therapy. This emerging axis between microbiota and oncology offers exciting opportunities to enhance cancer treatment efficacy, predict therapeutic response, and potentially reduce side effects. However, it also presents complex biological interactions that are only beginning to be understood [1].

Multiple studies have demonstrated that the gut microbiota can influence the effectiveness of chemotherapy, immunotherapy, and even radiotherapy. The mechanisms by which microbes exert these effects are diverse and multifactorial, involving direct interaction with drugs, modulation of host immune responses, and alteration of systemic inflammation. For example, certain bacterial species possess enzymatic activities that can activate or inactivate chemotherapeutic agents. An illustrative case is the microbial degradation of irinotecan into toxic metabolites by β-glucuronidase-producing bacteria, which contributes to severe gastrointestinal toxicity. Targeting such microbial enzymes using specific inhibitors has been proposed to mitigate these adverse effects without compromising antitumor efficacy.

The most striking discoveries in recent years relate to the microbiota's impact on Immune Checkpoint Inhibitors (ICIs), particularly therapies targeting PD-1 and CTLA-4. Preclinical mouse models have shown that antibiotic treatment or germ-free conditions, which deplete commensal bacteria, lead to impaired responses to ICIs. Conversely, the presence of specific bacteria such as *Bifidobacterium*, *Akkermansia muciniphila*, and *Faecalibacterium prausnitzii* has been correlated with enhanced antitumor immune responses and improved survival in cancer patients receiving immunotherapy.

Mechanistically, beneficial microbes appear to prime the immune system by enhancing antigen presentation, promoting T-cell infiltration into tumors, and upregulating pro-inflammatory cytokines. *Akkermansia muciniphila*, for instance, has been shown to restore response to PD-1 blockade in antibiotic-treated mice by inducing IL-12 production from dendritic cells, thereby boosting cytotoxic T-cell activity. Human studies have corroborated these findings, with fecal microbiota composition emerging as a potential biomarker for predicting immunotherapy response. Clinical trials are now underway to evaluate Fecal Microbiota Transplantation (FMT) as a strategy to restore or improve responsiveness to ICIs in refractory patients [2-4].

Diet and lifestyle, which strongly influence microbial diversity, also indirectly affect cancer outcomes. High-fiber diets, for example, promote the growth of butyrate-producing bacteria that exert anti-inflammatory and antitumor effects. On the other hand, Western-style diets rich in fats and processed foods can lead to dysbiosis, a state of microbial imbalance associated with chronic inflammation and carcinogenesis. Obesity-related dysbiosis has been linked to reduced efficacy of immunotherapy and increased tumor progression in certain cancers.

The interaction between the microbiota and cancer is bidirectional. While microbes influence therapy outcomes, cancer treatments themselves can alter the composition and function of the microbiota. Chemotherapy and radiation often lead to a reduction in microbial diversity, which may increase susceptibility to infections and gastrointestinal toxicity. Immune-related Adverse Events (irAEs), a common side effect of ICIs, have also been associated with shifts in gut microbial communities. Understanding these dynamics could inform prophylactic interventions aimed at maintaining or restoring a healthy microbiota during treatment [5-7].

Beyond the gut, microbiota at other body sites such as the oral, lung, and vaginal microbiomes are also being investigated for their roles in site-specific cancers. For instance, the lung microbiota may influence the development and progression of lung cancer, while alterations in the oral microbiome have been associated with head and neck cancers. These niches may serve

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as additional sources of predictive or prognostic biomarkers and offer novel targets for therapeutic modulation.

Efforts to modulate the microbiota for therapeutic benefit include the use of prebiotics, probiotics, synbiotics, antibiotics, and dietary interventions. Probiotic supplementation with strains such as Lactobacillus and Bifidobacterium has shown promise in reducing chemotherapy-induced mucositis and diarrhea, though more data are needed regarding their impact on long-term cancer outcomes. Prebiotics, non-digestible fibers that stimulate beneficial bacteria, may also enhance treatment efficacy when combined with ICIs.

Fecal Microbiota Transplantation (FMT), a more direct method of microbial modulation, has entered clinical trials in oncology. Preliminary results from small studies suggest that transferring microbiota from ICI responders into non-responders can improve therapeutic outcomes. However, challenges such as donor selection, standardization of protocols, and regulatory concerns remain before this can become mainstream practice [8-10].

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