Influence of tumor mycobiome on cancer pathogenesis (Review)

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Received March 17, 2023; Accepted October 18, 2023

DOI: 10.3892/ol.2023.14128

Abstract. Cancer tissues harbor a large microbiome. There is growing evidence that the tumor microbiome is significantly correlated with the prognosis of cancer patients, but the exact underlying mechanisms have remained elusive. Although the tumor mycobiome is less abundant than the biome of bacteria, it is prevalent in most cancers in humans. The present review describes in detail the impact of the tumor mycobiome on cancer pathogenesis. The tumor mycobiome promotes tumor progression and metastasis by affecting the human immune system, maintaining a pro-inflammatory environment, producing aflatoxins, attenuating cell adhesion mechanisms and fungal-bacterial interactions. Furthermore, the tumor mycobiome likewise has great potential for cancer prevention, diagnosis and treatment.

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Key words: fungi, cancer, tumor mycobiome, tumor microbiome

1. Introduction

Cancer is not only a major public health problem worldwide, but also one of the leading causes of human mortality. Host-microbe immune interactions profoundly influence cancer development, progression and treatment outcomes (1-11). Fungi and bacteria co-colonize the mammalian skin epithelium, respiratory tract, gastrointestinal tract and reproductive organs, forming a complex ecosystem of microbe-microbe and host-microbe interactions that significantly impact human health (12-21). Although only ~0.1% of microbial DNA is present in the gut (22), fungal infections cause more than 1.5 million deaths worldwide each year (23).

There is growing evidence linking the human microbiome (bacteria, fungi and viruses) to cancer and cancer outcomes (24,25). In recent years, several bacteria have been observed to be associated with cancer development and progression. *Helicobacter pylori* infection is the strongest risk factor for the development of malignant tumors in the stomach, and epidemiologic studies have determined that the attributable risk of gastric cancer due to *Helicobacter pylori* is ~75% (26). At the same time, in the lower gastrointestinal tract, genotoxic *Escherichia coli*, *Bacteroides fragilis*, *Streptococcus bovis* and *Fusobacterium nucleatum* are associated with the pathogenesis of colorectal cancer (27). Among these cancer-associated bacteria, they can modulate host immunity and cause chronic inflammation, which is thought to have oncogenic effects. Recent reports have also shown that bacterial DNA circulating in the blood of cancer patients can be used as a predictive biomarker for tumors (28,29) and intracellular bacteria have been found in numerous tumor types (30).

In recent times, scientists have been exploring the link between cancer and bacteria and viruses, but few studies have focused on the relationship between fungi and cancer. Although the human fungal biome is less abundant than the bacterial group, it can still significantly affect human health (31-33). Previous studies have demonstrated that fungal DNA is present in most human cancer tissues. However, the role and impact of the tumor mycobiome on cancer pathogenesis remain largely unknown.

2. Presence of tumor mycobiome within the tumor tissue

Narunsky-Haziza *et al* (34) statistically characterized the tumor mycobiome in 17,401 tissue, blood and plasma samples

from four independent cohorts of 35 cancer types using internal transcribed spacer sequencing and whole-genome sequencing methods. Statistics revealed that 5 fungi, including *Malasseziomycetes*, *Saccharomycetes*, *Diothideomycetes*, Sordariomycetes and *Candida*, were significantly enriched in all types of cancer (lung, breast, melanoma, osteosarcoma, ovarian, gastric, colorectal and head and neck tumors). By contrast, certain specific fungi (*Microbotryomycetes*, *Wallemiomycetes*, *Agaricomycetes*, *Tremellomycetes*) were only found in specific cancer sites, so the tumor mycobiome is prevalent in most cancers in humans (35).

3. Differences in fungal biome composition in cancer patients compared to healthy controls

Fungal biome imbalance was found in patients with gastric cancer. The fungal biome characteristics of patients with gastric cancer differed significantly from controls, with reduced diversity and enrichment of *Candida* and *Alternaria* in gastric cancer tissues (36). Colorectal fungi were altered in patients with colorectal cancer compared to normal subjects. Patients with colorectal cancer had increased *Malasseziomycetes*, decreased *Saccharomycetes* and a distorted ratio of *Basidiomycota* to *Ascomycota* (37). The distribution of the fungal genera *Aspergillus*, *Malassezia*, *Rhodotorula*, *Pseudogymnoascus*, *Kwoniella*, *Talaromyces*, *Debaryomyces*, *Moniliophthora*, *Pneumocystis* and *Nosemia* was altered in colorectal cancer, as verified in independent Chinese and European cohorts (38).

4. The tumor mycobiome is less abundant than the bacterial one, and both have a symbiotic relationship in tumors

Analysis of the tumor mycobiome in various body parts showed a maximum of 1 fungal cell per 10,000 tumor cells (39). In The Cancer Genome Atlas (TCGA) primary tumors, the average relative abundance of bacteria and fungi was 96 and 4%, respectively, which confirms the lower abundance of fungi compared to bacteria (34). It has been found that there is a symbiotic rather than competitive ecological interaction between fungal and bacterial biomes in the tumor microenvironment (35). However, this differs from the manifestation of alternating fungal and bacterial populations in the gastrointestinal tract (9,40).

5. The tumor mycobiome promotes cancer progression and metastasis

The tumor mycobiome not only resides in tumors but also promotes tumor progression and metastasis and spreads systemically by affecting the human immune system, maintaining a pro-inflammatory environment, producing aflatoxins, attenuating cell adhesion mechanisms and fungal-bacterial interactions (Fig. 1).

The tumor mycobiome affects the surveillance of cancer by the human immune system. As numerous cancer patients are immunosuppressed, they are more susceptible to fungal infections, which may further aggravate their condition (41). It has been demonstrated that fungal-driven pancreatic cancer occurs through complement cascade activation and IL-33 secretion (35). Aykut *et al* (31) have shown that *Malassezia* can secrete hydrolases to release host lipids and activate the C3 complement mannose-binding lectin pathway to promote an immunosuppressive tumor environment in pancreatic cancer. The tumor mycobiome activates dectin-1-mediated Src-Syk-caspase recruitment domain family member 9 (CARD9) signaling in the pancreas, leading to IL-33 secretion and tumor growth, and thus, this may be the mechanism by which the tumor mycobiome promotes pancreatic cancer progression (42).

The Colorectal Cancer Risk Factor Assessment report indicated that the human body has an inadequate immune response to fungi, such as inflammatory bowel disease (43) and ulcerative colitis (12). Antifungal treatment has been reported to exacerbate colitis and colorectal cancer, while colonic fungi enhance azoxymethane/dextran sodium sulfate-induced inflammatory vesicle activation in colitis (44).

The tumor mycobiome maintains a pro-inflammatory environment and promotes cancer progression. There are numerous hypotheses about tumor pathogenesis, among which the theory of an inflammatory mechanism is a widely accepted hypothesis. Inflammation is usually the basis for resistance to harmful stimuli, accelerating wound recovery and maintaining normal tissue function, and its role involves endothelial cells, immune cells and inflammatory factors (45).

Self-limiting acute inflammation benefits the healing process (46). However, when it gets out of control, it may develop into chronic inflammation that induces tissue lesions and predisposes to cancer (47), including tumorigenesis, progression and metastasis (48). Only a small percentage of cancers are attributed to germ cell lineage mutations, while 90% of cancers are associated with somatic mutations and environmental hazards, and the latter is always associated with chronic inflammation or infection (49). Epidemiological surveys have shown that inflammation is strongly associated with the development of ~20% of cancers (50). Available evidence suggests that hypoxia-associated inflammatory cytokines or chemokines, such as IL-1, IL-6 and TNF, are significantly elevated in the tumor microenvironment (51). Cancer patients may benefit from anti-inflammatory drugs, such as TNF blockers and non-steroidal anti-inflammatory drugs (52,53).

Malassezia. In cancer patients, higher levels of *Malassezi*a are associated with unfavorable prognosis (54). *Malassezia* also exhibits various pro-inflammatory biological properties, such as disruption of the epithelial barrier, enrichment of inflammatory factors and degradation of the extracellular matrix, all of which can promote tumor formation and malignant progression (54). *Malassezia* can activate NLR family pyrin domain containing 3 inflammasome via Dectin2/caspase recruitment domain family member 9 signaling and accelerate IL-1β production to exacerbate inflammation (55). Zhang *et al* (56) also demonstrated that *Malassezia* could produce nanovesicles rich in allergens or proteins, which may trigger and maintain inflammation by activating the NF-κB pathway and upregulating IL-6 production in the immune microenvironment (Fig. 2).

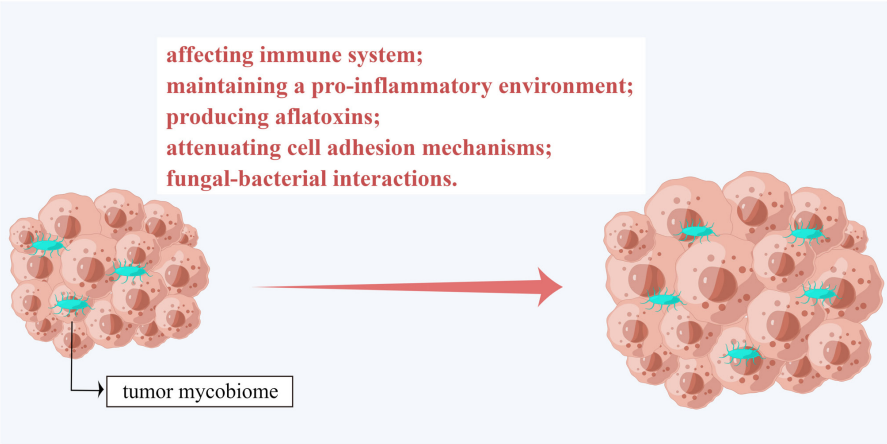

Figure 1. The tumor mycobiome promotes tumor progression and metastasis by affecting the human immune system, maintaining a pro-inflammatory environment, producing aflatoxins, attenuating cell adhesion mechanisms and fungal-bacterial interactions.

In addition, other mechanisms may be involved in *Malassezia*-associated inflammatory cancer transformation processes, such as DNA lesion accumulation and imbalance of oncogenes and anti-oncogenes. Inflammatory cells may induce DNA damage by releasing cytotoxic reactive oxygen species (57). A persistent inflammatory state may lead to increased and accumulated DNA damage in cells, which may promote genetic mutations, generate genomic instability and ultimately produce oncogenic effects (58).

Candida. *Candida* is functionally associated with a variety of cancers. Studies have shown that gastrointestinal cancers have different relative abundances of *Candida* and *Saccharomyce*, so gastrointestinal cancers can be classified as *Candida*- and *Saccharomyce*-associated tumors (35).

Candida-dominant tumors are associated with enhanced expression of IL-1 pro-inflammatory immune pathways and increased neutrophils, a major inflammatory cytokine that plays a crucial role in carcinogenesis and tumor progression (35). *Candida* increases inflammation, which promotes *Candida* colonization, thereby maintaining a pro-inflammatory environment, leading to a vicious cycle that persists (35). Therefore, prevention and management of *Candida* infection and associated inflammation may help to block this destructive inflammatory state in cancer and may be a reasonable combination therapy option during cancer treatment.

Of note, there are interactions between *Candida* and different bacteria in gastric cancer. *Candida* was observed to be positively correlated with *Lactobacillus* and negatively correlated with *Helicobacter pylori* (35).

The tumor mycobiome produces aflatoxins that promote cancer progression. Colorectal cancer is the third most common cancer type worldwide, with >500,000 related deaths per year (59,60). The contribution of the intestinal flora to colorectal cancer progression has been widely recognized (61-63). Intestinal fungi constitute a significant component of the human intestinal flora, but their role in colorectal cancer has remained elusive (64). Several studies have confirmed a correlation between intestinal fungi and colon cancer (38,44,65-67).

Lin *et al* (64) conducted a meta-analysis using shotgun metagenomics pooling 1,329 metagenomes from 8 cohorts (454 colorectal cancers, 350 adenomas and 525 healthy subjects) to evaluate the lesser bias of the gut fungal biome on colorectal cancer. Statistical analysis of the intestinal fungal biome composition showed that *Aspergillus rambellii* was identified as the most abundant fungal species. Seven of the eight cohorts showed a consistent association of *Aspergillus rambellii* with colorectal cancer. Further studies showed that *Aspergillus rambellii* promoted colorectal cancer cell growth *in vitro* and tumor growth in xenograft mice (64).

Aspergillus rambellii has been shown to have the ability to produce multiple aflatoxins (e.g., aflatoxin B, aflatoxin G and the aflatoxin precursor sterigmatocystin) (68-70). The association of *Aspergillus* spp. of fungi with cancer has been frequently reported (71). Aflatoxins are toxins of fungal origin classified as carcinogens and mutagens, exemplified by their powerful liver cancer-promoting effects (62). For instance, long-term consumption of foods containing aflatoxins was determined to be associated with a significantly increased risk of liver cancer (72). Because aflatoxins can damage macrophages and dendritic cells by activating Toll-like receptors, they can induce immune dysregulation and promote tumor progression (73,74) (Fig. 3).

The tumor mycobiome attenuates cell adhesion mechanisms and promotes cancer metastasis. In colon cancer, *Candida* not only predicts disease but is also associated with diminished cell adhesion mechanisms and tumor metastasis (35). Loss of epithelial barrier function and increased tight junction permeability are standard features of lower gastrointestinal cancers (75) and are high-risk factors for tumor metastasis (76). *Malassezia* can promote cancer metastasis by disrupting the epithelial barrier (54). Dohlman *et al* (39) found that tumor and blood samples from the same patient had highly similar fungal DNA, suggesting that an increased abundance of *Candida* in advanced metastatic gastrointestinal tumors directly or indirectly leads to genetic dysregulation of cell adhesion, resulting in a weakened epithelial barrier and translocation of fungal DNA from the primary tumor site into the bloodstream, promoting tumor metastasis.

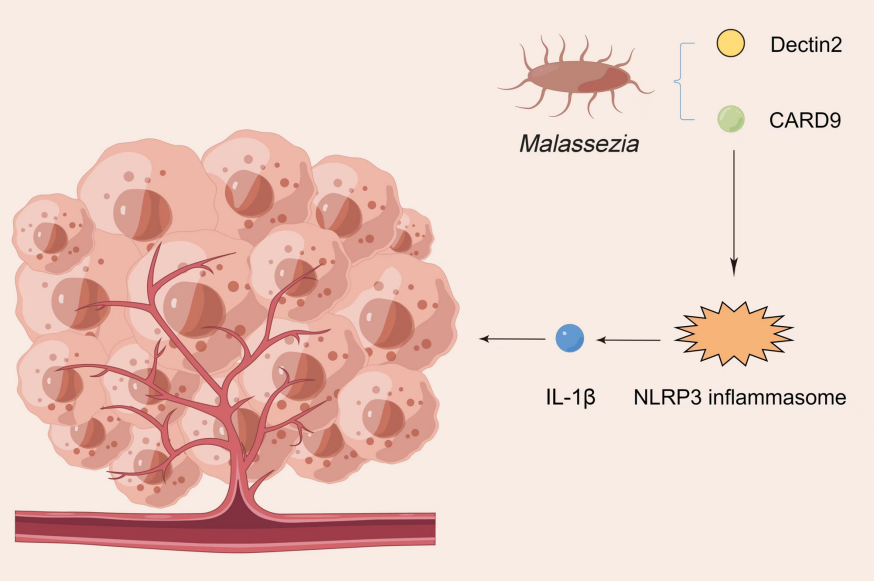

Figure 2. *Malassezia* can activate NLRP3 inflammasome via Dectin2/CARD9 signaling and accelerate IL-1β production to exacerbate inflammation. CARD9, caspase recruitment domain family member 9; NLRP3, NLR family pyrin domain containing 3.

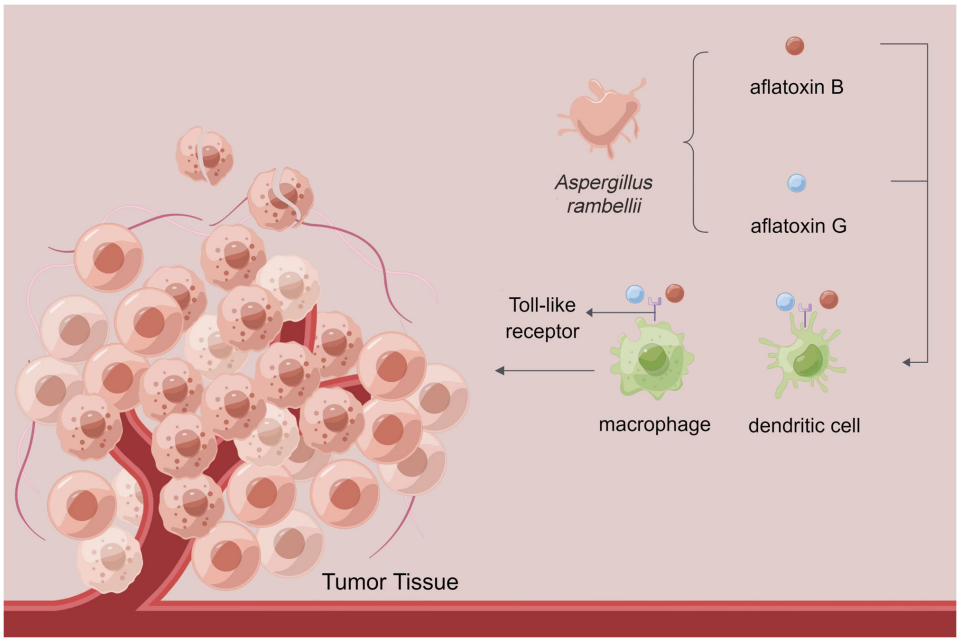

Figure 3. *Aspergillus rambellii* induces immune dysregulation and promotes tumor progression by producing aflatoxins (e.g., aflatoxin B, aflatoxin G), which in turn activate Toll-like receptors that damage macrophages and dendritic cells.

Tumor fungal-bacterial biome interactions promote cancer progression. Through extensive genomic analysis, tumor fungal-bacterial biome interactions can promote colorectal carcinogenesis through the upregulation of D-arginine and D-ornithine metabolic pathways and stimulation of the butanoate metabolic pathway (77). Liu *et al* (77) demonstrated that two marker genes, oraS and oraE, in the D-arginine and D-ornithine metabolic pathways were upregulated in colorectal cancer. The butanoate metabolic pathway, which is strongly activated in colorectal cancer but less studied, has also been identified (78). Tumor fungal-bacterial biome interactions promote colorectal cancer progression through upregulation of *bdhA* and *bdhB* gene expression in the butanoate metabolic pathway (77). Therefore, butanoate in the butanoate metabolic pathway is crucial in supporting the tumor microenvironment (79). Tumor fungal-bacterial biome interactions are being explored as an effective means of maintaining homeostasis in the gut.

6. The tumor mycobiome may be used as a marker for cancer diagnosis

Numerous studies have indicated the potential of bacteria as biomarkers for the diagnosis of colorectal cancer (64). Wirbel *et al* (80) and Thomas *et al* (81) performed meta-analyses

to identify several bacteria enriched in colorectal cancer with utility as diagnostic biomarkers for colorectal cancer.

By contrast, with the study of the tumor microbiome, fungi, in addition to bacteria, may be used as biomarkers for the noninvasive diagnosis of tumor patients. In TCGA cohorts, fungal biome richness varied significantly among cancers (35). For instance, *Candida*, *Saccharomyces cerevisiae* and *Cyberlindnera jadinii* are highly abundant in the gastrointestinal tumor fungal organism community and *Blastomyces* and *Malassezia* are highly abundant in lung cancer and breast cancer, respectively (39).

A further study performed qualitative and quantitative analyses of 20 different fungal DNAs released into the bloodstream and the results suggested that they may be used to distinguish patients with cancer from healthy individuals, even in early-stage disease (35). This suggests that the tumor fungal biome has utility in cancer diagnosis.

In the study conducted by Lin *et al* (64), the average areas under the receiver operating characteristic curves (AUC) of pure bacterial biomarkers was only 73%, while the combination of fungal and bacterial mixed biomarkers showed a significant improvement in diagnostic performance with an average AUC of 83% and an increase in the relative change in AUC of 1.44-10.60% (64). This suggests that the combination of fungal and bacterial biomarkers is more accurate than the combination of pure bacterial species in differentiating patients with colorectal cancer from healthy individuals, thus highlighting the potential use of the tumor mycobiome in clinical diagnostic applications.

In the study of colorectal cancer conducted by Liu *et al* (77), a comprehensive analysis of different national microbiomes was performed using colorectal cancer metagenomic datasets of 8 different cohorts. They found that fungi, archaea and viruses were able to distinguish patients with colorectal cancer from healthy controls in multiple geographic cohorts (77). Coker *et al* (38) successfully distinguished 184 patients with colorectal cancer from 204 healthy controls by detecting fungal biomes in the stool.

Candida is transcriptionally active in gastrointestinal tumors (35). Enrichment of tumor-associated *Candida* DNA was found to be significantly associated with reduced survival in patients with gastrointestinal tumors due to the association of *Candida* with gene expression for cytosolic DNA sensing, Toll-like receptor signaling and Nod-like receptor signaling in gastric cancer (39). This not only suggests that *Candida* increases the severity of gastrointestinal tumors but also that *Candida* may be a promising biomarker for predicting disease outcomes.

7. The tumor mycobiome has potential preventive or therapeutic value for cancer

The use of antimicrobial agents that target known pathogenic microorganisms effectively prevents the onset and progression of the disease. The use of targeted antifungal agents is helpful in the prevention or treatment of gastrointestinal cancers (37). In a mouse model of human pancreatic ductal adenocarcinoma, *Malassezia* infiltrates and accelerates the progression of human pancreatic ductal adenocarcinoma, a condition that can be reversed by antifungal treatment (31). Antifungal treatment targeting *Malassezia* resulted in a 40% reduction in the incidence of pancreatic cancer in mice (31). In a mouse model of esophageal cancer, the oral fungus *Dictyostelium* significantly increased the severity of esophageal squamous cell carcinoma, a condition that could be reversed by antifungal treatment (82).

In addition, the use of fungal probiotics can prevent and treat gastrointestinal cancers. Probiotics are microorganisms that improve health when consumed in the correct amounts. The most common probiotics are bacteria that have been shown to inhibit the proliferation of pathogenic intestinal microorganisms and to prevent carcinogenic inflammation in the esophagus, stomach, pancreas and colorectum (83-85). By contrast, fungi can also be ingested as probiotics and have been reported to be used to alleviate gastrointestinal cancers (37). The *Helicobacter pylori* eradication rate improved when *Saccharomyces boulardii* was combined with *Lactobacillus gasseri*, *Lactobacillus reuteri*, *Lactobacillus acidophilus*, *Streptococcus faecalis*, *Bacillus subtilis* and *Bifidobacterium* (86).

The use of fungal probiotics in treating gastrointestinal cancers is of great importance. Because of their characteristic cellular structure, they can survive in the unfavorable environment of the gastrointestinal tract (87,88). As more research on the efficacy and safety of fungal probiotics is conducted, they may directly or indirectly modulate the tumor microbiome to prevent and treat gastrointestinal cancers (37).

With the above summary and analysis, the fungal biome that targets and attacks tumors is likely to be a good way to treat cancer.

8. Conclusion and future perspective

This review provides a comprehensive summary of the impact of the tumor mycobiome on cancer pathogenesis. The tumor mycobiome promotes tumor progression and metastasis by affecting the human immune system, maintaining a pro-inflammatory environment, producing aflatoxins, attenuating cellular adhesion mechanisms and fungal-bacterial interactions. Furthermore, the tumor mycobiome also has tremendous potential for cancer prevention, diagnosis and treatment.

Although studies on the effect of the tumor mycobiome on cancer pathogenesis have become more frequent, the results are not uniform because of the differences between different populations and inconsistent standards for metagenomic data generation and processing. The future development of standardized and low-cost sequencing technologies and pipeline analysis methods to improve the quality of data collection and analytical processing, and the initiation of longitudinal studies with large sample sizes in different populations to clarify the specific mechanistic relationships, will be crucial for research in this field.

Acknowledgements

Not applicable.

Funding

This study was supported by a grant from the Natural Science Foundation of Shandong (grant no. ZR2017LH050).

Availability of data and materials

Not applicable.

Authors' contributions

WL wrote the manuscript, searched the literature and prepared the figures. ZL was involved in the design of the study and revised the manuscript. BH provided ideas to improve the article, modified the figures and revised the manuscript. XL, HC, HJ and QN performed the literature search and selected relevant articles. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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