Tumor-resident intracellular bacteria benefit metastasis

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Emerging evidence has revealed that bacteria are present in a variety of tumor types, including those thought to be sterile, such as brain and renal tumors (1-4). Indeed, tumors contain unique microbial communities that differ according to the tumor type and may persist during metastatic progression. Accordingly, polymorphic microbiomes have been newly assigned as a cancer hallmark (5). Intratumoral microbes, which frequently localize inside tumor cells, can directly or indirectly modulate the effectiveness of anticancer treatments by metabolizing drugs or by regulating antitumor immune responses (6-9). Currently, tumor-resident intracellular bacteria are an emerging field of cancer research; however, how intracellular bacteria regulate tumor progression remains unclear.

Tumor cells metastasize to distant organs in the course of their progression. Individuals with metastatic cancer typically have a poor prognosis; however, other than early treatment intervention, there is no way to avoid metastasis. In order to develop strategies to prevent metastasis, research is often focused on elucidating the mechanisms underlying tumor metastasis and the factors that affect this process. A recent study by Fu *et al.* (10) demonstrated that tumor-resident intracellular bacteria can improve the survival of circulating tumor cells and promote tumor metastasis, shedding new light on the mechanism by which tumors spread to other organs. Furthermore, Fu *et al.* (10) explored the functional significance of tumor-resident intracellular bacteria using the spontaneous mouse breast-tumor mouse mammary tumor virus-polyoma middle tumor-antigen (MMTV-PyMT) model. Bacteria were present in both tumorous and non-tumorous breast tissue. Similar species of bacteria were present in both types of tissue, but the number of bacteria in tumorous tissue was nearly 10-fold higher than that in non-tumorous tissue. Further analysis identified different microbial communities in tumorous and non-tumorous breast tissue. Specifically, the tumorous tissue had lower bacterial alpha diversity than the non-tumorous tissue, with *Staphylococcus*, *Enterococcus*, *Streptococcus*, and *Lactobacillus* forming the main components of the tumor microbiota. Intriguingly, recent research has linked these bacterial species to the production of quorum sensing peptides, which facilitate cancer metastasis (11).

The influence of intratumoral bacteria on tumor growth and progression differs from that of gut bacteria. Stool from colorectal cancer patients gavaged to mice altered the gut microbiome and upregulated genes involved in angiogenesis and metastasis in intestinal cells (12). Further, bacterial infections themselves have the potential to induce angiogenesis, a process that contributes to the formation of cancer metastasis (13). Most intratumoral bacteria inhabit the perinuclear cytoplasm of tumor cells (8,10,14). The elimination of intratumoral bacteria via the intravenous administration of antibiotics reduced the volume of metastatic lung tumors but did not affect primary tumor growth, suggesting that tumor-resident bacteria play a role in tumor metastasis, but not in tumor growth (10). In contrast, the elimination of gut and intratumoral bacteria via the oral administration of antibiotics reduced the tumor volume of both primary and metastatic tumors, indicating the role played by gut bacteria in tumor growth.

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Intratumoral bacteria can promote metastatic colonization. When recombinant *Staphylococcus xylosus* (*S. xylosus*) was applied to the primary breast tumor, the recombinant clones were observed in most lung areas where metastatic tumors were present but could not be identified in lung tissue without metastases (10). Furthermore, when recombinant *S. xylosus* was injected via the tail vein, the recombinant clones were detected in the lung only when injected with tumor cells. Indeed, the bacterial injection alone, even at a high dose, did not lead to the formation of colonies in the lung (10). These results suggest that bacteria travel through the circulatory system and settle in distant organs only when combined with tumor cells. When various bacteria, including *S. xylosus*, *Lactobacillus animalis* (*L. animalis*), and *Spilopsyllus cuniculi* (*S. cuniculi*), were injected into antibiotic-treated primary tumors, these bacteria invaded the tumor cells and increased the burden of metastatic lung tumors, but had no impact on the growth of the primary tumor (10). These results also suggest the role played by intratumoral bacteria not in tumor growth but in metastatic colonization.

Tumor-resident intracellular bacteria can increase the survival of tumor cells under mechanical stress during circulation. Single-cell RNA sequencing analysis of bacteria-containing cancer cells revealed that the invasion of tumor cells by *S. xylosus*, *L. animalis*, *S. cuniculi*, and *Streptococcus sanguinis* specifically activated the fluid shear stress pathway (10). When cancer cells enter the bloodstream during metastasis, they frequently undergo apoptosis due to fluid shear stress (15,16). However, bacteria-containing tumor cells exhibit higher viability than tumor cells without bacteria, possibly owing to the role played by intracellular bacteria in modulating the stress response (10). Indeed, stress fiber strength was significantly reduced after bacterial invasion into the tumor cells, suggesting that mechanical stress-induced contraction forces can be relieved by intracellular bacteria (10). Additionally, bacteria-containing tumor cells exhibited increased adherence and spread on a plate, suggesting that intracellular bacteria can modify the construction of the actin cytoskeleton.

The abovementioned findings have increased our understanding of how intratumoral bacteria benefit tumor progression and/or metastasis. Some mechanisms underlying tumor metastasis have been identified and may be targeted early to prevent metastasis (17). A recent study revealed that bacterial distribution within a tumor microenvironment is not random but is organized in microniches with specific tumor-promoting functions of immune and epithelial cells (14). Nevertheless, knowledge of the role of intratumoral bacteria in tumor progression is still limited and warrants further research.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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