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EXPLORING THE INTRICATE RELATIONSHIP BETWEEN METABOLIC DISORDERS AND CANCER: MECHANISMS, IMPLICATIONS, AND THERAPEUTIC OPPORTUNITIES

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Abstract

Metabolic disorders, including obesity, type 2 diabetes, and metabolic syndrome, are characterized by dysregulated metabolic processes such as glucose and lipid metabolism, leading to conditions like insulin resistance and chronic inflammation. In recent years, a growing body of evidence has highlighted the intricate relationship between metabolic disorders and cancer. This review aims to elucidate the underlying mechanisms linking these two conditions, exploring how metabolic dysregulation contributes to cancer development and progression. Additionally, we discuss the implications of this relationship for cancer prevention, diagnosis, and treatment, and we examine emerging therapeutic strategies targeting shared metabolic pathways. Understanding the complex interplay between metabolic disorders and cancer holds significant promise for improving patient outcomes and reducing the global burden of these interconnected diseases.

Keywords: Metabolic Disorders, Cancer, Interconnection, Cancer Mechanisms, Implications, Therapeutic Opportunities.

INTRODUCTION

Metabolic disorders, such as obesity, type 2 diabetes, and metabolic syndrome, represent a growing global health burden with profound implications for individuals' well-being and healthcare systems worldwide. Concurrently, cancer remains a leading cause of morbidity and mortality globally, posing significant challenges to public health initiatives and medical advancements. Traditionally viewed as distinct disease entities, recent scientific endeavors have unveiled a complex interplay between metabolic disorders and cancer, reshaping our understanding of these conditions and offering novel insights into their shared pathophysiological mechanisms and clinical implications (Lemieux and Després 2020, Regufe, Pinto et al. 2020, Fahed, Aoun et al. 2022). This review aims to explore the intricate relationship between metabolic disorders and cancer, delving into the underlying mechanisms, elucidating their implications for disease progression, and highlighting emerging therapeutic opportunities. By examining the convergence of metabolic dysregulation and oncogenesis, we endeavor to provide a comprehensive overview of this multifaceted relationship, emphasizing the critical intersections between metabolism, inflammation, and tumorigenesis(Chaube and Malvi 2023).

Metabolic disorders, characterized by dysregulated energy metabolism and homeostasis, encompass a spectrum of conditions ranging from obesity, characterized by excess adiposity, to type 2 diabetes, marked by insulin resistance and hyperglycemia, and metabolic syndrome, characterized by a cluster of metabolic abnormalities, including central obesity, dyslipidemia, hypertension, and insulin resistance (Han and Weiss 2021). These disorders pose significant health risks,

predisposing individuals to a myriad of complications, including cardiovascular diseases, neurodegenerative disorders, and cancer. In recent years, mounting evidence has underscored the close association between metabolic disorders and cancer, revealing shared pathophysiological mechanisms that drive disease initiation and progression (Saravanan and SUNDARAM 2021, Di Renzo 2024). Central to this relationship is the dysregulation of metabolic pathways, including glucose and lipid metabolism, which play pivotal roles in cellular growth, proliferation, and survival. Insulin resistance, a hallmark feature of obesity and type 2 diabetes, leads to hyperinsulinemia and elevated levels of insulin-like growth factor 1 (IGF-1), promoting tumor growth and proliferation by activating downstream signaling pathways involved in cell survival and proliferation (Subramanian, Kishorekumar et al. 2018, Anand, Bharathi et al. 2021, Brown 2021).

Moreover, dyslipidemia associated with metabolic disorders alters the composition of cell membranes, providing cancer cells with an abundant source of lipids for membrane biosynthesis and energy production, further fueling tumor growth and progression. Chronic inflammation, another hallmark of metabolic disorders, creates a tumor-promoting microenvironment through the release of pro-inflammatory cytokines and chemokines, facilitating tumor growth, invasion, and metastasis (Liu and Peng 2022). Adipose tissue dysfunction in obese individuals serves as a reservoir for adipokines and hormones that influence cancer cell behavior and contribute to the establishment of a pro-tumorigenic milieu. Beyond metabolic dysregulation, emerging evidence suggests that alterations in the gut microbiota composition observed in metabolic disorders also play a pivotal role in modulating systemic inflammation and metabolic homeostasis, thereby influencing cancer risk and progression (Ahmed, Sultana et al. 2021). Dysbiotic gut microbiota can promote inflammation and metabolic dysfunction through various mechanisms, including the production of pro-inflammatory microbial metabolites, activation of immune cells, and disruption of the intestinal barrier function, all of which contribute to the development and progression of metabolic disorders and cancer (Hrncir 2022).

The intricate interplay between metabolic disorders and cancer underscores the importance of adopting a holistic approach to disease prevention and management, addressing underlying metabolic dysregulation as a central component of therapeutic strategies (Clemente-Suárez, Beltrán-Velasco et al. 2023). By elucidating the underlying mechanisms linking metabolic disorders and cancer, this review aims to pave the way for the development of targeted interventions that exploit shared metabolic vulnerabilities, offering new avenues for cancer prevention, diagnosis, and treatment. Through collaborative efforts across disciplines, we can harness the power of metabolic insights to combat the rising tide of metabolic disorders and cancer, ultimately improving patient outcomes and reducing the global burden of these interconnected disease (Gyamfi, Kim et al. 2022)s.

Mechanisms Linking Metabolic Disorders and Cancer

Insulin Resistance and Hyperinsulinemia:

Insulin resistance, a central feature of both type 2 diabetes and obesity, represents a condition where cells in the body become less responsive to the effects of insulin. Insulin, a hormone secreted by the pancreas, plays a crucial role in regulating blood sugar levels and facilitating the uptake of glucose into cells for energy production. However, when cells develop resistance to insulin, they fail to respond adequately to

its signals, leading to elevated levels of glucose in the bloodstream, known as hyperglycemia (Wu and Ballantyne 2020). This state of insulin resistance triggers compensatory mechanisms within the body, including an increase in insulin secretion by the pancreas to overcome the resistance and maintain normal blood sugar levels. Consequently, individuals with insulin resistance often exhibit hyperinsulinemia, characterized by higher-than-normal levels of insulin circulating in the bloodstream. While initially intended as a compensatory response, chronic hyperinsulinemia can have detrimental effects on various physiological processes, including metabolism and cell growth (Prentki, Peyot et al. 2020).

One significant consequence of sustained hyperinsulinemia is the elevation of insulin-like growth factor 1 (IGF-1) levels. IGF-1 is a hormone with structural similarities to insulin and plays a crucial role in regulating cell growth, proliferation, and differentiation. Elevated levels of IGF-1, driven by hyperinsulinemia, have been implicated in promoting tumor growth and progression by activating downstream signaling pathways involved in cell survival and proliferation (Macvanin, Gluvic et al. 2023). The link between insulin resistance, hyperinsulinemia, and cancer development has been extensively studied, particularly in the context of obesity-related cancers such as breast, colon, and prostate cancer. One proposed mechanism through which elevated IGF-1 levels contribute to tumorigenesis is by activating the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, a signaling cascade implicated in promoting cell growth and inhibiting apoptosis (programmed cell death) (Miricescu, Totan et al. 2020).

Activation of the PI3K/Akt/mTOR pathway in response to elevated IGF-1 levels stimulates cell proliferation and inhibits apoptosis, thereby providing cancer cells with a growth-promoting advantage. Additionally, IGF-1 signaling can enhance angiogenesis, the process by which new blood vessels are formed, facilitating the supply of oxygen and nutrients to growing tumors. Furthermore, IGF-1 has been shown to interact with other signaling pathways involved in cancer development, including the mitogen-activated protein kinase (MAPK) pathway, further promoting tumor cell growth and survival (Kasprzak 2021, Stefani, Miricescu et al. 2021).

The association between insulin resistance, hyperinsulinemia, and cancer risk underscores the importance of addressing metabolic dysfunction as a potential target for cancer prevention and treatment. Strategies aimed at improving insulin sensitivity, such as lifestyle modifications (e.g., diet and exercise) and pharmacological interventions (e.g., insulin sensitizers like metformin), may help mitigate the risk of cancer development in individuals with metabolic disorders (Karra, Winn et al. 2022), The insulin resistance and hyperinsulinemia, hallmark features of type 2 diabetes and obesity, contribute to cancer development and progression by promoting elevated levels of insulin-like growth factor 1 (IGF-1). Elevated IGF-1 levels stimulate downstream signaling pathways involved in cell growth, proliferation, and survival, thereby providing a favorable environment for tumor initiation and progression. Targeting insulin resistance and hyperinsulinemia through lifestyle interventions and pharmacological approaches may represent promising strategies for reducing cancer risk in individuals with metabolic disorders (Zhao, An et al. 2023).

Role of Chronic Inflammation

Chronic inflammation is a critical component of metabolic disorders such as obesity, type 2 diabetes, and metabolic syndrome. This persistent low-grade inflammation

arises from various sources, including dysfunctional adipose tissue, immune cell activation, and metabolic dysregulation(Prathap and Lakshmanan 2022). In the context of obesity, excess adipose tissue secretes pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), as well as chemokines like monocyte chemoattractant protein-1 (MCP-1). These molecules contribute to the recruitment and activation of immune cells, including macrophages, within adipose tissue, further exacerbating the inflammatory response (Hanna and Frangogiannis 2020, Akhter, Wilson et al. 2021, Salas-Hernández, Espinoza-Pérez et al. 2021).

The tumor-promoting microenvironment generated by chronic inflammation creates a conducive setting for cancer initiation, progression, and metastasis. Pro-inflammatory cytokines and chemokines released by adipose tissue and infiltrating immune cells stimulate the proliferation and survival of cancer cells by activating various signaling pathways involved in cell growth and survival, such as nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) (Chrysanthakopoulos and Vryzaki 2023). Additionally, these inflammatory mediators enhance the angiogenic potential of tumors, promoting the formation of new blood vessels that supply nutrients and oxygen to support tumor growth. Furthermore, chronic inflammation contributes to the acquisition of invasive and metastatic properties by cancer cells. Pro-inflammatory cytokines and chemokines facilitate the epithelial-to-mesenchymal transition (EMT), a process whereby cancer cells lose their epithelial characteristics and acquire a more motile and invasive phenotype. This transition enables cancer cells to invade surrounding tissues and metastasize to distant sites, contributing to the spread of cancer throughout the body (Jonckheere, Adams et al. 2022).

Adipose tissue dysfunction is another hallmark feature of metabolic disorders, particularly obesity. In obese individuals, adipose tissue undergoes significant changes in structure and function, leading to alterations in the secretion of adipokines and hormones(BABU and MOHANRAJ 2020). Adipokines are bioactive molecules secreted by adipose tissue that regulate various physiological processes, including metabolism, inflammation, and immune function. Dysfunctional adipose tissue secretes increased levels of pro-inflammatory adipokines, such as leptin, resistin, and visfatin, while reducing the secretion of anti-inflammatory adipokines, such as adiponectin (Parrettini, Cavallo et al. 2020, Kirichenko, Markina et al. 2022). The imbalance between pro- and anti-inflammatory adipokines creates a pro-tumorigenic milieu within the adipose tissue microenvironment. Pro-inflammatory adipokines promote tumor growth and progression by stimulating cancer cell proliferation, survival, and angiogenesis, while also facilitating the recruitment and activation of immune cells that further promote tumor progression (Dumas and Brisson 2021). Additionally, adipokines can modulate the expression of genes involved in cell cycle regulation, apoptosis, and metastasis, further contributing to cancer development and metastatic spread (Pu and Chen 2021).

Moreover, adipose tissue serves as a reservoir for various hormones, including insulin, estrogen, and growth factors, which can influence cancer cell behavior. Dysregulated hormone secretion in obesity can promote cancer cell proliferation and survival by activating signaling pathways involved in cell growth and metabolism. For example, insulin and insulin-like growth factor 1 (IGF-1) promote tumor growth by activating the

PI3K/Akt/mTOR pathway, stimulating protein synthesis and cell proliferation (Stefani, Miricescu et al. 2021).

In summary, adipose tissue dysfunction in obesity contributes to the establishment of a pro-tumorigenic microenvironment characterized by dysregulated secretion of adipokines and hormones. These factors promote tumor growth, invasion, and metastasis by stimulating cancer cell proliferation, survival, angiogenesis, and metastasis. Targeting adipose tissue dysfunction and the inflammatory microenvironment may represent promising strategies for cancer prevention and treatment in individuals with metabolic disorders (Heyn, Corrêa et al. 2020, Herrada, Olate-Briones et al. 2021).

Gut Microbiota Dysbiosis

Gut microbiota dysbiosis refers to imbalances or alterations in the composition and function of the microbial community residing in the gastrointestinal tract. This phenomenon is commonly observed in individuals with metabolic disorders such as obesity, type 2 diabetes, and metabolic syndrome (Brüssow 2020). The gut microbiota plays a crucial role in maintaining various aspects of host physiology, including nutrient metabolism, immune function, and inflammation. However, disruptions in gut microbiota composition can lead to dysregulation of systemic inflammation and metabolic homeostasis, contributing to the development and progression of metabolic disorders and associated complications, including cancer (Brüssow 2020).

The gut microbiota is a complex ecosystem consisting of trillions of microorganisms, including bacteria, viruses, fungi, and archaea, which interact with each other and with the host to influence various physiological processes. In individuals with metabolic disorders, alterations in diet, lifestyle, and host genetics can disrupt the balance of gut microbial communities, leading to dysbiosis (Illiano, Brambilla et al. 2020). Dysbiotic gut microbiota are characterized by changes in microbial diversity, altered abundance of specific microbial taxa, and functional changes in microbial metabolism (Dixit, Chaudhari et al. 2021).

One of the key mechanisms through which gut microbiota dysbiosis influences cancer risk and progression is by modulating systemic inflammation. Dysbiotic gut microbiota can promote inflammation through several mechanisms, including the production of pro-inflammatory microbial metabolites, activation of immune cells, and disruption of the intestinal barrier function(Chockalingam, Sasanka et al. 2020). These inflammatory responses can contribute to the development of insulin resistance, dyslipidemia, and chronic low-grade inflammation, all of which are risk factors for cancer (Almeida, Oliveira et al. 2020, Yoo, Groer et al. 2020).

Moreover, dysbiotic gut microbiota can directly influence metabolic homeostasis by modulating host metabolism and energy balance. For example, certain gut microbes have been shown to ferment dietary fibers and produce short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, which serve as important energy sources for the host and regulate various metabolic processes. Dysbiosis-induced alterations in SCFA production and metabolism can affect host energy expenditure, lipid metabolism, and glucose homeostasis, contributing to the development of metabolic disorders and cancer (Chi, Tu et al. 2021, Wang, Zhu et al. 2021).

Implications for Cancer Prevention, Diagnosis, and Treatment

The intricate interconnections between metabolic disorders and cancer underscore the importance of addressing metabolic dysregulation as a key component in cancer prevention and treatment strategies. Lifestyle modifications, including dietary interventions and physical activity, play a crucial role in managing metabolic disorders and reducing cancer risk. Moreover, identifying biomarkers associated with metabolic dysfunction may aid in early cancer detection and risk stratification. Additionally, targeting common metabolic pathways and risk factors shared between metabolic disorders and cancer presents promising therapeutic opportunities for improving patient outcomes and reducing disease burden (Younossi, Corey et al. 2021, Jia, Liu et al. 2022).

Therapeutic Strategies Targeting Shared Metabolic Pathways

Novel therapeutic approaches aimed at modulating metabolic pathways implicated in both metabolic disorders and cancer are being actively investigated. These include pharmacological interventions targeting insulin signaling, lipid metabolism, and inflammation. Metformin, a widely used antidiabetic drug, has shown potential anticancer effects by improving insulin sensitivity and inhibiting tumor growth. Similarly, dietary interventions such as caloric restriction and ketogenic diets, which target metabolic pathways associated with both metabolic disorders and cancer, are being explored as adjunctive therapies. Additionally, emerging immunotherapeutic strategies leveraging the interplay between metabolism and immune function hold promise for enhancing cancer treatment efficacy (Ferrer, Mourikis et al. 2023).

CONCLUSION

In conclusion, the relationship between metabolic disorders and cancer is complex and multifaceted, involving intricate interconnections between dysregulated metabolic processes and tumorigenesis. Understanding these mechanisms and their implications for cancer prevention, diagnosis, and treatment is crucial for improving patient outcomes and reducing the global burden of these interconnected diseases. Continued research efforts aimed at elucidating the underlying molecular pathways and developing targeted therapeutic strategies hold promise for advancing our understanding and management of metabolic disorders and cancer.

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