

## Reprogramming Autophagy through the Intratumoral Microbiome in Oral Squamous Cell Carcinoma

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### ABSTRACT

Dear Editor-in-Chief,

Autophagy is no longer considered merely a cellular recycling mechanism but rather a critical regulator of metabolic adaptation, immune homeostasis, and stress responses. In cancer, its dual function enables context-dependent effects, acting as a tumor-suppressive mechanism during early carcinogenesis while supporting tumor survival and therapeutic resistance in established malignancies. Among stress-response pathways, autophagy occupies a central position at the interface of cellular metabolism, immune regulation, and microbial sensing. Dysregulated autophagy has been implicated in metabolic reprogramming, immune evasion, tumor progression, and resistance to anticancer therapies [1].

The intratumoral microbiome is increasingly recognized as a potential functional component of the tumor microenvironment (TME). Tumor-resident microorganisms and their metabolites can influence tumor biology, immune activity, and therapeutic responses, rather than acting merely as passive bystanders [2,3]. Importantly, microbial communities can engage in dynamic crosstalk with host signaling and metabolic pathways, including autophagy, while autophagy itself contributes to the regulation of host-microbe interactions and immune responses. The biological consequences of this bidirectional interplay are likely to depend on the microbial composition, cancer type, disease stage, and characteristics of the surrounding TME [4].

Oral squamous cell carcinoma (OSCC) provides a useful model for studying this interaction because it develops in a microbiota-rich environment where epithelial cells, immune cells, and microorganisms continuously interact.

Increasing evidence indicates that oral microorganisms can directly influence tumor behavior through inflammatory signaling, immune modulation, and alteration of host cellular pathways. Importantly, recent experimental studies have provided direct evidence linking specific oral microorganisms to autophagy in oral cancer. *Porphyromonas gingivalis* has been shown to promote OSCC progression by modulating autophagy [5], while outer membrane vesicles derived from *Fusobacterium nucleatum* activate autophagic flux and promote oral cancer invasion and metastasis [6]. Together, these findings suggest that microbial signals can actively shape autophagic responses in oral cancer.



These observations raise a broader question: do individual microorganisms exert isolated effects on autophagy, or does the intratumoral microbial ecosystem collectively shape autophagic plasticity within OSCC? Although specific microorganism–autophagy interactions have now been demonstrated, the broader relationship between the intratumoral microbiome and autophagy remains poorly defined. We propose that the intratumoral microbiome may function as an upstream regulator of autophagic plasticity, with the potential to influence tumor adaptation, immune escape, and therapeutic responsiveness. In this context, alterations in microbial composition or microbial-derived metabolites could potentially reprogram autophagic activity and modify the response of tumor cells to anticancer therapies. This concept also suggests a potential therapeutic opportunity. Rather than targeting autophagy or the tumor-associated microbiome independently, future approaches could explore whether manipulation of the intratumoral microbiome can be used to reprogram autophagy and restore therapeutic sensitivity. Such strategies may include targeted modulation of microbial communities or their metabolites, potentially in combination with agents that regulate autophagic activity. Future studies should therefore investigate the microbiome–autophagy axis at the level of microbial composition, microbial metabolites, host signaling pathways, and treatment response. Establishing the causal relationships within this axis could provide a new conceptual framework for precision therapeutic strategies in OSCC.

**Keywords:** Autophagy; Intratumoral Microbiome; Reprogramming; Oral Squamous Cell Carcinoma

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