The Intersection of the Upper Gastrointestinal Microbiome and Oesophageal Cancer: A Review of Pathways and Therapeutic Insights

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Abstract

The upper gastrointestinal microbiome, a complex ecosystem of microorganisms that have historically been difficult to identify, may play a pivotal role in the development of oesophageal cancer and postoperative outcomes. Dysbiosis, characterised by imbalances in microbial composition, is believed to drive tumorigenesis in various gastrointestinal cancers through mechanisms such as chronic inflammation, immune suppression, and epithelial barrier dysfunction. Additionally, dysbiosis may contribute to postoperative complications, including anastomotic leaks and infections following surgery. Most research to date has focused on colorectal cancer, demonstrating these complex relationships. Pathogenic bacteria exacerbate the dysregulation processes through mechanisms including pro-inflammatory cytokine release, immune evasion, and biofilm formation. Therapeutic strategies targeting microbiome hold promise for restoring microbial balance, reducing systemic inflammation, and improving surgical outcomes. This review synthesises current evidence on the microbiome's role in oesophageal cancer pathogenesis and postoperative outcomes, highlighting opportunities for therapeutic interventions and the potential for integrating microbiome strategies into oesophageal cancer management protocols.

Key Points

1. Dysbiosis promotes chronic inflammation, immune suppression, and epithelial barrier dysfunction, which can lead to tumorigenesis.

2. Microbial imbalances can exacerbate postoperative outcomes like anastomotic leaks and infections, as well as possible resistance to chemo- and radiation therapy.

3. Strategies include prebiotics and probiotics to restore microbial balance, targeted antimicrobial therapy to eliminate specific pathogens, and personalised microbiome-based diagnostics for tailored interventions.

INTRODUCTION

The gastrointestinal microbiome, a complex ecosystem of microorganisms residing in the oral cavity to the lower gut, may play a significant role in maintaining overall health. In recent years, the upper gastrointestinal (UGI) microbiome involvement in the pathogenesis of oesophageal cancer (EC) has garnered considerable attention. Emerging evidence suggests that dysbiosis, or the imbalance of the UGI microbiome, contributes to chronic inflammation, immune dysregulation, and carcinogenic processes, potentially increasing the risk of developing EC.[1,2]

This review aims to explore the multifaceted role of the UGI microbiome in EC, focusing on its contribution to cancer development and its influence on treatment outcomes. It will examine the mechanisms by which microbial dysbiosis promotes tumorigenesis, including its effects on inflammation, immune modulation, and epithelial barrier function. Additionally, the authors highlight the potential impact of the UGI microbiome on complications and recovery after EC surgery, such as infections, anastomotic healing, and resistance to adjuvant therapy. By synthesising current evidence, the authors aim to identify opportunities for therapeutic interventions, such as microbiome modulation, and to provide insights into the potential for integrating microbiome-targeted strategies into the management of EC.

UPPER GASTROINTESTINAL MICROBIOME IN OESOPHAGEAL CANCER

While the direct role of oesophageal microbiota in the pathogenesis of EC remains incompletely understood, emerging evidence highlights significant interactions between these microbes and tumour biology. Among these findings, microbial dysbiosis has gained recognition as a critical factor contributing to EC development.[3] Recent studies highlight the microbiome's role in promoting tumorigenesis through mechanisms involving chronic inflammation, immune modulation, and disruption of epithelial barrier function.[1,2,4] Pathogenic bacteria such as *Porphyromonas gingivalis* (*P. gingivalis*) and *Fusobacterium nucleatum* (*F. nucleatum*), commonly associated with periodontal disease or gingivitis, are found in higher abundance in the oesophageal tissues of patients with EC.[5,6] These bacteria can induce persistent inflammation by activating toll-like receptors and the NF-κB signalling pathway, triggering the production of pro-inflammatory cytokines.[5,6] This inflammatory cascade fosters a microenvironment that supports cellular proliferation, angiogenesis, and the survival of transformed cells.[7] Furthermore, chronic inflammation associated with microbial dysbiosis creates conditions favourable to DNA damage, oxidative stress, and impaired DNA repair mechanisms, all of which contribute to tumour initiation and progression.[8]

In addition to promoting inflammation, these pathogens can modulate the immune response, facilitating immune evasion by cancer cells. For instance, *F. nucleatum* has been shown to bind to immune receptors like TIGIT on T cells, suppressing their cytotoxic function.[9] Simultaneously, the dysbiotic microbiota may recruit immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells to the tumour microenvironment, further dampening antitumor immune responses.[10] This immunosuppressive milieu not only allows tumour cells to evade immune surveillance but can also facilitate their growth and metastasis.

Furthermore, microbial dysbiosis can compromise the integrity of the oesophageal epithelial barrier. Pathogenic bacteria associated with dysbiosis degrade tight junction proteins, such as occludin and claudins, weakening the epithelial barrier.[11] This breach enables bacterial translocation and systemic dissemination of microbial metabolites, such as lipopolysaccharides. Lipopolysaccharides act as a potent endotoxin, binding to Toll-like receptors on epithelial and immune cells, triggering chronic inflammation and promoting epithelial-mesenchymal transition, a key process in cancer metastasis.[4]

UPPER GASTROINTESTINAL MICROBIOME IMPACT ON OESOPHAGEAL CANCER TREATMENT OUTCOMES

Beyond its role in cancer development, the UGI microbiome may also significantly impact outcomes following EC surgery. Postoperative complications, such as anastomotic leaks and infections, have been linked to microbial imbalances in the gastrointestinal tract, including the oral cavity.[12,13] Bacterial translocation during surgery, compounded by pre-existing dysbiosis, may exacerbate these complications.[14] Furthermore, the UGI microbiome's influence on systemic inflammation and immune modulation could affect wound healing and recovery, emphasising the importance of understanding its role in surgical outcomes.[15]

Prior work investigated the relationship between the diversity of oral and gastric microbiomes and the incidence of anastomotic leaks following esophagectomy.[12] They found that patients who developed post-operative anastomotic leaks exhibited greater variability in their oral and gastric microbiomes at the time of surgery compared to those who did not experience leaks.[12] This increased variance suggests a potential link between microbiome diversity and the risk of postoperative complications. The impact of the microbiome on postoperative colorectal anastomotic leaks has been demonstrated multiple times, supporting this paradigm.[13,16-19] The microbiome may also play a role in influencing cancer treatment outcomes. In gastrointestinal cancers, the microbiome can modulate drug resistance, with studies showing that gut bacteria impact the metabolism of chemotherapy agents, alter immune responses, and reshape the tumour microenvironment.[20] For example, the gut microbiota can exacerbate chemoresistance through mechanisms such as enhancing senescence-associated secretory phenotypes, as seen in *F. nucleatum*, which promotes oesophageal squamous cell carcinoma resistance to platinum-based chemotherapy by activating DNA damage response pathways.[21] Similarly, microbiota dysbiosis can affect the efficacy of immunotherapies and radiotherapies, with pathogenic bacteria fostering an environment that undermines treatment.[20,21]

F. nucleatum and *P. gingivalis* have been increasingly recognised as key players in systemic inflammation, impaired wound healing, and heightened susceptibility to postoperative infections.[5,6] These bacteria are known to produce virulence factors that can degrade host tissues and evade immune responses. *F. nucleatum* is capable of adhering to and invading host cells, disrupting tight junction proteins, and compromising the integrity of epithelial barriers.[6,22] This not only facilitates bacterial translocation from the oral cavity to distant surgical sites but also allows for the systemic dissemination of bacterial toxins and metabolites, further fuelling inflammation.

Once these pathogenic microbes translocate to surgical sites, they contribute to local tissue damage and immune dysfunction, significantly increasing the risk of complications such as anastomotic leaks and surgical site infections. The presence of bacteria such as *P. gingivalis* at the surgical site has been shown to stimulate the release of pro-inflammatory cytokines like IL-6 and TNF-α, which exacerbate tissue damage and delay the healing of anastomotic junctions.[23] Furthermore, bacterial biofilm formation on sutures or wound surfaces can act as a physical barrier to immune cells and antibiotics, further complicating infection management.[24]

OPPORTUNITIES FOR THERAPEUTIC INTERVENTIONS

Therapeutic interventions targeting the microbiome present a promising frontier in the management and treatment of EC. The microbiome plays a critical role in modulating inflammation, immune responses, and tissue repair, all of which are central to cancer progression and surgical outcomes. By addressing dysbiosis, clinicians may be able to improve patient outcomes by reducing inflammation, enhancing immune function, and promoting epithelial barrier integrity. Maintaining oral health appears to be crucial for improving dysbiosis, which may influence the development of UGI tumours and impact treatment outcomes.[1,25] Poor oral health and its associated microbiome changes have been linked to various disease processes.[26-28] Tobacco use has been shown to disrupt the microbiome, while tobacco cessation could improve oral health and potentially mitigate microbial dysbiosis.[29,30]

One potential intervention is the use of probiotics and prebiotics to restore microbial balance. Probiotics, which introduce beneficial bacteria, can help suppress the growth of pathogenic species such as *F. nucleatum* and *P. gingivalis*, both of which have been implicated in EC progression and postoperative complications.[31] Prebiotics, which serve as nutrients for beneficial bacteria, can further encourage a healthy microbiome composition.[32] This combination can reduce systemic inflammation, improve immune regulation, and potentially mitigate adverse outcomes like anastomotic leaks and infections following esophagectomy.

Another promising strategy involves targeted antimicrobial therapies, such as the use of narrow-spectrum antibiotics or bacteriophages to selectively eliminate pathogenic bacteria while preserving beneficial species.[33] Unlike broad-spectrum antibiotics, which disrupt the entire microbial community, targeted approaches can address specific pathogens without causing collateral damage to the microbiome. Such therapies could be particularly useful in preoperative settings, reducing microbial burden and the risk of translocation of harmful bacteria during surgery.

In addition, recent research has underscored the significant influence of the microbiome on the efficacy of immunotherapy in EC. Studies have demonstrated that specific microbial profiles are associated with improved responses to immune checkpoint inhibitors, while dysbiosis correlates with treatment resistance.[34,35] For instance, certain bacterial species within the gut microbiome can enhance antitumour immunity by promoting the infiltration and activation of cytotoxic T cells within the tumour microenvironment.[34] Conversely, the presence of pathogenic bacteria may foster an immunosuppressive milieu, hindering the effectiveness of immunotherapeutic agents.[34]

Interventions aimed at modulating the microbiome are being explored to improve immunotherapy outcomes in patients with EC. Approaches such as the administration of probiotics, prebiotics, and dietary modifications seek to enrich beneficial microbial populations, thereby fostering a more favourable immune environment.[31,32] Additionally, faecal microbiota transplantation has been investigated as a means to restore a healthy microbiome composition, with some studies showing enhanced responses to immune checkpoint inhibitors following faecal microbiota transplantation.[36] These therapeutic strategies aim to shift the microbiome towards a state that supports robust antitumour immunity, potentially overcoming resistance to immunotherapy.

Finally, the emerging field of microbiome-based diagnostics and personalised medicine offers exciting opportunities for tailoring treatments. By analysing the microbiome composition of individual patients, clinicians could identify high-risk microbial profiles associated with poor outcomes.[37] This information could guide interventions, such as preoperative microbiome modulation or postoperative monitoring for complications. Additionally, combining microbiome therapies with conventional treatments like chemotherapy or immunotherapy could enhance their efficacy by mitigating treatment-associated dysbiosis and inflammation. Continued research into these therapeutic avenues holds the potential to transform the management of EC.

CONCLUSION

The UGI microbiome may potentially play a critical role in the development of EC and in influencing postoperative outcomes. Dysbiosis can drive chronic inflammation, immune suppression, and epithelial barrier dysfunction, which contribute to tumorigenesis. Additionally, microbial imbalances exacerbate postoperative complications, including anastomotic leaks and infections, by promoting systemic inflammation, delaying tissue healing, and enabling bacterial translocation to surgical sites. These imbalances can also contribute to poor treatment outcomes by fostering resistance to chemotherapy and other therapeutic interventions.

Therapeutic strategies targeting the microbiome offer significant potential to improve EC management. Approaches such as prebiotics, probiotics, and targeted antimicrobial therapies could restore microbial balance, reduce inflammation, and enhance immune responses. While these strategies are promising, further research is needed to better understand the microbiome's complex role in EC and to validate the clinical benefits of microbiome-based therapies.

References

1. Liu X et al. From microbes to medicine: harnessing the power of the microbiome in esopha-geal cancer. Front Immunol. 2024;15:1450927.
2. Talapko J et al. The impact of oral microbiome dysbiosis on the aetiology, pathogenesis, and development of oral cancer. Cancers. 2024;16(17):2997.
3. Baima G et al. The gum–gut axis: periodontitis and the risk of gastrointestinal cancers. Can-cers. 2023;15(18):4594.
4. Sharma T et al. Cross-talk between the microbiome and chronic inflammation in esophageal cancer: potential driver of oncogenesis. Cancer Metastasis Rev. 2022;41(2):281-99.
5. Gao S et al. Presence of Porphyromonas gingivalis in esophagus and its association with the clinicopathological characteristics and survival in patients with esophageal cancer. Infect Agent Cancer. 2016;11(1):3.
6. Lei J et al. Fusobacterium nucleatum promotes the early occurrence of esophageal cancer through upregulation of IL -32/ PRTN3 expression. Cancer Sci. 2023;114(6):2414-28.
7. Cao Y et al. NF-κB signaling pathway in tumor microenvironment. Front Immunol. 2024;15:1476030.
8. Ivleva EA, Grivennikov SI. Microbiota-driven mechanisms at different stages of cancer de-velopment. Neoplasia. 2022;32:100829.
9. Gur C et al. Binding of the Fap2 protein of fusobacterium nucleatum to human inhibitory re-ceptor TIGIT protects tumors from immune cell attack. Immunity. 2015;42(2):344-55.
10. Mohseni AH et al. Potential links between the microbiota and T cell immunity determine the tumor cell fate. Cell Death Dis. 2023;14(2):154.
11. Quante M et al. Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. Cancer Cell. 2012;21(1):36-51.
12. Reddy RM et al. Increased variance in oral and gastric microbiome correlates with esoph-agectomy anastomotic leak. Ann Thorac Surg. 2018;105(3):865-70.
13. Russ A, Casillas M. Gut microbiota and colorectal surgery: impact on postoperative compli-cations. Clin Colon Rectal Surg. 2016;29(03):253-7.
14. Doudakmanis C et al. Bacterial translocation in patients undergoing major gastrointestinal surgery and its role in postoperative sepsis. World J Gastrointest Pathophysiol. 2021;12(6):106-14.
15. Kleinstein SE et al. Inflammatory networks linking oral microbiome with systemic health and disease. J Dent Res. 2020;99(10):1131-9.
16. Boatman S et al. The influence of the microbiome on anastomotic leak. Clin Colon Rectal Surg. 2023;36(2):127-32.
17. Hajjar R et al. Modulating gut microbiota prevents anastomotic leak to reduce local Implan-tation and dissemination of colorectal cancer cells after surgery. Clin Cancer Res. 2024;30(3):616-28.
18. Hajjar R et al. Basal levels of microbiota-driven subclinical inflammation are associated with anastomotic leak in patients with colorectal cancer. Gut. 2024;73(6):1031-3.
19. Hajjar R et al. Gut microbiota influence anastomotic healing in colorectal cancer surgery through modulation of mucosal proinflammatory cytokines. Gut. 2023;72(6):1143-54.
20. Garajová I et al. The role of the microbiome in drug resistance in gastrointestinal cancers. Expert Rev Anticancer Ther. 2021;21(2):165-76.
21. Zhang JW et al. Fusobacterium nucleatum promotes esophageal squamous cell carcinoma progression and chemoresistance by enhancing the secretion of chemotherapy-induced senescence-associated secretory phenotype via activation of DNA damage response pathway. Gut Microbes. 2023;15(1):2197836.
22. Fan Z et al. Fusobacterium nucleatum and its associated systemic diseases: epidemiologic studies and possible mechanisms. J Oral Microbiol. 2023;15(1):2145729.
23. Pollreisz A et al. Enhanced monocyte migration and pro-inflammatory cytokine production by Porphyromonas gingivalis infection. J Periodontal Res. 2010;45(2):239-45.
24. Zhao A et al. Understanding bacterial biofilms: from definition to treatment strategies. Front Cell Infect Microbiol. 2023;13:1137947.
25. Sadeghi F et al. Oral microbiome dysbiosis is associated with precancerous lesions and dis-orders of upper gastrointestinal tract: A population-based study. Am J Gastroenterol. 2024;doi:10.14309/ajg.0000000000003279.
26. Pathak JL et al. The role of oral microbiome in respiratory health and diseases. Respir Med. 2021;185:106475.
27. Liccardo D et al. Periodontal disease: a risk factor for diabetes and

cardiovascular disease. Int J Mol Sci. 2019;20(6):1414.

28. Herrera D, Sanz M, Shapira L, et al. Association between periodontal diseases and cardio-vascular diseases, diabetes and respiratory diseases: Consensus report of the Joint Work-shop by the European Federation of Periodontology (EFP) and the European arm of the World Organization of Family Doctors (WONCA Europe). J Clin Periodontol. 2023;50(6):819-41.
29. Kumar PS et al. Tobacco smoking affects bacterial acquisition and colonization in oral bio-films. Morrison RP, ed. Infect Immun. 2011;79(11):4730-8.
30. Kadam S et al. Looking beyond the smokescreen: can the oral microbiome be a tool or tar-get in the management of tobacco-associated oral cancer? Ecancermedicalscience. 2021;15:1179.
31. Zhu Y et al. Competition between yogurt probiotics and periodontal pathogens in vitro. Acta Odontol Scand. 2010;68(5):261-8.
32. Zhou P et al. Unveiling the therapeutic symphony of probiotics, prebiotics, and postbiotics in gut-immune harmony. Front Nutr. 2024;11:1355542.
33. Stone VN, Xu P. Targeted antimicrobial therapy in the microbiome era. Mol Oral Microbiol. 2017;32(6):446-54.
34. Dadgar N et al. The influence of the microbiome on immunotherapy for gastroesophageal cancer. Cancers. 2023;15(18):4426.
35. Zhang W et al. Immune checkpoint inhibitors for esophageal squamous cell carcinoma: a narrative review. Ann Transl Med. 2020;8(18):1193.
36. Kim MS et al. Lung cancer surgery for patients with reduced left ventricular ejection frac-tion: clinical outcomes and long-term survival. Eur J Cardiothorac Surg. 2023;63(5):ezad152.
37. Shukla V et al. Targeting the microbiome to improve human health with the approach of personalized medicine: Latest aspects and current updates. Clin Nutr ESPEN. 2024;63:813-20.