
Interconnected Aspects of Cancer Biology and Treatment: A Survey on Immunotherapy, Glycolysis, Tumor Microenvironment, Cancer Metabolism, Hypoxia, and Metabolic Reprogramming

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Abstract

This survey paper explores the interconnected aspects of cancer biology, focusing on immunotherapy, glycolysis, the tumor microenvironment (TME), cancer metabolism, hypoxia, and metabolic reprogramming. It highlights the significance of these elements in shaping cancer progression and informing treatment strategies. Targeting glycolytic pathways, particularly the Warburg effect, emerges as a promising therapeutic strategy crucial for tumor progression and enhancing existing treatments. The complex interplay between metabolic signals and immune responses underscores the need for robust immune stimulation and strategic tumor elimination. The integration of antiangiogenic therapies with immunotherapy holds potential for improving clinical responses. Understanding the crosstalk between cellular adhesion and metabolism could unveil new therapeutic targets. The role of macropinocytosis as a metabolic adaptation in cancer cells is emphasized, presenting a therapeutic target to inhibit tumor growth. The survey underscores the necessity of equitable access to treatments and the potential of new technologies to enhance patient outcomes. It highlights the importance of circadian rhythms in therapeutic strategies and the role of SOWAHA as a cancer suppressor gene in metabolic reprogramming. Mathematical models offer insights into treatment dynamics, emphasizing the benefits of combining dietary and pharmacological interventions, and optimizing tumor vasculature through normalization. In conclusion, understanding the interconnected aspects of cancer biology is essential for developing innovative and effective cancer treatment strategies, advancing personalized approaches that enhance therapeutic efficacy and improve patient outcomes.

1 Introduction

1.1 Significance of Cancer Biology and Treatment

Understanding cancer biology is essential for developing effective treatments, as it involves an exploration of the complex interactions between cancer cells, their microenvironment, metabolic reprogramming, and immune evasion [1]. Notably, nutrient acquisition strategies like macropinocytosis in Ras-driven cancers underscore critical aspects of cancer metabolism and therapeutic targets [2]. The identification of genes such as SOWAHA, which significantly influence cancer progression, highlights the potential of prognostic biomarkers for personalized treatment approaches [3].

Cancer is increasingly viewed as a systems-level phenomenon, necessitating a holistic understanding of its biological foundations to devise innovative therapeutic strategies [4]. The diversity of cancer types complicates the identification of effective tumor markers for personalized diagnosis and treatment, particularly in the context of advanced immunotherapy. Metabolic reprogramming, a

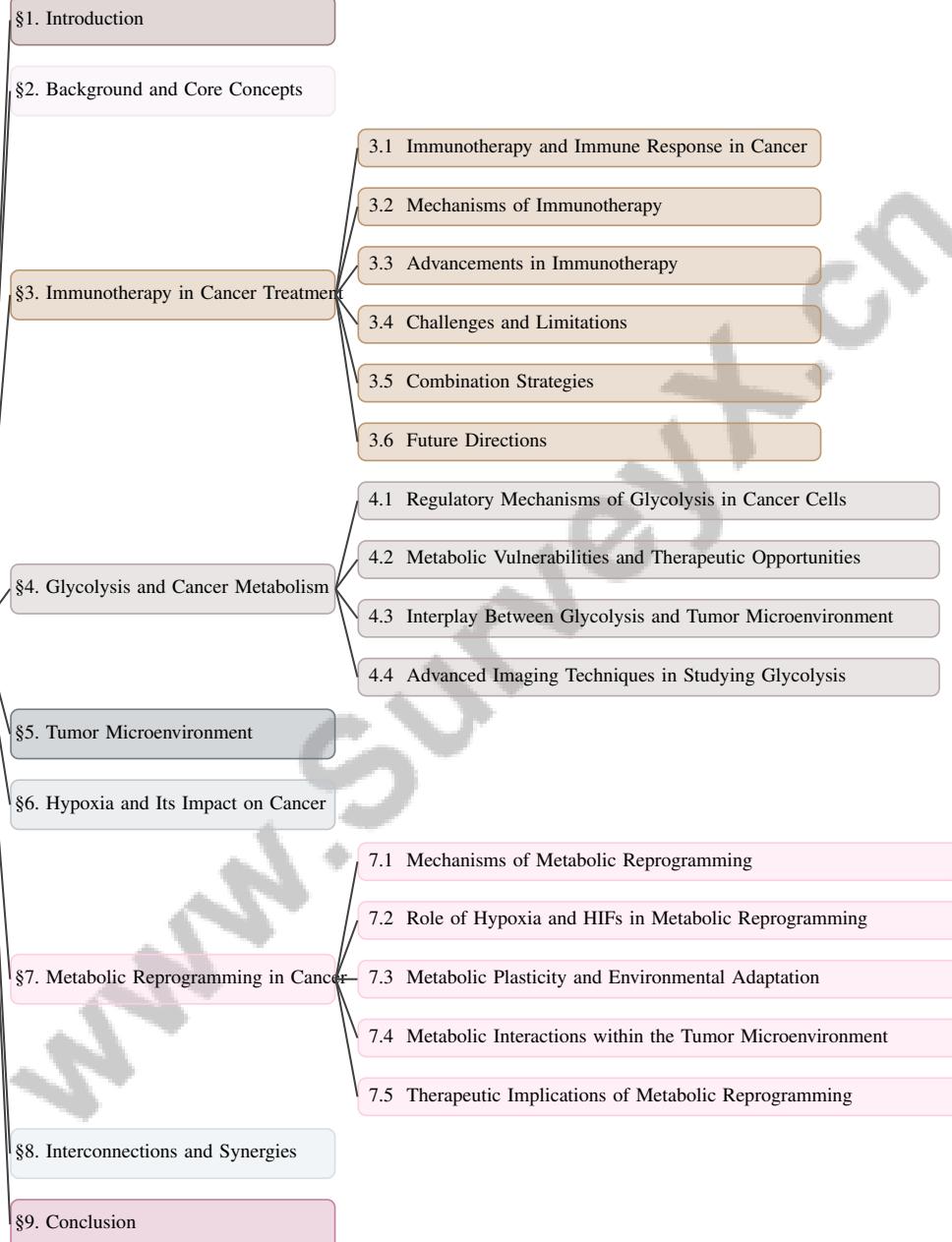


Figure 1: chapter structure

hallmark of cancer progression, is particularly crucial in cancers like pancreatic cancer, where metabolic alterations facilitate tumor growth and therapy resistance. Glycolysis plays a vital role in this context, emphasizing the need for targeted therapeutic strategies.

The intricate relationship between cell adhesion and cancer metabolism adds complexity to cancer biology, as these interactions influence cancer cell motility and invasion, necessitating metabolic reprogramming to meet increased energy demands during tumor progression. Effective interventions must address both the mechanistic roles of adhesion molecules and the metabolic pathways involved in cancer cell survival and proliferation [5, 6, 7, 8, 9]. Additionally, disruptions in circadian rhythms have been linked to increased cancer risk and metabolic alterations, highlighting the multifaceted nature of cancer biology. Insights from the historical progression of cancer immunotherapy emphasize the importance of understanding the immune landscape in treatment development.

Emerging technologies and novel research tools are vital for advancing cancer research and treatment capabilities. The complexity and heterogeneity of cancer necessitate a thorough evaluation of the oncology sector, including diagnostic methods and treatment options. A comprehensive understanding of cancer biology is crucial for driving innovation in effective therapies, particularly as oncology evolves with advancements in precision medicine, immunotherapy, and technology integration. Addressing the complexities of cancer, including its various forms and treatment challenges, can significantly enhance patient outcomes through targeted therapeutic and palliative approaches [10, 11].

1.2 Interconnected Nature of Key Concepts

The interplay between cancer metabolism, immune responses, and the tumor microenvironment (TME) exemplifies the interconnected nature of these key concepts in cancer biology and treatment. Integrating cell adhesion mechanisms with metabolic pathways is critical for influencing cancer progression and treatment outcomes, underscoring the necessity of understanding these interactions for effective therapeutic strategies [8]. The TME, a dynamic entity that significantly affects cell behavior and treatment response, highlights the importance of considering environmental factors in cancer outcomes [12].

The unpredictability of synergistic and antagonistic effects among different therapies poses a significant challenge in optimizing treatment strategies, necessitating careful consideration of these interconnections [13]. Addressing knowledge gaps regarding tumor heterogeneity and its impact on treatment outcomes is crucial for advancing personalized medicine [14]. Emerging technologies, such as microfluidic techniques, exosome biology, and 3D tumor models, enhance cancer treatment strategies by providing insights into the intricate interactions within the TME [15].

The evolution of cancer immunotherapy, intertwined with traditional treatments, reflects the fluctuating acceptance and integration of novel therapeutic approaches within the medical community [11]. The interplay between metabolic reprogramming and immune responses significantly influences antitumor immunity and treatment resistance, emphasizing the need for a comprehensive understanding of these processes [1]. Moreover, the interconnectedness of cancer stem cells, hypoxia, and inflammation contributes to their adaptability and survival in fluctuating environments, complicating treatment strategies [4]. Collectively, these interrelated concepts form a complex network that influences cancer progression and treatment, necessitating a holistic approach to cancer research and therapy development.

1.3 Structure of the Survey

This survey is structured to comprehensively explore the interconnected aspects of cancer biology and treatment. It begins with an introduction that establishes the significance of understanding cancer biology and the intricate relationships between key concepts such as immunotherapy, glycolysis, the tumor microenvironment, cancer metabolism, hypoxia, and metabolic reprogramming. The first section outlines the importance of these elements in developing innovative therapeutic strategies.

Following the introduction, the survey delves into the background and core concepts, offering detailed explanations of each concept's role and significance in cancer biology and treatment. An in-depth examination of immunotherapy follows, highlighting its mechanisms, recent advancements, challenges, and potential future directions [11].

The survey then transitions to glycolysis and cancer metabolism, discussing the regulation of glycolysis in cancer cells and identifying metabolic vulnerabilities that present therapeutic opportunities [8]. The interplay between glycolysis and the tumor microenvironment is analyzed to understand their collective impact on cancer progression [12].

Subsequent sections explore the tumor microenvironment, its components, and the dynamics influencing tumor growth and therapy response. The discussion extends to hypoxia and its impact on cancer, focusing on the mechanisms of hypoxia sensing, metabolic reprogramming, and implications for therapeutic interventions [4].

The survey further investigates metabolic reprogramming in cancer, detailing how cancer cells alter their metabolic pathways to support rapid growth and survival. The role of hypoxia and hypoxia-inducible factors in these metabolic changes is also examined [1].

The survey comprehensively examines the intricate interconnections and synergies between metabolic changes and immune responses, focusing on how alterations in cellular metabolism impact the efficacy of cancer treatments. It highlights the competition for nutrients between cancer and immune cells within the tumor microenvironment, significantly influencing treatment outcomes and the overall effectiveness of immunotherapy. By analyzing these relationships, the survey aims to identify metabolic vulnerabilities that could enhance therapeutic strategies in cancer treatment [16, 1, 17, 18]. The potential for combination therapies and the use of mathematical models to predict cancer progression and treatment responses are also discussed. The conclusion summarizes key findings, emphasizing the importance of understanding these interconnected aspects for advancing cancer treatment strategies. The following sections are organized as shown in Figure 1.

2 Background and Core Concepts

2.1 Core Concepts Overview

A thorough understanding of cancer biology's core concepts is essential for unraveling tumor progression mechanisms and devising effective therapies. Central to this is the Warburg effect, which describes cancer cells' preference for glycolysis over oxidative phosphorylation, even in aerobic conditions, leading to increased lactate production that promotes tumor growth and survival. This phenomenon is particularly evident in liver cancer, affecting proliferation, immune evasion, invasion, metastasis, angiogenesis, and drug resistance, with key glycolytic enzymes like hexokinase 2 (HK2), phosphofructokinase 1 (PFK1), and pyruvate kinase M2 (PKM2) playing pivotal roles [19].

The tumor microenvironment (TME), consisting of immune cells and stromal components, critically modulates metabolic pathways and influences cancer progression. Interactions between cancer-associated fibroblasts (CAFs) and tumor cells reveal complex mechanisms impacting tumor metabolism [20]. Metabolic regulation within the TME is shaped by interactions among cancerous and non-cancerous cells, tumor location, heterogeneity, and overall metabolic homeostasis [5]. The competition for glucose and amino acids between tumor and immune cells highlights intricate metabolic interactions that govern tumor dynamics and immune responses, with metabolites like lactate and adenosine suppressing immune activity [16]. Macropinocytosis, particularly in Ras-mutated cancer cells, serves as a critical nutrient-scavenging pathway affecting cancer metabolism [2].

Epithelial-mesenchymal transition (EMT) is another crucial process that contributes to metastasis and treatment resistance through metabolic reprogramming. EMT involves transcription factors, microRNAs, and long non-coding RNAs, influencing glycolysis, the TCA cycle, and lipid and amino acid metabolism [21]. Cancer stem cells exhibit plasticity and rigidity, enhancing adaptability and survival, complicating tumor heterogeneity and treatment resistance [4].

Reprogramming of fatty acid metabolism provides cancer cells with adaptive advantages under nutrient-deprived conditions, supporting growth and survival [21]. Glutamine metabolism, particularly significant in prostate cancer and other malignancies, underscores its role in cancer biology. Overflow metabolism, where cells release glycolytic byproducts, is associated with imbalances in inter-cellular exchange networks, crucial for sustaining a viable microenvironment [22].

These core concepts form the foundation for understanding the complex mechanisms of cancer biology, emphasizing the importance of metabolic and environmental interactions in developing therapeutic strategies. The complexity and heterogeneity of tumor ecosystems necessitate a holistic

approach to address cancer biology and treatment challenges. Additionally, the circadian clock's influence on physiological processes and metabolic changes related to cancer contributes to the multifaceted nature of cancer biology [23].

3 Immunotherapy in Cancer Treatment

Category	Feature	Method
Immunotherapy and Immune Response in Cancer	Mathematical Analysis	PULSAR[24]
Mechanisms of Immunotherapy	Mathematical and Computational Modeling	OCS-CCT[13]
Advancements in Immunotherapy	Real-Time Analysis Multiplexed Imaging Techniques Advanced Culture Models	Raman[25] CF-HistoGAN[26] MDOTS/PDOTS[27]
Challenges and Limitations	Cancer Treatment Dynamics	DRS[28], SILAC-2D-LC-MS/MS[29]
Combination Strategies	Therapeutic Optimization	AED[30], MMBCD[31]

Table 1: Overview of Methods and Features in Immunotherapy Research: This table categorizes various methods and features related to immunotherapy and immune response in cancer treatment. It highlights advancements such as real-time analysis and multiplexed imaging techniques, while also addressing challenges and combination strategies aimed at optimizing therapeutic outcomes.

Table 2 offers a comprehensive summary of the methods and features associated with immunotherapy and immune response in cancer, highlighting the advancements, challenges, and combination strategies central to ongoing research efforts. Immunotherapy has revolutionized cancer treatment by leveraging the body's immune system to target malignancies, fundamentally shifting oncological therapeutic paradigms. A deeper understanding of the interaction between immunotherapy and the immune response in cancer is crucial. This examination focuses on how immunotherapy modulates innate and adaptive immune responses, offering insights into its efficacy and challenges. Table 1 provides a comprehensive summary of the methods and features associated with immunotherapy and immune response in cancer, illustrating the advancements, challenges, and combination strategies that are central to current research efforts. As illustrated in Figure 2, the hierarchical structure of key concepts in immunotherapy for cancer treatment encompasses immune response modulation, mechanisms of action, advancements, challenges, and future directions. The diagram categorizes these concepts into primary topics, subtopics, and specific details, thereby providing a comprehensive overview of the complex interactions and innovations in the field. The following subsection delves into these dynamics, emphasizing the interplay between tumor biology and immune activation, which informs innovative therapeutic strategies.

3.1 Immunotherapy and Immune Response in Cancer

Immunotherapy is a transformative oncology approach, enhancing innate and adaptive immune responses to target cancer cells [10]. Tumor metabolism and immune evasion interplay significantly, as altered cancer cell metabolic pathways can suppress immune responses [16]. The tumor microenvironment (TME) and tumor-infiltrating immune cells (TIICs) significantly impact immunotherapy efficacy [32]. Addressing 'cold' tumors that resist immunotherapy requires combination strategies to boost immune responses [33]. Innate immune cells, like Natural Killer cells and macrophages, are being explored alongside adaptive responses to improve outcomes, notably in triple-negative breast cancer (TNBC) [34].

To illustrate the complex interrelations among these components, Figure 3 presents a hierarchical structure of key concepts in immunotherapy and immune response in cancer. This figure categorizes the concepts into tumor microenvironment, mathematical models, and innovative strategies, highlighting their interconnections and the focus areas of current research.

Mathematical models optimize treatment protocols by analyzing immune-tumor cell interactions [35]. The timing of therapeutic interventions, such as radiation, affects immune responses and tumor control, highlighting precise scheduling's importance [24]. Circadian rhythms may also influence immune responses, linking circadian disruption to cancer biology and affecting immunotherapy outcomes [23].

Predictive biomarkers, such as PD-L1, are crucial for identifying effective cancer immunotherapy targets [30]. Understanding TME metabolic interactions and their impact on immune function is

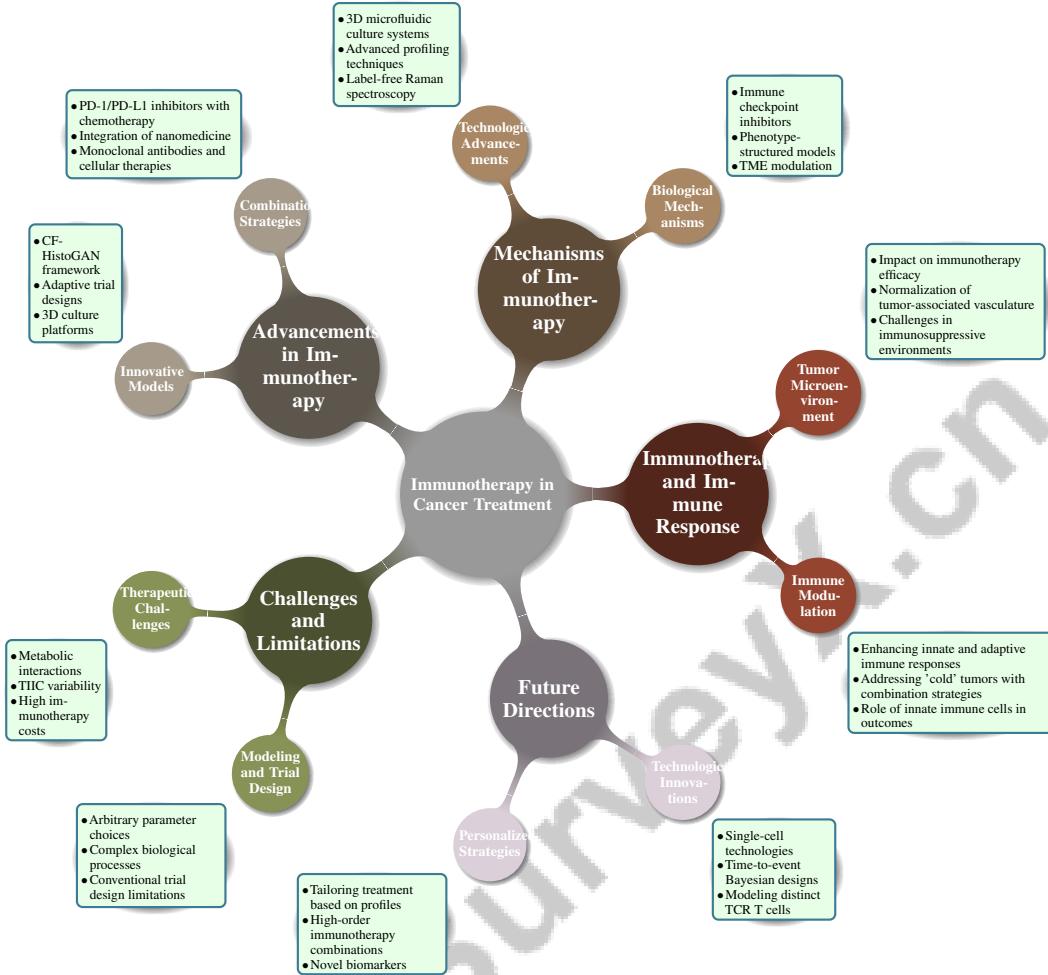


Figure 2: This figure illustrates the hierarchical structure of key concepts in immunotherapy for cancer treatment, including immune response modulation, mechanisms of action, advancements, challenges, and future directions. The diagram categorizes these concepts into primary topics, subtopics, and specific details, providing a comprehensive overview of the complex interactions and innovations in the field.

critical for uncovering new therapeutic targets and enhancing immunotherapy efficacy [36]. These advancements in immunotherapy and immune response modulation represent a paradigm shift, with the potential to improve patient outcomes by understanding the immune landscape and its interaction with cancer cells. Addressing immunosuppressive TME challenges and therapy-related toxicities is essential for optimizing immunotherapy efficacy [37]. Normalizing tumor-associated vasculature is another promising strategy to enhance immune cell dynamics and improve responses [38]. Innovative models, like patient- and murine-derived organotypic tumor spheroids, offer a more representative platform for studying immune checkpoint blockade and overcoming resistance to single-agent immunotherapy. Delivering immunotherapy agents to solid tumors remains challenging, with ongoing research focused on minimizing adverse effects while enhancing responses [17].

3.2 Mechanisms of Immunotherapy

Immunotherapy harnesses various biological mechanisms to target cancer cells, with immune checkpoint inhibitors like anti-PD-1 and anti-CTLA-4 antibodies blocking cancer cell pathways that evade immune surveillance, enhancing T cell activity against tumors [39]. Tumor and immune cell interactions are influenced by their phenotypes, dictating aggressiveness and efficacy, as highlighted in phenotype-structured models [35]. Mathematical models elucidate tumor control and immune

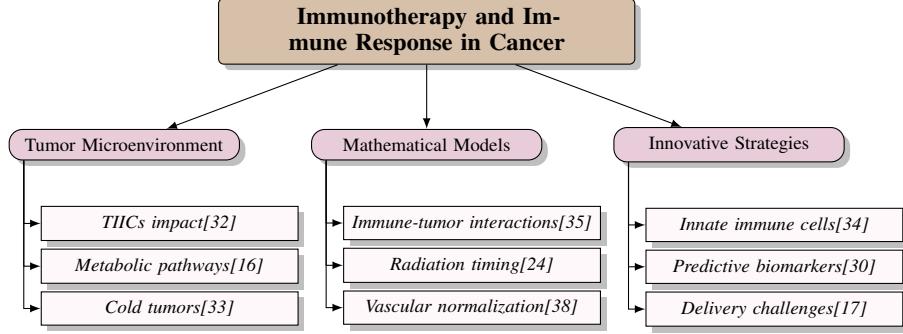


Figure 3: This figure illustrates the hierarchical structure of key concepts in immunotherapy and immune response in cancer, categorizing them into tumor microenvironment, mathematical models, and innovative strategies, highlighting their interrelations and research focus areas.

response dynamics, using ordinary differential equations to capture complex interactions under various treatments [13]. Delayed response models in immune checkpoint blockade therapy provide insights into immunotherapeutic intervention timing and efficacy [40]. Adaptive enrichment design allows data-driven biomarker subpopulation selection, optimizing treatment efficacy [30].

The TME modulates immune responses, often creating an immunosuppressive milieu that hinders antitumor immunity. 3D microfluidic culture systems maintain the TME, enabling more physiologically relevant immune response evaluations [27]. Advanced profiling techniques, like CIBERSORT, use gene expression profiles from purified leukocyte subsets and machine learning to characterize tumor-infiltrating lymphocytes, offering insights into the immune landscape. Label-free Raman spectroscopy, coupled with machine learning, provides a novel method for monitoring tumor biochemical changes post-immunotherapy, enabling real-time treatment efficacy assessment [25].

Integrating these diverse mechanisms and technologies underscores immunotherapy's complexity and potential to revolutionize cancer treatment by effectively mobilizing the immune system against malignancies. These advancements highlight the importance of comprehensively understanding immunotherapy's biological mechanisms to enhance efficacy and overcome existing challenges [37].

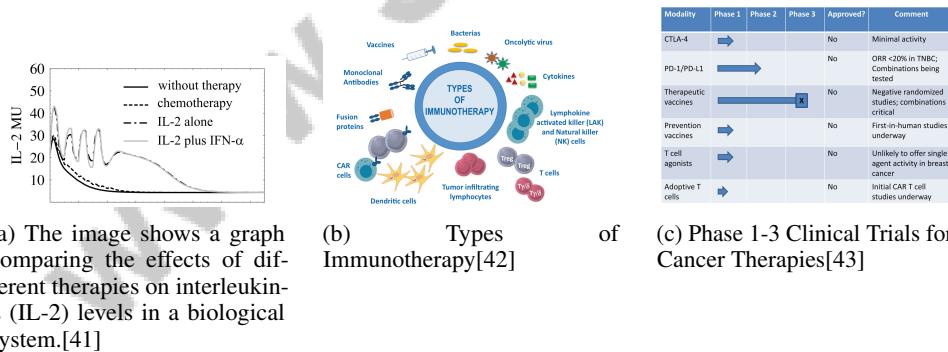


Figure 4: Examples of Mechanisms of Immunotherapy

As shown in Figure 4, Immunotherapy has emerged as a groundbreaking approach in cancer treatment, leveraging the body's immune system to combat malignancies more effectively. The example provided elucidates the multifaceted mechanisms of immunotherapy through a series of illustrative figures. The first image presents a graph that compares the effects of various therapies on interleukin-2 (IL-2) levels, a critical cytokine in immune response modulation, highlighting the impact of combining IL-2 with other agents like IFN-. The second image offers a comprehensive overview of different immunotherapy types, encapsulating their mechanisms and applications with visual aids such as vaccine illustrations, underscoring the diversity within immunotherapy strategies. Lastly, the third image is a detailed table that tracks the progression of various cancer therapies through clinical trial phases, providing insights into their development stages and approval status. Together, these figures

underscore the complexity and promise of immunotherapy as a pivotal frontier in cancer treatment. [? Jisaeva2008differentstrategiescancertreatment, varade2021human, vanderheide2017immunotherapy)

3.3 Advancements in Immunotherapy

Recent advancements in immunotherapy have significantly enhanced cancer treatment, emphasizing combination strategies. PD-1/PD-L1 inhibitors have shown promise in enhancing immune responses against tumors [44]. These inhibitors block pathways that enable cancer cells to evade immune detection, restoring immune targeting capabilities.

Integrating nanomedicine with immunotherapy has opened personalized treatment avenues by leveraging patient-specific biomarkers to tailor therapies, improving outcomes by enhancing drug delivery and targeting [45]. Monoclonal antibodies and cellular therapies offer superior efficacy over traditional methods, providing precise cancer cell targeting [42].

Advanced imaging techniques, like label-free Raman spectroscopy, monitor tumor biochemical changes in response to treatment, offering potential biomarkers for assessing treatment response and facilitating real-time therapeutic strategy adjustments [25]. The CF-HistoGAN framework, evaluated on datasets like colorectal cancer (CRC) and cutaneous T cell lymphoma (CTCL), uses highly multiplexed tissue imaging to study therapy effects on disease progression, enhancing understanding of tumor-immune interactions [26].

Adaptive trial designs, such as pragmatic adaptive enrichment design (AED), have emerged as significant innovations. This two-stage AED incorporates real-time data to select target populations, contrasting traditional fixed designs and optimizing treatment efficacy by focusing on specific patient groups [30]. Mathematical models using control theory and optimization techniques identify optimal treatment schedules, ensuring timely and effective interventions [37].

Combining PDL1 immune checkpoint inhibitors with chemotherapy has shown potential in improving survival rates for advanced Oesophagogastric Adenocarcinoma (OGA) patients, highlighting integrated treatment benefits [28]. Developing 3D culture platforms modeling tumor responses to immune checkpoint blockade has demonstrated significant advantages over traditional 2D methods, providing a more accurate representation of tumor-immune interactions and enhancing preclinical study predictive power [27].

These advancements underscore immunotherapy's transformative potential in oncology, driven by innovative approaches enhancing precision and efficacy. As research advances, breakthroughs in understanding the tumor microenvironment and developing innovative drug delivery systems pave the way for more effective, personalized cancer therapies, enhancing antitumor immune responses while minimizing adverse effects, ultimately improving patient outcomes across diverse cancer types. By focusing on cancer cell and surrounding non-cancerous cell interplay and leveraging advanced biomaterials, these approaches promise to revolutionize cancer care [17, 46].

3.4 Challenges and Limitations

Immunotherapy in cancer treatment faces challenges and limitations that hinder effectiveness across diverse populations. Metabolic interactions within tumors complicate therapeutic strategies and present side effects when targeting pathways like glutamine metabolism [1]. The TME's immunosuppressive nature impedes immune cell infiltration and functionality, limiting immunotherapy effectiveness [33]. TIIIC variability and complex TME interactions challenge predicting patient responses [32].

Arbitrary parameter choices in mathematical models, due to empirical data absence, affect predictive accuracy, crucial for understanding tumor-immune dynamics and optimizing protocols [35]. Complex biological processes in radiation therapy and immune responses complicate effective combination therapy scheduling [29]. Classifying tumors for treatment, optimizing schedules, and designing effective combinations remain primary challenges in advancing immunotherapy [37].

Conventional trial designs struggle with late-onset responses and co-primary endpoints, causing power loss and logistical difficulties in interim decisions, complicating immunotherapy efficacy evaluation. AED offers a solution by adapting to emerging data, enhancing effective treatment population

identification and trial efficiency [30]. However, gastric cancer's complex immune microenvironment complicates effective predictive biomarker identification [28].

High immunotherapy costs, drug resistance emergence, and care access disparities pose additional barriers. High-dose cytokine therapies face toxicity, narrow therapeutic windows, and need improved pharmacokinetic profiles to enhance anti-tumor effects. The TME's stochastic cell interaction nature challenges adequately capturing dynamics while deriving deterministic therapeutic models [14]. Existing models' reliance on simplified assumptions may not capture all tumor-immune interaction complexities in real systems [40].

Addressing these challenges requires innovative approaches integrating insights from metabolic competition, tumor-immune interactions, and improved trial designs. Implementing advanced strategies, like targeted drug delivery systems and combination therapies, is essential for addressing current cancer immunotherapy limitations, improving effectiveness, and minimizing immune modulation adverse effects [33, 47, 48, 17, 49].

3.5 Combination Strategies

Combination strategies in cancer treatment enhance immunotherapy efficacy by integrating it with other modalities, overcoming resistance mechanisms, and improving outcomes. Combining immunotherapy with chemotherapy enhances immune cell infiltration and activity in the TME. Pembrolizumab with chemotherapy significantly improves outcomes in advanced TNBC patients, particularly Elite Responders with low PD-L1 CPS, demonstrating increased innate immune cell infiltration, suggesting a unique response mechanism contributing to improved survival [34, 33, 17, 50].

Integrating antiangiogenic therapy with immunotherapy normalizes tumor vasculature, enhancing immune cell infiltration and activity, improving outcomes [49]. Targeting cancer cell metabolic pathways presents additional combination therapy opportunities. Exploiting metabolic vulnerabilities and adhesion mechanisms crosstalk in cancer cells develops novel targets [8]. Pharmacological strategies targeting glutamine metabolism are investigated, with clinical trials highlighting combination therapy potential [9].

Mathematical modeling optimizes combination therapy regimens. Models integrating dietary interventions, like a ketogenic diet, with immunotherapy and endocrine therapy explore combined effects on ER-positive breast cancer [31]. These models help understand therapy interactions and generate personalized regimens improving outcomes over traditional methods.

Adaptive trial designs, like pragmatic AED, evaluate combination therapy efficacy. A trial assessing atezolizumab plus chemotherapy versus chemotherapy alone in early TNBC uses pathological complete response as a primary endpoint, demonstrating adaptive designs' potential in optimizing strategies [30]. Additionally, combining immuno- and vaso-modulatory interventions enhances cancer treatment outcomes, indicating combination strategies' potential [38].

Future research should focus on targeted delivery systems overcoming solid tumor barriers and exploring combination therapies enhancing immune responses [17]. Identifying effective combinatorial therapies for microsatellite stable (MSS) tumors and exploring novel immunotherapies, continuing to evaluate immune checkpoint inhibitors' role in various contexts, is necessary [51]. Developing combination therapies enhancing immune responses, exploring personalized vaccine strategies, and integrating immunotherapy into adjuvant and neoadjuvant settings are critical research areas [50].

These insights highlight combination strategies' transformative potential in cancer treatment, integrating immunotherapy, chemotherapy, and targeted therapies. By harnessing diverse approaches' strengths, these strategies aim to enhance antitumor efficacy, overcome single-agent therapy resistance, and improve outcomes, especially for metastatic cancers previously deemed incurable. Ongoing trials and innovative preclinical models pave the way for more effective combination therapies tailored to individual needs [33, 39]. As research evolves, integrating immunotherapy with other treatments promises improved outcomes across cancer types.

3.6 Future Directions

Immunotherapy's future in cancer treatment is poised for transformative advancements, driven by personalized strategies, combination therapies, and novel technological innovations. Personalized

immunotherapy, tailoring treatment based on patient profiles and tumor characteristics, is anticipated to gain prominence, benefiting from further clinical validation, enhancing therapeutic precision [11]. Developing combination therapies targeting multiple immune suppression pathways remains a focus. These strategies are crucial for converting 'cold' tumors, typically unresponsive to immunotherapy, into 'hot' tumors amenable to immune-based treatments [33].

Future research should explore high-order immunotherapy combinations and novel biomarkers to better understand immune interactions across cancer contexts. Specific immune cell populations, like M1 macrophages and NK cells, particularly in TNBC, are promising therapeutic exploration areas, potentially leading to new strategies targeting these cells [33]. Incorporating spatial dynamics and immune exhaustion mechanisms into models enhances tumor-immune interaction understanding and informs more effective therapeutic interventions [40].

Advancements in single-cell technologies are anticipated to improve TIIC characterization and immune interaction spatial dynamics within the TME. These insights will be instrumental in developing strategies enhancing immunotherapy effectiveness [11]. Refining models with experimental data and exploring non-genetic instability optimize immune checkpoint inhibitor treatment schedules [40].

Exploring AEDs in complex trial settings, beyond binary endpoints, will refine immunotherapy application in trials [33]. Integrating time-to-event Bayesian optimal phase II designs offers a flexible framework for real-time clinical trial decisions, enhancing immunotherapeutic intervention evaluation efficiency. Future research should focus on modeling distinct TCR T cells and cytokine interactions, refining treatment protocols and improving immune dynamics understanding within cancer [40]. Collectively, these future directions highlight ongoing research and innovation's transformative potential in immunotherapy, aiming for more precise, effective, and personalized cancer treatments.

Feature	Immunotherapy and Immune Response in Cancer	Mechanisms of Immunotherapy	Advancements in Immunotherapy
Mechanism of Action Challenges	Immune System Enhancement Cold Tumor Resistance	Checkpoint Inhibition Immunosuppressive Tme	Nanomedicine Integration Predictive Biomarker Complexity
Advancements	Combination Strategies	Mathematical Modeling	Adaptive Trial Designs

Table 2: This table presents a comparative analysis of various aspects of immunotherapy and immune response in cancer, focusing on their mechanisms of action, associated challenges, and recent advancements. It categorizes key features into three main areas: immune system enhancement, checkpoint inhibition, and nanomedicine integration, providing a comprehensive overview of the current landscape and future directions in cancer immunotherapy research.

4 Glycolysis and Cancer Metabolism

The intricate relationship between glycolysis and cancer metabolism is crucial for supporting the energetic and biosynthetic demands of rapidly proliferating tumor cells. Understanding the regulatory mechanisms governing glycolysis is essential for elucidating the metabolic reprogramming characteristic of cancer. The following subsection explores these mechanisms, emphasizing their significance in tumor progression and potential therapeutic interventions.

4.1 Regulatory Mechanisms of Glycolysis in Cancer Cells

Glycolysis regulation in cancer cells is multifaceted, meeting the energetic and biosynthetic demands of tumors. The tumor suppressor gene p53 plays a pivotal role by promoting a metabolic shift favoring glycolysis, known as the Warburg effect, where cancer cells exhibit increased aerobic glycolysis even in the presence of oxygen [52]. This shift provides a selective advantage, allowing a higher ATP production rate relative to protein mass and volume [53]. Post-transcriptional modifications, such as m6A, also significantly influence glycolysis and the Warburg effect [54].

Targeting glycolytic enzymes like hexokinase 2 (HK2), phosphofructokinase 1 (PFK1), and pyruvate kinase M2 (PKM2) has emerged as a therapeutic strategy to reduce aerobic glycolysis in hepatocellular carcinoma cells [19]. The complexity of glycolytic regulation is further compounded by its interplay with other metabolic pathways, necessitating a thorough understanding of these interactions [55]. Mathematical models integrating constraint-based metabolic network modeling and statistical mechanics offer insights into emergent behaviors in cell populations, elucidating conditions that lead to synchronization and chaos within glycolytic processes [31].

These regulatory mechanisms underscore glycolysis's critical role in cancer metabolism, offering avenues for therapeutic intervention and a deeper understanding of tumor biology.

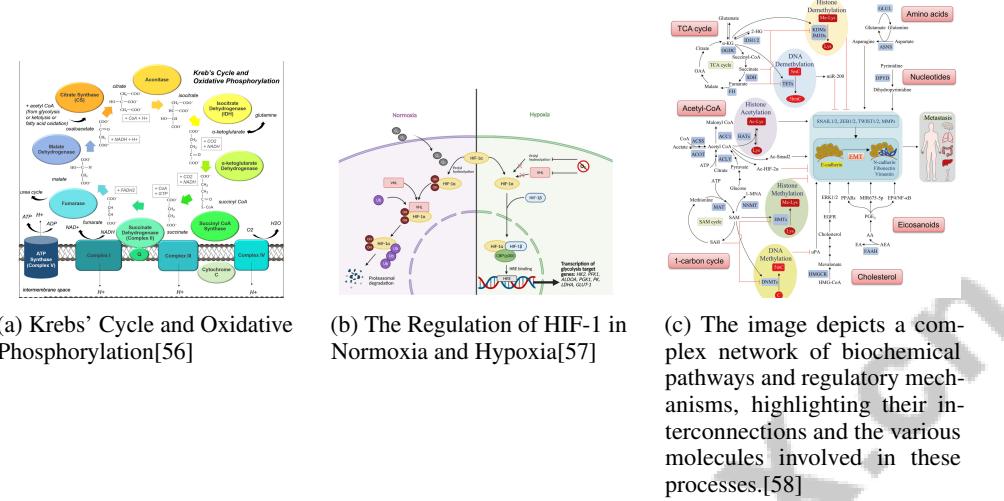


Figure 5: Examples of Regulatory Mechanisms of Glycolysis in Cancer Cells

As illustrated in Figure 5, the regulatory mechanisms governing glycolysis in cancer cells are depicted through a series of figures. The first figure details the Krebs cycle and oxidative phosphorylation, emphasizing crucial enzymes such as Citrate Synthase and Aconitase. The second figure illustrates the regulation of HIF-1 under varying oxygen conditions, highlighting its stabilization in hypoxia. The third figure presents a network of biochemical pathways and regulatory mechanisms, emphasizing the interconnections that are pivotal in cancer metabolism. Together, these visual representations provide insights into potential therapeutic targets for disrupting cancer metabolism [56, 57, 58].

4.2 Metabolic Vulnerabilities and Therapeutic Opportunities

Identifying metabolic vulnerabilities in cancer cells is essential for developing targeted therapies. The Warburg effect, characterized by a preference for glycolysis over oxidative phosphorylation (OXPHOS) even in oxygen-rich environments, provides a strategic advantage for energy demands [29]. Targeting glycolytic pathways presents therapeutic opportunities, as inhibiting these pathways can reduce tumor growth and enhance immunotherapy efficacy [59].

Key regulatory steps in the glycolytic pathway serve as potential therapeutic targets. Inhibiting enzymes like HK2, PFK1, and PKM2 has shown promise in reducing tumor growth in hepatocellular carcinoma (HCC) and improving sensitivity to treatments like sorafenib [19]. However, challenges remain in specifically targeting cancer cell glycolysis without adversely affecting normal tissues. The multifactorial nature of epithelial-mesenchymal transition (EMT) and context-dependent roles of metabolic pathways complicate this endeavor [60].

Beyond glycolysis, other metabolic pathways present exploitable vulnerabilities. Macropinocytosis, utilized by cancer cells for nutrient uptake in depleted environments, highlights additional targets for disrupting cancer metabolism [2]. The role of SOWAHA in metabolic reprogramming emphasizes specific vulnerabilities within cancer metabolism [3].

Feedback mechanisms from gluconeogenesis and adenine nucleotide cycles, as incorporated in advanced theoretical models, enhance understanding of glycolytic dynamics and metabolic vulnerabilities [60]. Evaluating metabolic parameters, such as lactate fluxes, through statistical techniques sheds light on environmental acidification implications as a therapeutic target [22].

These insights into metabolic vulnerabilities underscore the potential for targeted therapies exploiting the unique metabolic characteristics of cancer cells, primarily their reliance on glycolysis and glutamine metabolism, crucial for tumor growth and survival. By specifically targeting these pathways, researchers aim to enhance the efficacy of conventional treatments like chemotherapy and immunotherapy, potentially overcoming challenges such as drug resistance [7, 61, 9].

4.3 Interplay Between Glycolysis and Tumor Microenvironment

The interplay between glycolysis and the tumor microenvironment (TME) is pivotal in cancer progression, influencing both the metabolic landscape and cellular dynamics within tumors. Upregulated glycolysis leads to increased lactate production and TME acidification, supporting rapid cancer cell proliferation and modulating the TME to favor tumor growth [29]. This metabolic reprogramming not only enhances energy production but also impacts processes such as angiogenesis, metastasis, and immune evasion.

The TME comprises stromal and immune cells influenced by cancer cell metabolic activity. Exosomes mediate communication between cancer cells and the stroma, facilitating the transfer of metabolic products and signaling molecules that promote tumor progression [62]. Additionally, metabolic reprogramming, including glycolysis alterations, is linked to EMT, enhancing metastatic potential and therapy resistance [63].

Environmental factors, particularly oxygen levels and extracellular matrix stiffness, significantly impact the glycolysis-TME interplay. ESL modeling systematically illustrates these effects, demonstrating their influence on tumor cell dynamics during chemotherapy [12]. Oxygen availability affects the balance between glycolysis and OXPHOS, impacting tumor dynamics and therapy responses [29]. The role of p53 in orchestrating glucose metabolism dynamics, including glycolysis and OXPHOS, underscores the complexity of these interactions and their therapeutic potential.

Structural analysis of metabolic networks derived from glycolytic pathways reveals intricate interactions within the TME. Targeting glycolysis sensitizes cancer cells to therapies, improving treatment outcomes [7]. Theoretical frameworks, such as dissipative structures theory, elucidate self-organization in open nonlinear systems, further clarifying glycolysis-TME dynamics [60].

The relationship between glycolysis and the TME is a dynamic interaction crucial for cancer progression, as tumor cells adapt their metabolic processes to thrive in nutrient-deficient and hypoxic conditions. This interplay highlights the metabolic plasticity of cancer cells and underscores the potential for therapeutic strategies targeting these pathways to disrupt cancer development [6, 64, 59]. Understanding these interactions is vital for developing therapies that target the metabolic dependencies of cancer cells while considering the broader TME context.

4.4 Advanced Imaging Techniques in Studying Glycolysis

Benchmark	Size	Domain	Task Format	Metric
mIF/mIHC[65]	268	Tumor Immune Microenvironment	Virtual Phenotyping	F1, IOU
RNMT[66]	1,000,000	Oncology	Prognostic Analysis	Cox regression analysis, Kaplan-Meier survival analysis

Table 3: Table summarizing representative benchmarks utilized in the study of tumor microenvironments and oncology. The benchmarks include information on dataset size, domain specificity, task format, and evaluation metrics, providing a comprehensive overview of the tools employed in cancer research. This detailed categorization aids in understanding the scope and methodologies applied in the analysis of cancer-related metabolic processes.

Advanced imaging techniques are critical for elucidating glycolytic processes in cancer cells, providing insights into the metabolic reprogramming that characterizes tumor progression. These techniques enable visualization and quantification of metabolic activities, such as glucose uptake and lactate production, hallmark features of the Warburg effect. Positron emission tomography (PET) using the glucose analog 2-deoxy-2-[fluorine-18]fluoro-D-glucose (FDG) is a well-established imaging technique for evaluating glycolytic activity in tumors, allowing for non-invasive assessment of glucose metabolism, which is essential for understanding tumor behavior, therapeutic resistance, and TME dynamics. This method leverages the Warburg effect, where cancer cells preferentially utilize glycolysis for energy production, providing insights into aggressive phenotypes and potential vulnerabilities for targeted therapies [7, 67, 59].

Magnetic Resonance Spectroscopy (MRS) complements PET by enabling non-invasive detection of key metabolic intermediates and end-products, including lactate and ATP, within the TME. This capability elucidates metabolic adaptations of tumor cells in response to hypoxia and acidosis, critical

factors influencing tumor progression and therapeutic resistance. Integrating data from both PET and MRS offers a comprehensive understanding of tumor metabolic landscapes, aiding in targeted therapy development [68, 59, 67, 69, 70].

Furthermore, integrating mathematical models with imaging data provides a powerful tool for simulating and analyzing glycolytic processes. These models simulate glucose conversion to lactate, ATP, and water, offering a comprehensive framework for understanding glycolysis dynamics in cancer cells [60]. By combining experimental data with theoretical models, researchers gain deeper insights into regulatory mechanisms governing glycolysis and explore potential therapeutic targets.

The integration of advanced imaging techniques, such as PET, with mathematical modeling significantly enhances glycolysis investigation in cancer research, providing detailed insights into metabolic reprogramming. This combination improves understanding of the Warburg effect, where increased glycolytic dependence supports proliferation and survival while contributing to therapeutic resistance. Effectively visualizing and quantifying these metabolic changes allows for better exploration of strategies to target glycolysis, improving the efficacy of conventional cancer treatments like chemotherapy, radiotherapy, and immunotherapy [7, 67]. These approaches provide a detailed understanding of metabolic alterations in tumors, aiding in the development of targeted therapies that exploit the unique metabolic dependencies of cancer cells.

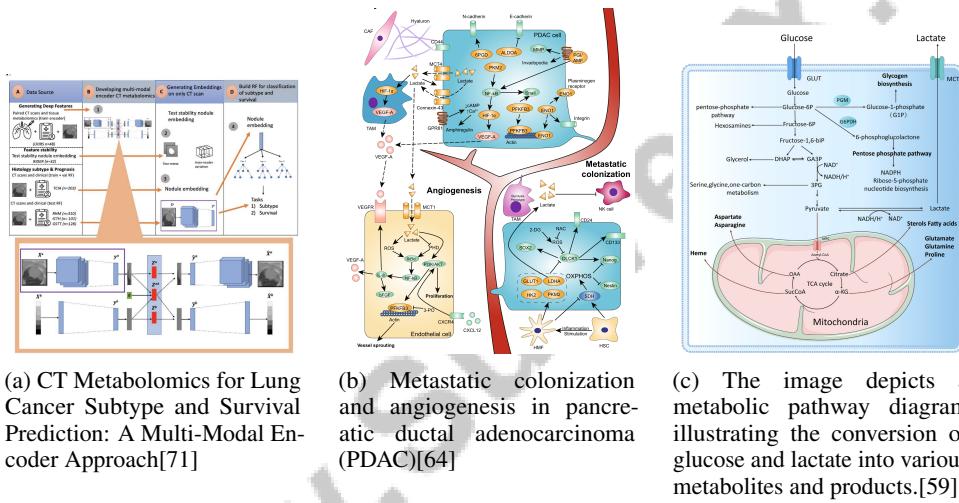


Figure 6: Examples of Advanced Imaging Techniques in Studying Glycolysis

As shown in Figure 6, the study of glycolysis and cancer metabolism has advanced significantly through cutting-edge imaging techniques. The first example illustrates a multi-modal encoder approach that integrates CT scans and tissue metabolomics to predict lung cancer subtypes and patient survival, enhancing diagnostic precision. The second example focuses on the interactions in pancreatic ductal adenocarcinoma (PDAC), emphasizing metastatic colonization and angiogenesis. Lastly, a metabolic pathway diagram visualizes the conversion processes of glucose and lactate into various metabolites, underscoring metabolic reprogramming in cancer cells. These examples collectively demonstrate the power of advanced imaging techniques in unraveling glycolysis and cancer metabolism complexities, paving the way for improved diagnostic and therapeutic strategies [71, 64, 59]. Additionally, Table 3 presents a detailed overview of the benchmarks employed in the study of tumor microenvironments and oncology, highlighting the dataset sizes, domains, task formats, and evaluation metrics used in cancer research.

5 Tumor Microenvironment

5.1 Components and Dynamics of the Tumor Microenvironment

The tumor microenvironment (TME) is a multifaceted network crucial for cancer progression, metastasis, and therapy response. It encompasses malignant cells, cancer-associated fibroblasts (CAFs), adipocytes, immune cells, and endothelial cells, all interacting dynamically with the extracellular

matrix (ECM) [72]. The spatial arrangement and polarization of immune cells, such as macrophages, significantly influence tumor dynamics and treatment efficacy, with phenotypes varying under hypoxic conditions [73]. The ECM provides structural support and modulates cellular behavior through biochemical and mechanical signals, affecting proliferation, differentiation, and migration. Exosomes within the TME facilitate communication between cancer cells and stroma, promoting invasive behavior, angiogenesis, and metabolic reprogramming, particularly under hypoxia [74, 62, 75, 76]. Theoretical models, including Markovian perspectives, elucidate cell state transitions, highlighting the impact of intercellular interactions and metabolic exchanges on tumor dynamics and immune responses [77, 78, 79, 80, 22]. Targeting these complex interactions is essential for improving therapeutic strategies.

5.2 Heterogeneity and Complexity in the Tumor Microenvironment

The TME's complexity and heterogeneity, consisting of diverse cellular and molecular components, critically influence tumor behavior and therapeutic outcomes. This variability poses challenges for effective cancer treatment, contributing to therapy resistance and recurrence, particularly in breast and prostate cancers [81, 82]. Dynamic interactions among CAFs, immune cells, and endothelial cells add to the TME's complexity, impacting tumor initiation and progression. The adaptability of tumor cells to therapeutic pressures, facilitated by TME heterogeneity, complicates treatment efficacy as cancer cells exploit varying microenvironmental conditions to develop resistance mechanisms. Intercellular competitive growth dynamics within the TME regulate functional cell competition, influencing aging and cancer development [79]. Understanding these dynamics is crucial for developing effective therapeutic strategies [83].

5.3 Therapeutic Strategies Targeting the Tumor Microenvironment

Targeting the TME is vital for enhancing treatment efficacy and overcoming resistance in cancer therapy. Recent advancements have identified potential therapeutic targets within the TME, leading to innovative strategies that modify its cellular and molecular landscape [72]. Exosomes play a pivotal role in cancer biology, influencing angiogenesis, invasion, and immune modulation. Targeting exosome pathways, especially under hypoxic conditions, offers viable therapeutic approaches [74]. Normalizing the TME aims to improve patient responses to immunotherapies by addressing structural and functional abnormalities, thus enhancing immune cell accessibility and effectiveness [76]. Combination therapies, particularly those integrating immune checkpoint inhibitors with anti-VEGF agents, have shown increased efficacy in specific TME subgroups, suggesting a tailored approach to cancer treatment [76]. Addressing the TME's heterogeneity and complexity requires innovative approaches that consider the multifaceted interactions within the tumor ecosystem. Integrating spatial interactions and mechanical growth models can enhance predictions of tumor dynamics, leading to more effective therapeutic interventions [84]. Ultimately, targeting the TME underscores the necessity of considering microenvironmental factors in cancer treatment to improve patient outcomes [72].

5.4 Immune Cell Interactions and Immunotherapy

Interactions among immune cells within the TME are critical for determining immunotherapy efficacy, significantly influencing tumor progression and treatment outcomes. The TME includes various immune cells, such as T cells, macrophages, and natural killer (NK) cells, each playing distinct roles in modulating immune responses against cancer [72]. The spatial distribution and functional states of these immune cells are crucial for the effectiveness of immune checkpoint inhibitors (ICIs) and other immunotherapeutic strategies [73]. The TME's heterogeneity complicates the development of effective treatment strategies [76]. Tumor-stromal interactions dynamically influence immune cell behavior, contributing to therapeutic resistance [72]. Hypoxia, a TME characteristic, induces cellular responses facilitating immune evasion, impacting immunotherapy efficacy [85]. Understanding hypoxia-immune cell dynamics is essential for overcoming these barriers and improving therapeutic outcomes [59]. Enhancing innate immune responses, particularly targeting macrophages and NK cells, could improve outcomes in advanced triple-negative breast cancer (TNBC) patients with low CPS scores [34]. However, replicating complex immune cell interactions remains challenging, as current platforms, such as 3D culture systems, have limitations in mimicking T-cell priming and naïve immune cell recruitment [27]. Advanced computational methods, like CIBERSORT, estimate immune cell proportions in tumor samples, offering insights into the immune landscape of tumors.

This approach, combined with immune and stromal scores, shows promise in enhancing treatment strategies and prognostic predictions [76]. Additionally, label-free Raman spectroscopy detects subtle biochemical changes in tumor composition, correlating with treatment response and providing potential biomarkers for assessing immunotherapy efficacy [73].

6 Hypoxia and Its Impact on Cancer

Hypoxia is a pivotal factor in cancer, influencing cellular processes that drive tumor development and progression. This section examines the mechanisms by which cancer cells detect and adapt to hypoxic conditions, focusing on the role of hypoxia-inducible factors (HIFs) and their downstream effects on tumor biology. Understanding these mechanisms is crucial for developing therapies that target the adaptive strategies tumors employ in response to hypoxia.

6.1 Mechanisms of Hypoxia Sensing and Response

Cancer cells possess a sophisticated ability to sense and adapt to hypoxia, a hallmark of the tumor microenvironment that significantly impacts tumor progression and therapeutic resistance. Central to this adaptation are HIFs, predominantly HIF-1 and HIF-2, which regulate genes involved in angiogenesis, metabolism, and survival pathways [86]. Under hypoxic conditions, HIF stabilization leads to upregulation of glycolytic enzymes and angiogenic factors like VEGF, facilitating metabolic reprogramming and vascularization to support tumor growth [87]. This metabolic shift enhances glucose uptake and lactate production, crucial for cancer cell survival in low-oxygen environments.

The interaction between HIFs and the nuclear factor-kappa B (NFB) pathways is critical in regulating inflammation and immune responses under hypoxia, complicating the tumor microenvironment [87]. Hypoxia impairs T cell proliferation and cytokine production, promoting immune evasion and tumor survival [86]. Additionally, hypoxia drives spatial dynamics within tumors, selecting for phenotypic variants with enhanced resistance to therapies [88]. Advanced imaging techniques, such as MRI and optical imaging, enable measurement of pH and oxygen levels in tumors, providing insights into the hypoxic landscape [86]. Integrating these techniques with systemic modeling approaches captures complex interactions between environmental factors and tumor cell responses, offering predictive tools for optimizing chemotherapy outcomes.

Targeting key regulators like HIFs and associated signaling pathways may enhance cancer treatment efficacy and address challenges posed by hypoxic tumor microenvironments, potentially mitigating therapy resistance exacerbated by hypoxia-induced alterations in gene expression, metabolism, and tumor biology [89, 74, 86, 90, 91].

6.2 Hypoxia-Induced Metabolic Reprogramming

Hypoxia-induced metabolic reprogramming is a fundamental adaptive strategy for cancer cells to survive under low oxygen conditions. HIFs orchestrate transcriptional responses that modify metabolic pathways to support tumor growth and survival [86]. HIF-1 enhances glycolysis and alters mitochondrial function, facilitating cancer cell adaptation to hypoxic environments [29]. This metabolic shift, known as the Warburg effect, is characterized by increased glucose uptake and lactate production, enabling rapid ATP generation and biosynthetic precursor availability for tumor growth.

Lactate accumulation in the tumor microenvironment serves as an energy source and influences cellular behavior, promoting immune evasion and contributing to therapeutic resistance. The flexibility in metabolic pathways allows cancer cells to utilize alternative carbon sources for lipid synthesis, supporting growth under nutrient-deprived conditions [3]. Additionally, hypoxia impacts lipid metabolism, with HIFs promoting lipid accumulation essential for membrane biosynthesis and energy storage [86].

Hypoxia-induced metabolic reprogramming also influences epithelial-to-mesenchymal transition (EMT) and angiogenesis, both critical for cancer progression and metastasis. These processes are affected by the tumor's vascular status, influencing tumor evolution and response to treatments such as hyperthermia, as hypoxic cells demonstrate particular sensitivity to thermal effects [29]. Mathematical models quantifying hypoxia's effects on tumor dynamics incorporate factors like

oxygen concentration, metabolic gradients, and protein expression, influencing cellular behavior and enhancing understanding of tumor evolution and therapeutic outcomes [92, 93, 94].

Understanding these metabolic alterations is essential for developing targeted therapeutic strategies that exploit the vulnerabilities of hypoxic tumors, potentially improving treatment outcomes. Incorporating insights regarding hypoxia's role in tumor biology and its impact on immune responses could significantly enhance immunotherapy effectiveness [33, 87, 95, 17, 49].

6.3 Hypoxia-Induced Angiogenesis and Tumor Progression

Hypoxia within the tumor microenvironment is a key driver of angiogenesis and tumor progression, primarily through activating HIFs that regulate pro-angiogenic factors like VEGF [96]. This process is essential for tumor growth, facilitating new blood vessel formation to ensure an adequate supply of oxygen and nutrients to rapidly proliferating cancer cells [97]. Hypoxia's role extends beyond HIF-mediated pathways, as emerging research highlights HIF-independent mechanisms and the integration of metabolic responses in driving angiogenesis and tumor growth [97].

The spatial heterogeneity of oxygen and pH levels within tumors influences tumor cell distribution and behavior, with aggressive phenotypes often dominating hypoxic and acidic regions [94]. Recognizing hypoxia as a critical factor influencing treatment outcomes has spurred interest in developing hypoxia-targeted therapies to improve patient responses to conventional treatments like radiation therapy [98].

Moreover, hypoxia profoundly impacts immune cell metabolism and function, complicating the tumor microenvironment and contributing to immune evasion [99]. The interplay between hypoxia-induced angiogenesis and immune modulation highlights hypoxia's multifaceted impact on tumor progression, emphasizing the need for comprehensive therapeutic strategies targeting both angiogenic and immune pathways.

6.4 Therapeutic Implications and Future Directions

Hypoxia in the tumor microenvironment presents significant challenges in cancer therapy due to its role in promoting metabolic reprogramming, angiogenesis, and immune evasion, contributing to treatment resistance. The stabilization of HIFs under low oxygen conditions drives these processes, making HIFs critical therapeutic targets [100]. Ongoing research focuses on specific HIF inhibitors and their potential integration into combination therapies, particularly with immunotherapeutic agents, to effectively target hypoxic tumors [89].

The eco-evolutionary dynamics of tumor cells, significantly influenced by oxygen availability, lead to distinct phenotypic compositions affecting tumor growth and treatment resistance, highlighting the need for strategies considering these dynamics [101]. Enhancing p53 activation has been shown to reverse the Warburg effect, restoring normal metabolic states and improving therapeutic sensitivity, underscoring the potential of targeting metabolic pathways.

Advancements in imaging technologies, such as integrating PET and MRI, promise to enhance non-invasive hypoxia assessment in clinical practice, providing early biomarkers of treatment efficacy and improving monitoring accuracy. Simulation results demonstrate strong agreement with experimental data, revealing complex internal patterns and flows within tumor spheroids, offering new insights into tumor microenvironments and potential therapeutic strategies [102].

Understanding metabolic adaptations to hypoxia can inform novel therapeutic strategies aimed at overcoming tumor resistance [103]. Identifying hypoxia as a major barrier to effective immunotherapy suggests that targeting hypoxia could enhance therapeutic outcomes [95]. Future research should explore integrating hypoxia-related mechanisms across various diseases and investigating novel therapeutic targets in hypoxia biology [96].

The therapeutic implications and future directions in targeting hypoxia emphasize the need for comprehensive strategies integrating anti-hypoxic agents with existing modalities. Addressing the adaptive mechanisms of cancer cells in hypoxic environments aims to enhance treatment efficacy and overcome challenges posed by hypoxia in cancer therapy, suggesting that future treatments should consider both malignant and non-malignant cellular interactions [46].

7 Metabolic Reprogramming in Cancer

7.1 Mechanisms of Metabolic Reprogramming

Cancer cells undergo extensive metabolic reprogramming to sustain rapid proliferation, characterized by significant alterations in metabolic pathways. Central to this is the Warburg effect, where cancer cells favor glycolysis over oxidative phosphorylation (OxPhos) despite oxygen presence, facilitating rapid ATP production and biosynthetic precursor generation essential for high proliferation rates [59]. Theoretical models, such as reaction-diffusion-taxis equations, highlight glycolysis's critical role in tumorigenesis by elucidating interactions among cancer cells, endothelial cells, and the tumor microenvironment (TME) [104].

Hypoxia-inducible factors (HIFs) are pivotal in orchestrating this metabolic reprogramming under low oxygen conditions, promoting glycolysis and angiogenesis to adapt to hypoxia [88]. This involves upregulating glycolytic enzymes while downregulating mitochondrial respiration, enhancing metabolic flexibility for tumor growth. Lactate, a glycolytic byproduct, influences metabolic pathways in cancer and immune cells, contributing to immune evasion and tumor progression [2].

Beyond glycolysis, cancer cells exploit various metabolic pathways to meet energetic and biosynthetic needs. Mechanisms like macropinocytosis allow cancer cells to adapt metabolism in nutrient-depleted environments, crucial for tumor growth [2]. Studies on SOWAHA highlight its role in altering metabolic pathways, supporting rapid cancer cell growth and survival [3]. The modularity of metabolic gene expression patterns serves as a prognostic biomarker for hepatocellular carcinoma (HCC), indicating the potential of metabolic profiling in cancer prognosis [88].

Identifying specific metabolic vulnerabilities in tumors offers therapeutic intervention opportunities [5]. Targeting these vulnerabilities can disrupt the metabolic adaptations cancer cells rely on, potentially enhancing treatment efficacy and overcoming resistance mechanisms [4]. Understanding these reprogramming mechanisms is vital for developing therapies that exploit cancer cells' unique metabolic dependencies, paving the way for improved cancer treatment strategies.

7.2 Role of Hypoxia and HIFs in Metabolic Reprogramming

Hypoxia and hypoxia-inducible factors (HIFs) are crucial in orchestrating the metabolic reprogramming necessary for cancer cell survival under low oxygen conditions. HIF-1 modulates gene expression involved in glycolysis, angiogenesis, and lipid metabolism, facilitating the metabolic flexibility required for tumor growth [86]. Under hypoxic conditions, HIFs enhance glycolytic flux by upregulating key glycolytic enzymes, enabling rapid ATP production that supports tumor proliferation despite oxygen scarcity.

HIFs also impact lipid metabolism, promoting lipogenesis and inhibiting fatty acid oxidation, providing cancer cells with essential lipids for membrane synthesis and energy storage [86]. The modularity of metabolic gene networks enhances evolutionary fitness in high-stress environments like cancer, underscoring HIFs' role in metabolic reprogramming [88].

Cancer metabolism's dynamic nature incorporates pathways such as glutaminolysis and the pentose phosphate pathway, highlighting the complexity of hypoxia-driven metabolic adaptations. Targeting HIF-1 and associated metabolic pathways represents a promising therapeutic strategy, as this approach can disrupt adaptive mechanisms contributing to drug resistance and tumor progression. Addressing hypoxia-driven metabolic reprogramming may improve treatment efficacy and overcome challenges posed by the TME [90, 105, 7].

The role of hypoxia and HIFs in metabolic reprogramming is crucial for understanding cancer cells' adaptive strategies. Elucidating hypoxia-induced metabolic changes can inform targeted therapies that exploit hypoxic tumors' vulnerabilities, enhancing cancer treatment outcomes [86].

7.3 Metabolic Plasticity and Environmental Adaptation

Cancer cells exhibit remarkable metabolic plasticity, enabling adaptation to fluctuating environmental conditions to sustain growth and survival. This adaptability stems from the dynamic interplay between various metabolic pathways, allowing efficient management of nutrient and energy resources

in response to environmental stresses [5]. A key aspect is the ability to switch between glycolysis and oxidative phosphorylation (OxPhos), influenced by hypoxia-inducible factors (HIFs) [86].

Under hypoxic conditions, cancer cells upregulate glycolytic pathways to compensate for reduced OxPhos efficiency, known as the Warburg effect [29]. This shift is critical for ATP production and supports macromolecule biosynthesis necessary for rapid cell division. Moreover, cancer cells exploit alternative nutrient sources through pathways such as macropinocytosis and glutaminolysis, providing essential building blocks for growth in nutrient-deprived environments [2].

The modularity of metabolic gene networks enhances cancer cells' evolutionary fitness, allowing them to thrive in diverse and often hostile microenvironments [88]. This modularity facilitates the integration of signaling pathways that regulate metabolic reprogramming, enabling swift adaptation to changes in the TME, including variations in pH, oxygen levels, and nutrient availability [86].

Metabolic plasticity is a hallmark of cancer cells, providing flexibility to withstand environmental challenges and maintain proliferative capacity. Understanding this plasticity is crucial for developing therapies that disrupt cancer cells' metabolic dependencies, potentially leading to more effective cancer treatments [5].

7.4 Metabolic Interactions within the Tumor Microenvironment

The tumor microenvironment (TME) is a complex ecosystem where cancer cells interact metabolically with various cellular and non-cellular components, significantly influencing tumor progression and therapeutic resistance. These interactions shape the metabolic landscape of tumors, as cancer and stromal cells, including fibroblasts, immune cells, and endothelial cells, engage in a bidirectional exchange of metabolites that support tumor growth and survival. The metabolic crosstalk within the TME encompasses the intricate exchange of nutrients and signaling molecules, fulfilling the high energetic and biosynthetic demands of rapidly proliferating cancer cells while influencing immune responses and promoting angiogenesis. This dynamic interaction is characterized by metabolic heterogeneity and involves various cell types, including cancer-associated fibroblasts, which contribute to tumor progression and immunomodulation through the secretion of specific metabolites. Understanding these metabolic interactions unveils potential therapeutic targets for disrupting the supportive niche that tumors create, thereby enhancing treatment efficacy [5, 6, 8, 16, 58].

A critical aspect of metabolic interactions in the TME is the competition for essential nutrients, such as glucose and amino acids, between cancer cells and activated immune cells. Cancer cells, which have heightened metabolic demands and often rely on glycolysis for rapid energy production, compete with cytotoxic lymphocytes that also switch to glycolysis upon activation. This competition shapes tumor-immune dynamics and can influence outcomes such as tumor elimination, dormancy, or unrestrained growth. Additionally, amino acids play diverse roles beyond energy provision, including biosynthesis and supporting immune responses, complicating the nutrient competition landscape within the TME [6, 106, 107]. Such competition can suppress immune cell function, contributing to immune evasion and tumor progression. Furthermore, cancer-associated fibroblasts (CAFs) significantly modulate the TME by secreting metabolites and cytokines that influence cancer cell metabolism and promote a pro-tumorigenic environment.

The spatial dynamics of these metabolic interactions are crucial for understanding tumor heterogeneity and therapeutic resistance development. Recent advancements in cancer modeling have extended existing ordinary differential equation (ODE) models to partial differential equation (PDE) systems that incorporate mechanical growth, accounting for spatial dynamics within the TME [84]. These models provide insights into how spatial variations in nutrient availability and metabolic activity influence tumor progression and therapy response.

Metabolic interactions within the TME are fundamental to cancer biology, enabling cancer cells to adapt to fluctuating nutrient conditions while contributing to the intricate dynamics of tumor ecosystems. These interactions involve a complex interplay between cancer cells and various non-cancerous cell types, such as cancer-associated fibroblasts and immune cells, shaping the TME's metabolic landscape. This metabolic niche influences tumor progression, immune evasion, and overall tumor heterogeneity, highlighting potential therapeutic targets for more effective cancer treatments [108, 6, 5, 76]. Understanding these interactions is essential for developing therapeutic strategies that target cancer cells' metabolic dependencies while considering the broader TME context. Disrupting

the metabolic crosstalk within the TME may enhance the efficacy of cancer therapies and address the challenges posed by tumor heterogeneity and resistance.

7.5 Therapeutic Implications of Metabolic Reprogramming

Targeting metabolic reprogramming in cancer cells presents significant therapeutic implications, offering opportunities to disrupt the unique metabolic dependencies that sustain tumor growth and survival. A central strategy focuses on hypoxia-induced metabolic reprogramming, pivotal for cancer cells adapting to low oxygen environments. Hypoxia-inducible factors (HIFs) are integral to these adaptations, making them attractive targets for therapeutic interventions aimed at improving outcomes, particularly in hepatocellular carcinoma (HCC) [88]. By targeting HIFs, researchers can develop therapies that hinder the metabolic flexibility cancer cells rely on, potentially enhancing existing treatment efficacy.

The interplay between metabolic pathways and processes such as epithelial-mesenchymal transition (EMT) highlights the potential for targeting these interactions to create new therapeutic opportunities. Understanding the crosstalk between adhesion and metabolism allows for the development of strategies that effectively target metabolic reprogramming, disrupting pathways that contribute to tumor progression and resistance [8]. Additionally, targeting cancer-associated fibroblasts (CAFs) and their related metabolic pathways presents a promising avenue for therapeutic development, given their role in modulating the TME and promoting cancer growth [20].

Utilizing three-dimensional (3D) models, such as the 3D alginate-based pancreatic cancer model, provides a valuable platform for exploring therapeutic strategies that target metabolic reprogramming in response to chemotherapy. These models offer insights into the complex interactions within the TME and enable the evaluation of novel therapeutic approaches in a more physiologically relevant context. The evolutionary dynamics of vascularized tumors, influenced by oxygen levels, underscore the importance of considering environmental factors in therapeutic strategies, as chemotherapy can remove selective barriers against resistant variants [109].

Future research should focus on integrating these insights into personalized treatment strategies, potentially enhancing the precision of cancer therapies. By targeting the altered metabolic pathways underpinning cancer cell survival and proliferation, researchers can develop therapies that disrupt these processes, ultimately improving treatment outcomes and offering new hope for cancer patients. The modularity of metabolic gene networks may serve as a prognostic biomarker, further refining personalized treatment strategies for HCC and other cancers [88].

8 Interconnections and Synergies

8.1 Metabolic Signals and Immune Responses

Metabolic alterations within the tumor microenvironment (TME) play a critical role in modulating immune responses and influencing therapeutic outcomes, highlighting the complex interplay between cancer metabolism and immunotherapy. The Warburg effect, characterized by a preference for glycolysis over oxidative phosphorylation, confers a survival advantage in hypoxic conditions and supports rapid cancer cell proliferation [29]. This metabolic reprogramming creates a competitive environment for glucose, potentially leading to immune evasion [16]. Notably, enhanced tumor glycolytic activity correlates with increased immune activity, affecting immunotherapy responses [59].

Hypoxia exacerbates cancer progression by inducing treatment resistance and altering immune cell function, largely mediated by hypoxia-inducible factors (HIFs) that enhance cell survival and energy homeostasis [3]. These metabolic shifts facilitate immune evasion and tumor growth, underscoring the need for targeted therapies to counteract hypoxia and improve treatment efficacy [99]. Research continues to explore how hypoxia-induced inflammation contributes to chronic pathologies [87].

Emerging imaging techniques, such as label-free Raman spectroscopy, provide non-invasive methods for real-time monitoring of tumor responses to immunotherapy [22]. Metabolic interventions hold promise for enhancing immune responses and improving cancer therapy outcomes [1]. Understanding immune cells' metabolic needs can guide targeted interventions to bolster anti-tumor responses [16].

Combining antiangiogenic therapies with immunotherapy can significantly enhance anti-tumor immunity, especially in tumors with challenging microenvironments [51]. Metabolic changes driven by adhesion molecules also influence immune responses, necessitating personalized approaches that consider these dynamics [3]. The interplay of HIF signaling with pathways like NFB and mTOR adds complexity, with significant implications for disease management [86].

8.2 Combination Therapies and Treatment Synergies

Combination therapies offer a promising strategy for enhancing cancer treatment efficacy by integrating multiple modalities to overcome resistance mechanisms and improve patient outcomes. This approach is particularly effective in addressing cancer metabolism and immune evasion, where targeting cancer stem cells (CSCs) and their metabolic interactions with non-stem cancer cells can significantly influence treatment success. The spatial distribution of tumor cells, shaped by metabolic and environmental factors, is crucial for developing effective therapeutic strategies [22].

Mathematical models are instrumental in optimizing combination therapy regimens, providing insights into complex interactions within the TME and facilitating the integration of radiotherapy into treatment plans. These models, which incorporate tumor vasculature effects, support the potential for synergistic therapies to enhance treatment efficacy. Developing personalized treatment strategies that leverage insights from tumor-immune interactions and advanced computational modeling is essential for optimizing immunotherapy approaches [17, 37].

Integrating immunotherapy with AI-based predictive analytics shows promise for improving treatment efficacy in advanced cancer patients. Evidence suggests that combination therapies generally yield superior outcomes compared to monotherapies, although effectiveness varies across cancer types and treatment regimens. Future research should refine models to include realistic microenvironmental dynamics, elucidating complex TME interactions and informing combination therapy development [17].

Targeting metabolic pathways such as macropinocytosis, which allows cancer cells to scavenge nutrients, alongside other therapeutic strategies, presents promising avenues for enhancing treatment efficacy by exploiting tumor metabolic vulnerabilities [7, 110, 9, 2]. Coordination among cells in managing overflow metabolism further underscores the importance of understanding metabolic interactions within the TME. Addressing these dynamics, combination therapies hold significant potential for improving cancer treatment outcomes, emphasizing the need for continued interdisciplinary research.

8.3 Mathematical Models and Predictive Frameworks

Mathematical models and predictive frameworks are vital for understanding and optimizing cancer progression and treatment responses, providing insights into the intricate dynamics of tumor biology. These models simulate therapeutic interactions, enabling exploration of combination strategies and refinement of treatment protocols [13]. By integrating individual cell behaviors and their environmental interactions, mathematical models enhance our understanding of the TME's impact on treatment efficacy [102].

Models utilizing both ordinary differential equations (ODEs) and partial differential equations (PDEs) offer a comprehensive framework for capturing spatial and temporal dynamics of tumor growth and treatment responses. These models systematically integrate data acquisition and cell interaction dynamics, extending to PDE models that account for mechanical growth within the TME [84]. Such approaches are crucial for predicting the formation and disruption of tumor structures, such as pseudopalisades, critical for glioma patterning [104].

Future research should focus on refining cytokine delivery methods, exploring combination therapies, and understanding the TME's role in cytokine efficacy [111]. Leveraging mathematical models' predictive power can optimize therapeutic interventions and enhance patient outcomes. These models facilitate identifying optimal treatment schedules and evaluating potential synergies among different therapeutic modalities, ultimately contributing to more effective and personalized cancer treatment strategies.

The integration of advanced mathematical models and predictive frameworks into cancer research represents a transformative advancement in deciphering and influencing complex TME interactions.

These models, ranging from data-driven kinetic approaches to mechanistic PDE models, enhance our understanding of tumor-immune spatial relationships and cellular interaction dynamics. By systematically characterizing biologically distinct tumor regions and their effects on nearby immune cells, researchers can develop more effective immunotherapies tailored to individual tumor complexities. This evolving methodology enriches our comprehension of tumor biology and informs rational treatment strategy design, propelling advancements in cancer immunotherapy [80, 84, 37]. By providing a quantitative basis for predicting cancer progression and treatment responses, these models pave the way for more effective and targeted therapeutic interventions.

9 Conclusion

This survey elucidates the integral roles of metabolic reprogramming, immune dynamics, and the tumor microenvironment in shaping cancer biology and informing therapeutic strategies. The glycolytic pathways, particularly the Warburg effect, are identified as pivotal therapeutic targets that can significantly influence tumor progression and enhance the effectiveness of current cancer treatments. The glucose competition between tumors and immune cells underscores the necessity for therapies that not only target tumors but also robustly stimulate immune responses. The potential of combination therapies, such as the integration of antiangiogenic treatments with immunotherapy, is highlighted for their capacity to strengthen anti-tumor immunity and improve clinical outcomes. Furthermore, the interplay between cellular adhesion and metabolism presents new avenues for therapeutic intervention, while macropinocytosis is recognized as a critical metabolic adaptation that may be exploited to inhibit tumor growth. The survey also emphasizes the significance of ensuring equitable access to emerging treatments and technologies, which hold promise for improving patient outcomes. Additionally, the integration of circadian rhythm considerations into therapeutic strategies is suggested to enhance treatment efficacy. The role of the SOWAHA gene as a cancer suppressor offers further insights into advancing treatment approaches through its involvement in metabolic pathways. Lastly, the application of mathematical models provides valuable perspectives on optimizing cancer treatment dynamics, particularly through the integration of dietary and pharmacological interventions, and highlights the importance of tumor vasculature normalization in creating opportunities for effective immune responses.

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