

Gut Microbiome: Pancreas-liver Axis and Health

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Introduction

The human gut microbiome has emerged as a central regulator of host physiology, extending its influence far beyond the gastrointestinal tract to distant organs. A growing body of research highlights the profound and intricate communication pathways that exist between the gut microbiota and vital metabolic organs, particularly the liver and the pancreas. These interactions, often referred to as the gut-liver axis and the gut-pancreas axis, are critical in maintaining metabolic homeostasis and are increasingly recognized for their involvement in the pathogenesis and progression of various diseases.

Complex interplay exists between the gut microbiome and pancreatic cancer development and progression, where microbial dysbiosis significantly influences host cell signaling, immune responses, and metabolic profiles within the pancreas. This dysbiosis contributes to carcinogenesis and impacts therapeutic outcomes, suggesting new avenues for diagnostic biomarkers and targeted interventions [1].

Similarly, the gut-pancreas axis reveals a critical role for microbiota-derived metabolites in conditions like Type 2 Diabetes. These metabolites, including short-chain fatty acids and bile acids, can modulate pancreatic beta-cell function, insulin signaling, and systemic glucose homeostasis, offering novel therapeutic perspectives [3]. Further reinforcing this connection, critical interactions between the gut microbiome and pancreatic beta-cell function are central to glucose homeostasis. Microbial metabolites, immune modulation, and gut barrier integrity are all factors influencing beta-cell proliferation, insulin secretion, and sensitivity, thereby impacting diabetes development and progression [5]. The bidirectional communication between the gut microbiota and the pancreas, encompassing both exocrine and endocrine functions, also shows how microbial dysbiosis can affect pancreatic cell signaling, modulate immune responses, and alter nutrient metabolism, contributing to conditions like pancreatitis, diabetes, and pancreatic cancer [7]. This evolving understanding of the gut-pancreas axis and the critical role of the gut microbiota in pancreatic diseases, including pancreatitis and pancreatic cancer, emphasizes how microbial dysbiosis can influence pancreatic cell signaling, immune responses, and metabolic pathways, affecting disease onset and progression [10].

Concurrently, the gut-liver axis demonstrates an intricate relationship in the pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD). Gut dysbiosis is linked to altered microbial metabolites and impaired barrier function, which subsequently influence hepatic cell signaling, inflammation, and lipid metabolism, thereby driving NAFLD progression [2]. The impact of gut microbiota-derived metabolites extends to various liver diseases, including NAFLD and liver cirrhosis. These metabolites, such as short-chain fatty acids, bile acids, and amino acid derivatives, modulate inflammatory cell signaling pathways and metabolic processes in the liver, contributing significantly to disease pathogenesis and progression [6].

Moreover, complex interplay within the microbiota-gut-liver axis contributes to hepatic metabolic dysregulation, where gut microbial alterations affect host signaling pathways, bile acid metabolism, and immune responses in the liver, contributing to conditions like NAFLD and metabolic syndrome [8]. Specific attention is given to Short-Chain Fatty Acids (SCFAs), which are crucial mediators between the gut microbiota and liver health. SCFAs, primarily produced by microbial fermentation, influence hepatic cell signaling, modulate inflammation, and regulate lipid and glucose metabolism, playing a significant role in liver diseases such as NAFLD and cirrhosis [9].

Among the key microbial mediators, bile acids (BAs) and their receptors, such as FXR and TGR5, serve as crucial signaling molecules across the gut, liver, and pancreas. The gut microbiome profoundly influences BA metabolism and signaling, thereby impacting host metabolic homeostasis, inflammation, and disease states like NAFLD and diabetes [4]. This comprehensive view of gut-organ axes highlights that microbial dysbiosis is not merely an associated factor but a pivotal driver of pathogenesis across a spectrum of metabolic and oncological diseases affecting the pancreas and liver.

Collectively, the insights from these reviews underscore the immense therapeutic potential of modulating the gut microbiota. Understanding these complex communications and their downstream effects on host cell signaling, immune responses, and metabolic pathways offers new avenues for diagnostic biomarkers and targeted interventions. These interventions range from microbiome-based strategies to precise modulation of specific metabolic pathways, aiming to restore metabolic homeostasis, mitigate inflammation, and ultimately prevent or treat diseases affecting the pancreas and liver.

Description

The complex relationship between the gut microbiome and the pancreas is a critical area of investigation, particularly concerning serious pathologies like pancreatic cancer [1]. Microbial dysbiosis within the gut can profoundly influence the pancreatic microenvironment, affecting host cell signaling pathways, immune responses, and metabolic profiles. These alterations are not merely correlative; they are implicated as potential contributors to carcinogenesis and can significantly impact the efficacy and outcome of therapeutic interventions. Developing a deeper understanding of these microbial interactions provides promising avenues for identifying novel diagnostic biomarkers and for designing more effective, targeted therapeutic strategies for pancreatic cancer [1].

Beyond cancer, the gut-pancreas axis plays a pivotal role in metabolic disorders, notably Type 2 Diabetes. Gut microbiota-derived metabolites, such as Short-Chain Fatty Acids (SCFAs) and Bile Acids, are key communicators in this axis. These

metabolites can modulate crucial pancreatic functions, including beta-cell function, insulin signaling pathways, and systemic glucose homeostasis [3]. The intricate interactions extend to directly influencing beta-cell proliferation, insulin secretion, and overall sensitivity to insulin, which are fundamental processes in glucose regulation [5]. Disruptions in gut barrier integrity and immune modulation by the microbiome further contribute to the development and progression of diabetes, highlighting potential targets for microbiome-based interventions to restore metabolic balance [5, 7]. Moreover, the comprehensive bidirectional communication between the gut microbiota and the pancreas, encompassing both its exocrine and endocrine functions, underscores how microbial dysbiosis can lead to altered pancreatic cell signaling and nutrient metabolism, contributing to various pancreatic conditions, including pancreatitis and diabetes [7, 10].

Shifting focus to the gut-liver axis, its intricate relationship is central to the pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD) and liver cirrhosis [2]. Gut dysbiosis is a major contributor, leading to altered microbial metabolite production and compromised gut barrier function. These factors, in turn, critically influence hepatic cell signaling pathways, trigger inflammatory responses, and disrupt lipid metabolism within the liver, thereby accelerating NAFLD progression [2, 8]. The complex interplay within the Microbiota-Gut-Liver Axis consistently demonstrates how microbial alterations contribute to hepatic metabolic dysregulation and conditions like metabolic syndrome [8].

Microbiota-derived metabolites are not just general influencers; specific classes play distinct roles. Short-Chain Fatty Acids (SCFAs), primarily produced through microbial fermentation, are crucial mediators linking the gut microbiota to liver health. SCFAs influence hepatic cell signaling, modulate inflammation, and regulate lipid and glucose metabolism, making them significant players in liver diseases like NAFLD and cirrhosis. Targeting SCFA pathways presents a promising therapeutic avenue [9]. Similarly, bile acids (BAs) and their receptors, such as FXR and TGR5, act as critical signaling molecules not only in the gut but also in the liver and pancreas [4]. The gut microbiome's profound influence on BA metabolism and signaling directly impacts host metabolic homeostasis, inflammation, and disease states like NAFLD and diabetes. These microbiota-derived metabolites, including SCFAs, BAs, and amino acid derivatives, collectively modulate inflammatory cell signaling pathways and metabolic processes in the liver, playing a key role in disease pathogenesis and progression [6].

The collective insights from these studies highlight a common thread: understanding the nuanced interactions within these gut-organ axes is paramount for developing effective interventions. Whether it's pancreatic cancer, diabetes, NAFLD, or other liver diseases, microbial dysbiosis and its metabolic consequences are frequently identified as underlying mechanisms. Therefore, the therapeutic implications of targeting the gut microbiome and its derived metabolites are substantial. Strategies could include microbiome-based interventions to restore gut health, or precise targeting of specific metabolic pathways influenced by SCFAs and BAs, aiming to restore metabolic homeostasis and mitigate disease progression across these diverse conditions [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. This comprehensive understanding offers a blueprint for future diagnostic tools and personalized therapeutic approaches.

Conclusion

This body of research underscores the critical and complex interplay between the gut microbiome and host health, particularly concerning the pancreas and liver. A significant focus is placed on the gut-pancreas axis, where microbial dysbiosis is intricately linked to the pathogenesis and progression of serious conditions such as pancreatic cancer, pancreatitis, and Type 2 Diabetes. Specifically, alterations in the gut microbiota are shown to influence host cell signaling pathways, immune

responses, and metabolic profiles within the pancreas, potentially contributing to carcinogenesis and impacting therapeutic outcomes. Furthermore, the gut microbiome's impact extends to pancreatic beta-cell function, which is central to glucose homeostasis, affecting insulin secretion, sensitivity, and diabetes development. Parallely, the gut-liver axis is highlighted as a key player in hepatic metabolic dysregulation, particularly in Non-Alcoholic Fatty Liver Disease (NAFLD) and liver cirrhosis. Gut dysbiosis can lead to profound changes in microbial metabolites, including Short-Chain Fatty Acids (SCFAs) and bile acids (BAs), alongside impaired gut barrier function. These changes, in turn, critically influence hepatic cell signaling pathways, inflammation, and lipid metabolism, driving disease progression in the liver. Bile acids, in particular, are recognized as multifaceted signaling molecules whose metabolism and receptor interactions are profoundly modulated by the gut microbiome, impacting metabolic homeostasis across the gut, liver, and pancreas. Collectively, this research emphasizes that understanding these intricate gut-organ communications is pivotal. It opens new avenues for developing diagnostic biomarkers and targeted therapeutic interventions, which include microbiome-based strategies and precise modulation of metabolic pathways to restore balance and mitigate disease progression.

Acknowledgement

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Conflict of Interest

None.

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