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Editorial

Gut fungal, friends or foes? Exploring the role of mycobiome in pancreatic cancer

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1. Introduction

In an era marked by remarkable advances in medical science and technology, the battle against cancer remains one of the most formidable challenges of our time. Among the many forms of this relentless adversary, pancreatic cancer stands out as one of the deadliest forms of cancer, continues to challenge the medical community, with limited treatment options and a low survival rate. Its early symptoms are subtle, its diagnosis often late, and its prognosis grim. Overcoming this disease requires a deeper understanding of its intricacies and a willingness to explore innovative approaches. Despite ongoing research, the causes and mechanisms underlying this disease remain elusive. Recent breakthroughs in microbiome research have opened new doors to understanding the role of the gut microbiome in health and disease. The gut microbiome, comprised of both bacteria and fungi, wields a powerful influence on digestion, metabolism, and the immune system, and recent revelations underline the importance of the often-overlooked mycobiome. While much attention has been devoted to the bacterial components of our microbial communities, a less-known but equally important player has emerged—the mycobiome. The mycobiome, or the fungal community residing in the human gut, has gained prominence. The emerging concept of the mycobiome-immune axis suggests that these fungi may play a pivotal role in shaping the immune response, offering a novel perspective on pancreatic cancer research. This novel concept not only challenges conventional wisdom but also promises to unveil a hitherto uncharted frontier in our understanding of pancreatic cancer.

This editorial cum opinion article delves into the evolving landscape of the mycobiome, particularly its potential role in shaping our immune responses, and how it intersects with the multifaceted challenge of pancreatic cancer. It argues that understanding the mycobiome and its interaction with immune system could not only bring us closer to unravelling the mysteries of this formidable malignancy but also pave the way for innovative treatments that harness the power of our fungal inhabitants, possibly revealing groundbreaking therapeutic avenues. As we embark on this exploration, it becomes evident that the mycobiome represents a remarkable yet underappreciated

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facet of our health. By shifting our perspective from the conventional to the uncharted, we may discover a new frontier in the fight against pancreatic cancer and, in doing so, open a door to a future where innovative therapies and improved outcomes become more than just a distant hope.

2. The Microbiome: Bacterial and Fungal Communities with Clinical Implications

The human gut is a bustling ecosystem teeming with diverse microorganisms that collectively make up what we commonly refer to as the microbiome. When discussing the microbiome, the spotlight often falls on its bacterial residents, who have been the subject of intense scientific scrutiny and popular interest in recent years. However, as we delve deeper into the intricate web of our gut inhabitants, we begin to realize that bacteria are only part of the story. In addition to bacteria, the gut is also home to a vibrant and diverse community of fungi, forming the mycobiome. This fungal contingent, largely understudied until recent years, plays a significant role in our overall health and well-being. Much like their bacterial counterparts, these fungi are integral to the complex symbiosis within our gastrointestinal tract, influencing our physiology, metabolism, and immune system. The mycobiome is a rich tapestry of fungal species, each with its own unique characteristics and potential effects on human health. This community includes both beneficial fungi that aid in digestion and contribute to our well-being, as well as potentially harmful species that, under certain conditions, may lead to infections or imbalances within the gut. They may also play a crucial role in health conditions and diseases, from gastrointestinal disorders and autoimmune diseases to cancer. This evolving knowledge holds the potential to revolutionize our approach to healthcare, offering new insights into the prevention and treatment of various diseases and emphasizing the importance of maintaining a harmonious balance among the diverse inhabitants of our gut microbiome.

Microbiomes have diverse clinical applications that extend to multiple areas of healthcare. The gut microbiome, in particular, is of significant interest due to its influence on digestion, metabolism, and the immune system. Understanding the composition and function of the gut microbiome is pivotal for managing digestive disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Moreover, fecal microbiota transplantation (FMT) has proven effective in treating recurrent Clostridium difficile infections. Beyond the gut, microbiome research has shed light on the relationship between microbial communities and immune function, impacting conditions like autoimmune diseases and allergies, as well as metabolic reprogramming (diabetes and obesity), mental health, and several dermatological conditions.[1] Interestingly, the role of microbiome in cancer immunotherapy and antibiotic stewardship is also emerging, with potential applications in personalized cancer treatment and antibiotic usage optimization.

3. The Mycobiome in Pancreatic Cancer: Friend or Foe?

The gut microbiome, comprised of both bacteria and fungi, wields a powerful influence on digestion, metabolism, and the immune system, and has its implications in various diseases.[2] The mycobiome, the fungal component of the human microbiome, is gaining increasing attention for its relatively understudied role in the complex landscape of cancer. A team of researchers conducted a comprehensive analysis of the cancer mycobiome using a large dataset comprising 17,401 patient tissue, blood, and plasma samples from 35 different cancer types across four independent cohorts.[3] The results of this study revealed the presence of fungal DNA and cells in low abundances within numerous major human cancers. Importantly, the research identified variations in the compositions of fungal communities that differed among cancer types, even after accounting for technical factors. Additionally, fungal histological staining of tissue microarrays provided support for the existence of fungi within tumor tissues, often in close proximity to cancer cells and macrophages.

The mycobiome in pancreatic cancer is an emerging field of research that explores the intricate interplay between the fungal community residing within the human body, known as the mycobiome, and the role of immune system in the development and progression of pancreatic cancer. This axis holds significant implications for understanding the disease. Fungal imbalances within the mycobiome can contribute to chronic inflammation, a well-established driver of pancreatic cancer, by influencing immune responses. Dysregulated immune interactions can create a pro-inflammatory environment conducive to tumor growth.[4] Moreover, the mycobiome can impact how patients respond to various treatments, including chemotherapy and immunotherapy, thus affecting therapeutic outcomes. Specific fungal species or patterns within the mycobiome may also serve as potential biomarkers for early detection and prognosis of pancreatic cancer, offering opportunities for earlier interventions.[5] Additionally, modulating the mycobiome through dietary or therapeutic strategies presents potential for reducing the risk of pancreatic cancer and optimizing treatment outcomes. While this field shows promise, it is still in its early stages, and further research is essential to fully elucidate the complex interactions within the mycobiome-immune axis in the context of pancreatic cancer.

In 2019, a revolutionary study conducted by Aykut and co-workers[2] showcased compelling evidence that disturbances within the mycobiome have the capacity to initiate the development of pancreatic cancer, thereby uncovering an aspect of fungal involvement in pancreatic

ductal adenocarcinoma (PDAC) that had hitherto been underestimated. The gut luminal mycobiome is observed to migrate to the pancreas through the sphincter of Oddi. As anticipated, this investigation discovered that when specific fungi were used to treat PDAC cells, they released IL33. Additionally, when the mycobiome was eliminated in the PDAC mouse model through anti-fungal treatment, it resulted in a notable reduction in tumor size and a decrease in TH2 and ILC2 infiltration. As scientists delve deeper into this field, it becomes increasingly evident that the mycobiome may play a crucial role in the development, progression, and even treatment of this lethal disease. A study conducted by Wei and colleagues[6] investigated the link between oral mycobiota and PDAC, enrolling 34 PDAC patients and 35 healthy controls. The findings revealed that PDAC patients had significantly increased fungal abundance and reduced fungal diversity compared to healthy controls. Certain fungal groups, such as Basidiomycota and Ascomycota, were associated with an elevated PDAC risk. Remarkably, Aspergillus and Cladosporium showed high accuracy in distinguishing PDAC patients. These results suggest that salivary mycobiota analysis, with its rapid and cost-effective methods, holds promise for early PDAC detection and prevention, potentially offering insights into cancer risk and detection. Notably, Alam et al[7] confirmed the presence of intratumor mycobiome in PDAC, with fungal communities being more abundant within tumors, particularly the Malassezia species. In vitro experiments demonstrated that certain fungi, notably Alternaria alternata, triggered a time-dependent loss of IL-33 in PDAC cells. The secreted IL-33 was found to activate innate lymphoid cell type 2 (ILC2) cells, promoting the secretion of IL-5. Furthermore, the study explored the impact of depleting fungi on IL-33 secretion and type 2 immune response in the PDAC tumor microenvironment (TME). Depletion of gastrointestinal fungi through oral amphotericin B treatment led to reduced tumor burden, increased survival, and decreased infiltration of ILC2 and TH2 cells. Conversely, the administration of specific fungi, such as Malassezia globosa or Alternaria alternata, resulted in increased tumor growth and enhanced immune cell infiltration within the tumor. This insight opens up an avenue to explore the potential role of antifungal agents in the treatment of PDAC.

While the topic has gained attention in recent years, the volume of dedicated studies remains relatively small compared to other aspects of PDAC research. This limited research hinders the development of a comprehensive understanding of the role of fungi in PDAC. Studies in this area have faced challenges related to the reproducibility of results. Factors like small sample sizes, methodological variations, and the complexity of the fungal microbiome can lead to inconsistent findings across different studies. The efforts by Fletcher and team of other Duke researchers[6] to replicate the 2019 findings[2] failed to establish a clear association between fungi and the onset of pancreatic cancer in humans. Using the original research team's raw sequencing data, as well as examining pancreatic cancer tissue from Duke Repositories, they were unable to reproduce the initial results.[8] This follow-up research suggests a more complex relationship between the pancreatic microbiome and the development of pancreatic cancer, warranting further investigation. Moreover, the activation of C3 due to the interaction of fungi with MBL has the potential to influence innate and adaptive immune responses that are otherwise suppressed by bacteria within the TME. This modulation could subsequently affect the function of T cells and, by extension, the immune landscape in the tumor environment. In contrast, the presence of bacteria in the TME can initiate immune suppression, and this may interact in a complex manner with the MBL-C3 pathway associated with fungi.[9] These complexities that potentially arise due to the interplay between the components of microbiome should also be taken into consideration.

To sum it up, the exploration of the fungal tumor microenvironment (TME) in pancreatic ductal adenocarcinoma (PDAC) offers promising insights into the disease's underlying mechanisms. However, the transition from fundamental research to practical clinical applications presents formidable challenges. Early detection is paramount for enhancing PDAC outcomes. Nevertheless, devising early detection strategies based on fungal components is a multifaceted undertaking. It entails not only the identification of specific fungal species or biomarkers linked to early-stage PDAC but also the development of non-invasive and cost-effective diagnostic methods. These methods must exhibit the necessary accuracy for clinical adoption. PDAC showcases significant heterogeneity among patients, and differences in the fungal TME among individuals further complicate efforts for clinical translation. A crucial consideration for personalized medicine in PDAC is the customization of potential interventions or diagnostic strategies to align with individual patient profiles. By shifting our perspective from the conventional to the uncharted, we may discover a new frontier in the fight against pancreatic cancer and, in doing so, open a door to a future where innovative therapies and improved outcomes become more than just a distant hope.

4. Future Implications and Therapeutic Strategies

The mycobiome offers a new frontier in the quest to understand and combat pancreatic cancer. By exploring the role of the mycobiome in modulating immune responses and inflammation, we may uncover novel therapeutic strategies. One possible avenue is the development of probiotics or prebiotics tailored to modulate the mycobiome, thereby enhancing the body's own immune response

against pancreatic cancer.[10] Additionally, personalized treatment approaches that consider the patient's mycobiome composition could lead to more effective treatments and better outcomes. It is important to acknowledge that the research on the mycobiome and its role in cancer, including pancreatic cancer, is still in its infancy. There is much to learn and understand before practical applications can be developed. However, the potential is promising, and as our knowledge deepens, we may discover ways to improve the lives of those affected by this devastating disease.

5. Conclusion

Pancreatic cancer remains a formidable challenge in the field of oncology, with limited treatment options and a high mortality rate. The mycobiome-and-immunoinflammatory axis introduces a novel perspective on the disease, offering the potential for a deeper understanding of its etiology and the development of innovative treatment strategies. While research into the mycobiome and its role in pancreatic cancer is ongoing, the implications are profound. By understanding how gut fungi influence the immune system and inflammation, we may uncover new avenues for early detection, prevention, and personalized treatment. The mycobiome is the next frontier in pancreatic cancer research, and its exploration holds great promise for patients and researchers alike.

6. Conflict of Interest

None.

References

1. Kumar A, Pramanik J, Goyal N, Chauhan D, Sivamaruthi BS, Prajapati BG, et al. Gut Microbiota in Anxiety and Depression: Unveiling the Relationships and Management Options. *Pharmaceuticals (Basel)*. 2023;16(4):565. doi:10.3390/ph16040565.
2. Aykut B, Pushalkar S, Chen R, Li Q, Abengozar R, Kim JI, et al. The fungal mycobiome promotes pancreatic oncogenesis via activation of MBL. *Nature*. 2019;574(7777):264–7.
3. Narunsky-Haziza L, Sepich-Poore GD, Livyatan I, Asraf O, Martino C, Nejman D. Pan-cancer analyses reveal cancer-type-specific fungal ecologies and bacteriome interactions. *Cell*. 2022;185(20):3789–806.
4. Inamura K. Beyond Bacteria: Fungi in the Tumor Microbiome. *Cancers (Basel)*. 2023;15(3):572. doi:10.3390/cancers15030572.
5. Li X, Saxena D. The mycobiome-immune axis: The next frontier in pancreatic cancer. *Cancer cell*. 2022;40(2):120–2.
6. Wei A, Zhao H, Cong X, Wang L, Chen Y, Gou J, et al. Oral mycobiota and pancreatic ductal adenocarcinoma. *BMC Cancer*. 2022;22(1):1251.
7. Alam A, Levanduski E, Denz P, Villavicencio HS, Bhatta M, Alhorebi L, et al. Fungal mycobiome drives IL-33 secretion and type 2 immunity in pancreatic cancer. *Cancer Cell*. 2022;40(2):153–67.
8. Fletcher AA, Kelly MS, Eckhoff AM, Allen PJ. Revisiting the intrinsic mycobiome in pancreatic cancer. *Nature*. 2023;620(7972):E1–6.
9. Wang H, Capula M, Krom BP, Yee D, Giovannetti E, Deng D, et al. Of fungi and men: role of fungi in pancreatic cancer carcinogenesis. *Ann Transl Med*. 2019;8(19):1257.
10. Qin X, Gu Y, Liu T, Wang C, Zhong W, Wang B, et al. Gut mycobiome: A promising target for colorectal cancer. *Biochim Biophys Acta Rev Cancer*. 2021;1875(1):188489. doi:10.1016/j.bbcan.2020.188489.

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