Editorial Commentary

The emerging role of intra-tumoral bacteria

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Following a period of little emphasis, focus on microbiota as a whole has grown steadily in recent decades. Research on the bacteria that constitute the human "holobiont" has probably been overlooked, and has deservedly gained ever-increasing attention recently.

A growing amount of literature is shedding light on the substantial influence that the microbiota has on several human systems, both in preserving a physiological homeostasis and contributing to pathological conditions.

According to a recent report, approximately 15% of cancer are attributable to recognized carcinogenic infections (1). Causative agents are predominately viruses (i.e., human papillomavirus, hepatitis B/C viruses, and Epstein-Barr virus). *H. pylori* is the strongest evidence of bacterial carcinogenetic role.

This field of research is as suggestive as tricky, and the precise impact of a singular bacterial species is extremely difficult to unravel. To begin, the number of bacteria that populate our body is astonishing, and the composition of each microbial community varies with age and the host's contingent or chronic comorbidities. In addition, the association of a bacterium with cancer does not imply correlation or causation. Although many studies suggest that the composition of the colonic microbiota influences tumor development and response to immunotherapies, conclusive evidence for each individual bacterial species is not yet well established.

The cancers developing from the epithelium of the colon or lung tracts are forcefully exposed to the resident epithelial surface microflora. While some resident bacteria exert a dominant role in inducing cancer development, others may function as symbiotics throughout tumoral growth. Focusing on colon cancer specifically, *F. nucleatum* can modify the transcriptome of colonic cells and promote tumor growth in mice that have been exposed to a common experimental colon carcinogen (2). Furthermore, this bacterium can translocate across the epithelium and can be detected in metastatic lesions (3). Moreover, some reports suggest an association between the degree of *F. nucleatum* infection, evaluated in terms of DNA load, and some molecular phenotypes such as microsatellite instability-high (MSI-H), or with the CpG island hypermethylation phenotype (CIMP) (4). Particularly, the role of the intra-tumoral microbiota in shaping the immune texture has recently been recognized (5,6).

The role of intra-tumoral bacteria has been revealed in other gastrointestinal cancers. Intra-tumoral microbiome is shown to be highly predictive of survival in different cancer

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types, probably by shaping immune infiltration and T cell activation (7,8).

A pivotal study in pancreatic cancer patients elucidated the prognostic value of specific intra-tumoral signatures (i.e., *Pseudoxanthomonas-Streptomyces-Saccharopolyspora-Bacillus clausii*) (7). With the advent of immunotherapy, the predictive role of tumor associated bacteria in terms of response is undoubtedly worth of investigation.

Recently Wu *et al*. investigated the role of intra-tumoral *Streptococcus* signatures as predictive of response to neoadjuvant chemoimmunotherapy (9). The authors identified bacteria-like structures both intracellularly and extracellularly by transmission electron microscopy. The presence of intra-tumoral bacteria was further confirmed by quantitative real-time polymerase chain reaction (qRT-PCR) (9). The authors also reported a greater abundance of *Streptococcus* in the neoadjuvant chemo-immunotherapy responder subgroups and identified live *Streptococcus* in cultured dissociated tumor cells. The reported the area under the curve (AUC) value of *Streptococcus* in discriminating neoadjuvant chemo-immunotherapy responders was higher than 0.8 (9). Intriguingly, this signature seems to correlate with $CD8^+$ T-cell infiltration and fecal microbiota transplantation experiments in mice confirmed the potential of microbiota from responder donors in enhancing the immune infiltrations and tumor response after anti-programmed cell death protein 1 (PD-1) treatment (9).

This intriguing research could be a first step to prompt the investigations on intra-tumoral bacterial species that may impact on tumoral immune-infiltrate and cancer response.

Conclusions

These new findings confirm the role of tumor resident bacterial signature in modifying cancer response to immunotherapies and pave the way for a detailed evaluation of the role of distinct bacterial species that colonize tumors.

Interestingly, the intertumoral microbiota likely varies depending on where the cancer is located, particularly for tumors that develop from an epithelial layer rather than an internal organ.

Probably, the aerobic, anaerobic or facultative metabolisms of each bacterial species, as well as their intracellular growth capacity, could have an impact on the colonization and/or "mutualism" between the bacteria and different tumor histotypes or even on the distinct localization at inside the tumor itself.

The potential of microbial products in cancer treatment has long been proposed with contradictory results (10,11). In particular, the inherent anti-tumor activity of certain streptococcal strains has already been studied (11).

New investigations into the microbial communities of the tumor microenvironment (TME) and their relationship with the tumor immune microenvironment (TIME) are strictly required to finally exploit the suggested antitumor potential of some bacterial strains.

Finally, an interdisciplinary approach combining various expertise, such as biologist, microbiologist, pharmacologist, chemical, immunologist, and medical oncologist, is essential to fully define the therapeutic potential of the tumor microbiome effectively.

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