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COMMENTARY

A new paradigm for treating lung cancer by targeting the intratumoral microbiome

KEY WORDS

Intratumoral microbiome;
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Extracellular vesicles

Microorganisms reside throughout the human body, including the skin, oral cavity, and gastrointestinal tract. Advances in next-generation sequencing have provided unprecedented insights into microbial communities and their associations with human health and disease. The traditional view of tumor tissue as a "sterile" site has been overturned: diverse microbial communities have now been identified in various solid tumors[1-3], including lung cancer[4,5]. Although recent methodological refinements have led to lower estimated microbial loads within tumors, the existence of an intratumoral microbiome remains well supported and, indeed, more rigorously confirmed[6,7].

Tumor progression is regulated by its surrounding tumor microenvironment (TME), which comprises immune cells, cytokines, and other non-immune components[8]. As the polymorphic microbiota is increasingly recognized as a tumor hallmark, crosstalk between microbes and immune cells within the TME has become a major research focus. For example, M2-type macrophage infiltration is elevated in "bacteria-dominant" and "HBV-dominant" subtypes of hepatocellular carcinoma[9]. In ovarian cancer, microbial profiles differ between "immune-enriched" and "immune-deficient" tissues, and intratumoral *Acinetobacter* has been shown to inhibit macrophage migration[10]. Notably, the impact of intratumoral microbes on anti-tumor immunity is dual-faceted: they can activate anti-tumor responses through STING signaling, T/NK-cell activation, tertiary lymphoid structure maturation, and microbial antigen presentation; conversely, they may suppress immunity by upregulating ROS, fostering an anti-inflammatory milieu, inactivating T cells, and promoting immunosuppression[11]. Because the efficacy of immune-checkpoint inhibitors (ICIs) depends on the immune status of the TME, dismantling immunosuppressive networks is crucial to maximizing ICI response[11].

Given the evidence for microbiome−immunity interplay within tumors, targeting intratumoral microbes represents a promising therapeutic approach. Current strategies mainly aim to eliminate harmful bacteria (*e.g.*, with antibiotics) or supplement beneficial ones (*e.g.*, probiotics). However, these approaches often lack specificity, risk harming commensal flora, and may disrupt systemic microbial balance[12]. A central challenge remains: how can we precisely and personally reshape the intratumoral microbial ecosystem? Owing to high inter-patient variability in intratumoral microbiota, a "one-size-fits-all" strategy has limited potential.

In a recent study, Jin Yang and colleagues analyzed lung adenocarcinoma (LUAD) samples using single-cell RNA sequencing (scRNA-seq). They identified five bacterial genera, *Lysinibacillus*, *Stenotrophomonas*, *Weissella*, *Comamonas*, and Aeromonas, with significantly different abundances between tumor and adjacent normal tissues. By correlating their presence with immune infiltration patterns, the authors classified *Lysinibacillus* and *Stenotrophomonas* as "harmful" (associated with immunosuppression) and *Weissella*, *Comamonas*, and *Aeromonas* as "beneficial" (related to anti-tumor immune activation). Guided by the principle of "selectively eliminating harmful bacteria while preserving/promoting beneficial ones", they screened a compound library and identified the natural product berberine as a dual-action modulator. *In vitro*, berberine inhibited the growth of the two "harmful" bacteria while stimulating the "beneficial" ones. To overcome berberine's poor aqueous solubility and limited tumor targeting, the team encapsulated it into tumor cell-derived extracellular vesicles (EVs), generating EV-ber. This biomimetic

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carrier has a natural tumor-targeting advantage and can efficiently deliver berberine to the tumor site. In murine models, EV-ber reshaped the intratumoral microbiome towards an anti-tumor phenotype and boosted anti-tumor immunity (such as increasing $CD8^+$ T cells and promoting the polarization of macrophages to the M1 type). Furthermore, EV-ber inhibited *in situ* tumor growth and distant metastasis and synergized with anti-PD-L1 immunotherapy.

This study has successfully addressed three pivotal challenges in the current field of targeting intratumoral microbiome: first, it defines individualized microbial targets by shifting from population level patterns to patient specific signatures through scRNA-seq, thereby providing a strong rationale for personalized intervention; second, it achieves selective microbiome modulation through berberine's ability to simultaneously suppress harmful bacteria while promoting beneficial ones, thus avoiding the non-specific effects of broad spectrum antibiotics and enabling precise microbial editing; and third, it enables efficient and tumor targeting drug delivery by employing tumor derived extracellular vesicles, which overcome the pharmacokinetic limitations of free berberine and allow for low toxicity targeted therapy.

The strategy shifts from mere "eradication" to "re-education" of the intratumoral microbiome, aiming to reconstruct a microbial ecosystem that favors anti-tumor immunity. Its integrated "detection−subtyping−intervention" framework lays the groundwork for future companion diagnostics and personalized treatment regimens. The successful combination of microbial intervention and immune checkpoint inhibitors offers a promising therapeutic approach for overcoming immunotherapy resistance. Moreover, the "EVs + functional molecule" delivery platform could be extended to other microbiome-associated conditions, such as inflammatory bowel disease or metabolic syndrome.

Several limitations warrant attention in future research: the translatability of findings may be constrained by species differences, as the study was conducted in mouse models, and substantial distinctions between murine and human intratumoral microbiomes and immune systems necessitate validation of the five bacterial genera in larger clinical cohorts; moreover, while EV-ber was shown to remodel the microbiome and influence antitumor immunity, the specific molecular pathways, such as how bacterial metabolites communicate with immune cells, remain to be fully elucidated; additionally, the long-term safety of sustained intratumoral microbiome manipulation, including risks of microbial resistance and off target effects, awaits further prolonged assessment.

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