Mitochondrial Metabolism and Cancer: A Survey of Metabolic Reprogramming and Drug Resistance in Colorectal Cancer

Abstract

This survey paper provides a comprehensive analysis of the intricate relationship between mitochondrial metabolism, metabolic reprogramming, and cancer progression, with a specific focus on colorectal cancer. The paper explores how alterations in mitochondrial dynamics contribute to metabolic reprogramming, enabling cancer cells to develop drug resistance and chemoresistance, complicating treatment strategies. Key sections include an examination of mitochondrial metabolism in cancer, highlighting the role of mitochondrial dynamics in cancer cell survival, and the adaptation of these dynamics to support proliferation. The survey further delves into metabolic reprogramming in colorectal cancer, identifying critical pathways and their implications for cancer progression. Mechanisms of drug resistance, including the roles of cancer stem cells and ABC transporters, are analyzed to understand their contribution to chemoresistance. The paper also explores potential therapeutic interventions targeting mitochondrial metabolism and dynamics, emphasizing the need for innovative strategies to overcome resistance. Future directions are discussed, highlighting emerging molecular targets and the integration of advanced computational models to enhance treatment efficacy. Overall, this survey underscores the significance of mitochondrial processes in cancer biology and their potential as therapeutic targets to improve outcomes in colorectal cancer treatment.

1 Introduction

1.1 Overview of Paper Structure

This survey meticulously explores the intricate relationship between mitochondrial metabolism and cancer, particularly focusing on metabolic reprogramming and drug resistance in colorectal cancer. The **Introduction** establishes the significance of mitochondrial dynamics and metabolic reprogramming in cancer biology. The subsequent section, **Background and Definitions**, defines key concepts such as mitochondrial metabolism, cancer metabolism, and chemoresistance, laying a foundation for understanding their interconnections in cancer progression.

In the **Mitochondrial Metabolism in Cancer** section, we investigate the unique role of mitochondria in cancer cell metabolism, emphasizing their importance for survival in colorectal cancer. The **Adaptation of Mitochondrial Metabolism in Cancer Cells** subsection further explores how cancer cells modify their mitochondrial metabolism to promote proliferation and survival, with a focus on mitochondrial mutations and dynamics that enhance adaptability.

Transitioning to **Metabolic Reprogramming in Colorectal Cancer**, we discuss alterations in metabolic pathways that support rapid cancer cell growth and survival, identifying key pathways and their implications for cancer progression. The influence of cellular signaling on metabolic reprogramming is examined, incorporating insights from studies like Park et al. [1], which elucidate the interplay between cancer metabolism and signaling pathways.

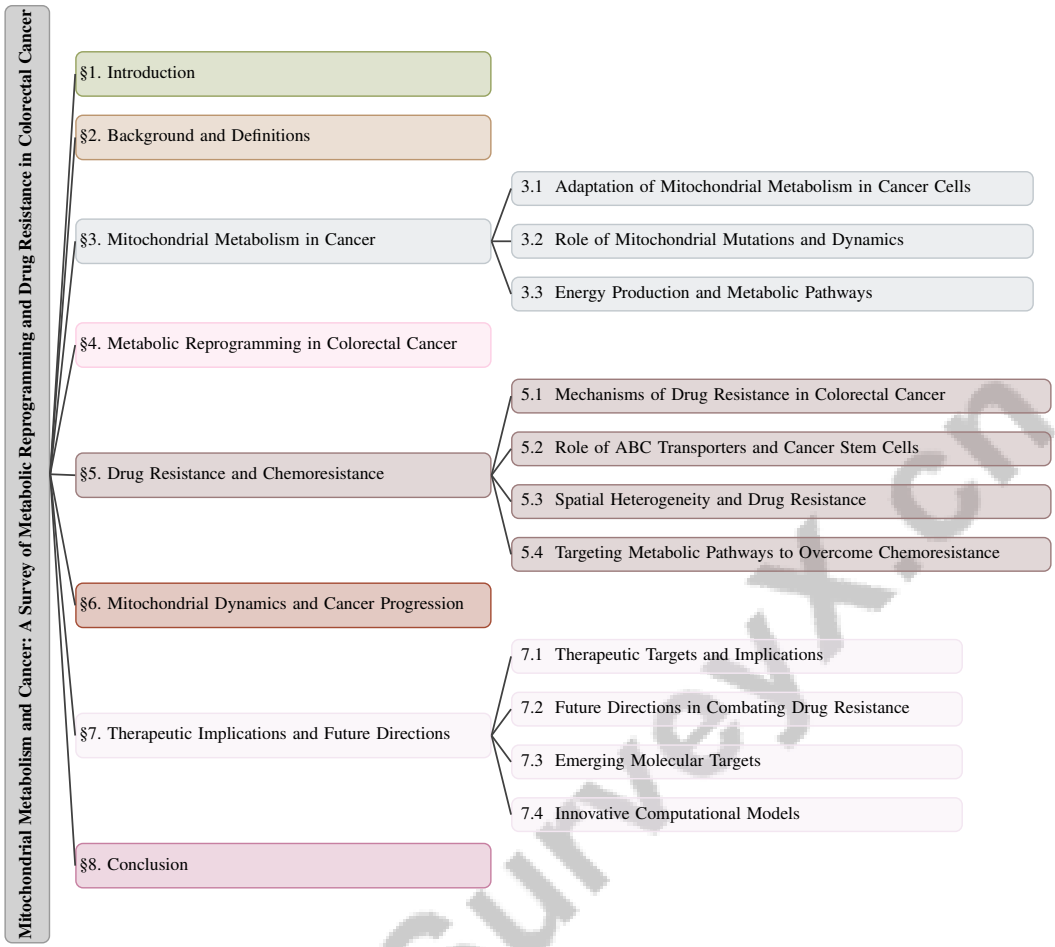


Figure 1: chapter structure

The **Drug Resistance and Chemoresistance** section analyzes mechanisms by which colorectal cancer cells develop chemotherapy resistance, highlighting the role of mitochondrial metabolism and dynamics. Chen et al. [2] emphasize the importance of metabolic regulation in reversing chemoresistance, while strategies targeting metabolic pathways to overcome this resistance are also explored.

The section **Mitochondrial Dynamics and Cancer Progression** investigates how mitochondrial fission and fusion influence cancer cell adaptability and survival, with recent findings underscoring their impact on treatment outcomes and chemoresistance, thereby identifying potential therapeutic targets.

Finally, the survey concludes with **Therapeutic Implications and Future Directions**, discussing strategies to target mitochondrial metabolism and dynamics to combat drug resistance. Emerging research, such as the innovative treatment combining radiofrequency ablation and melatonin by Li et al. [3], is presented alongside future research directions and clinical application potentials.

This comprehensive structure not only offers a detailed examination of current research but also synthesizes insights from various studies, including the impact of competition between cancer and healthy cells on treatment outcomes [4] and a novel framework for understanding imipridones' anticancer activity [5], thereby providing a holistic understanding of the complex interplay between mitochondrial metabolism, cancer progression, and therapeutic resistance.The following sections are organized as shown in Figure 1.

AI-generated, for reference only.

2 Background and Definitions

2.1 Emerging Concepts in Cancer Biology

Recent advancements in cancer biology have highlighted the critical interplay between mitochondrial metabolism and drug resistance. A significant focus is on the adaptation of cancer cell amino acid metabolism, which often depends on external sources due to mutations that impair biosynthetic capabilities, as noted by Vettore et al. [6]. This metabolic flexibility is crucial for cancer cell survival and proliferation within the tumor microenvironment (TME).

The mitochondrial phosphatase PGAM5 is essential for maintaining mitochondrial fission; its absence results in hyperfusion and accelerates cellular senescence, as discussed by Yu et al. [7]. These findings underscore the importance of mitochondrial dynamics in regulating cell fate and highlight potential therapeutic targets for modulating mitochondrial function in cancer.

The role of YAP/TAZ in cancer metabolic reprogramming and its impact on tumor energy metabolism is a key issue, as identified by Zhang et al. [8]. These transcriptional regulators are involved in multiple signaling pathways that influence cancer cell metabolism, affecting tumor progression and resistance mechanisms.

SOWAHA, a gene linked to cancer prognosis, may influence metabolic reprogramming, suggesting a broader role in tumor biology, as observed by Yi et al. [9]. This relationship underscores the potential for discovering novel biomarkers and therapeutic targets by examining the genetic foundations of metabolic alterations in cancer.

The dysregulation of Sirt4, associated with aging-related disorders, has a context-dependent role in cancer, as described by Tomaselli et al. [10]. Investigating the interplay between Sirt4 and mitochondrial metabolism may provide insights into aging and cancer progression, presenting new avenues for therapeutic intervention.

Innovative modeling approaches, such as those proposed by Ramazzotti et al. [11], offer efficient methods for inferring cancer progression involving genetic alterations. These models, coupled with mathematical oncology tools, provide robust frameworks for studying cancer dynamics and treatment outcomes, addressing challenges in drug resistance and therapy optimization as highlighted by Malinzi et al. [12].

Integrating emerging concepts like mathematical modeling and combination cancer therapies enables the development of more effective therapeutic strategies targeting the intricate mechanisms of cancer progression and drug resistance. This multifaceted approach addresses factors such as cell heterogeneity, drug target alterations, and microenvironmental adaptations, aiming to enhance treatment outcomes and improve patient survival rates. As precision medicine and immunotherapy continue to evolve, these strategies hold promise for overcoming significant challenges in oncology, including high treatment costs and persistent drug resistance [12, 13].

In recent years, the understanding of mitochondrial metabolism in cancer has evolved significantly, revealing intricate adaptations that cancer cells employ to thrive. Figure 2 illustrates the hierarchical structure of mitochondrial metabolism in cancer, highlighting key adaptations, the role of mitochondrial mutations and dynamics, and the interplay of energy production and metabolic pathways. Each section of this figure addresses the complex mechanisms that cancer cells utilize to sustain growth and survival, thereby providing valuable insights into potential therapeutic targets. This comprehensive depiction serves to enhance our understanding of the metabolic reprogramming in cancer and underscores the importance of targeting mitochondrial functions in therapeutic strategies.

3 Mitochondrial Metabolism in Cancer

3.1 Adaptation of Mitochondrial Metabolism in Cancer Cells

Cancer cells demonstrate significant adaptability in reprogramming mitochondrial metabolism, crucial for their growth and survival across various environments. This adaptability involves a complex interaction between glycolysis and oxidative phosphorylation (OXPHOS), influenced by the Warburg effect, which favors glycolysis even in oxygen-rich conditions to support rapid proliferation [1]. The tumor suppressor protein p53 plays a central role in balancing glycolytic and mitochondrial

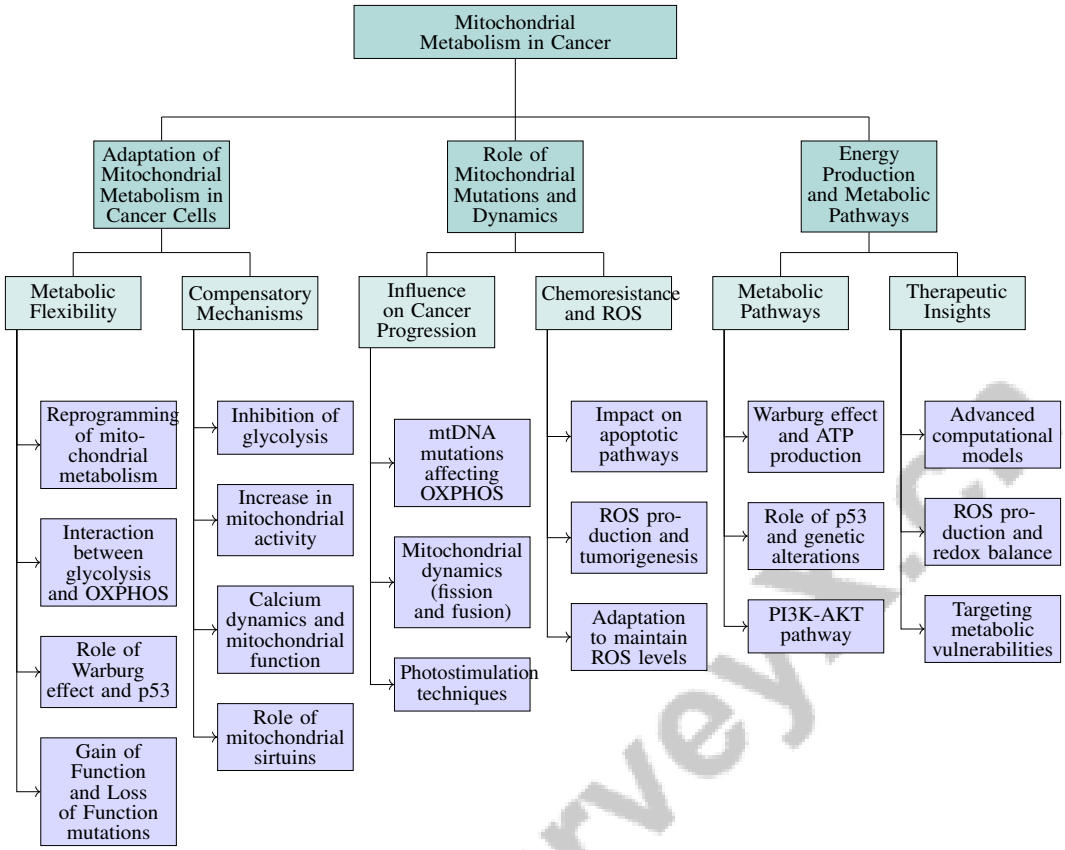


Figure 2: This figure illustrates the hierarchical structure of mitochondrial metabolism in cancer, highlighting key adaptations, the role of mitochondrial mutations and dynamics, and the interplay of energy production and metabolic pathways. Each section addresses the complex mechanisms cancer cells utilize to sustain growth and survival, providing insights into potential therapeutic targets.

pathways, thereby regulating cancer metabolism and enhancing survival under stress [14]. Mutations within cellular regulatory networks, including Gain of Function (GoF) and Loss of Function (LoF) mutations, further enhance metabolic flexibility, allowing cancer cells to optimize resource use amid nutrient fluctuations [15].

Inhibiting glycolysis often triggers compensatory increases in mitochondrial activity, altering metabolic profiles to favor survival during metabolic stress [16]. This adaptation enhances ATP production via OXPHOS and meets biosynthetic and redox demands. The interaction between calcium dynamics and mitochondrial metabolism is critical, with kinetic models showing that calcium signaling optimizes mitochondrial function [17]. Advanced techniques, such as photostimulation with femtosecond laser pulses, have provided insights into mitochondrial dynamics, revealing how cancer cells regulate mitochondrial morphology and function to meet metabolic needs [18]. The enzymatic activity of mitochondrial sirtuins, especially Sirt4, illustrates the dual role of mitochondrial enzymes in regulating metabolism and stress responses [10].

Figure 3 illustrates the hierarchical categorization of key concepts related to the adaptation of mitochondrial metabolism in cancer cells, highlighting metabolic pathways, regulatory mechanisms, and research methods. These findings reveal a complex network of regulatory mechanisms enabling cancer cells to adapt mitochondrial metabolism, supporting sustained growth and survival in the tumor microenvironment.

3.2 Role of Mitochondrial Mutations and Dynamics

Mitochondrial mutations and dynamics are pivotal in cancer progression, influencing metabolism and apoptosis regulation. Mutations in mitochondrial DNA (mtDNA) can impair OXPHOS, disrupting

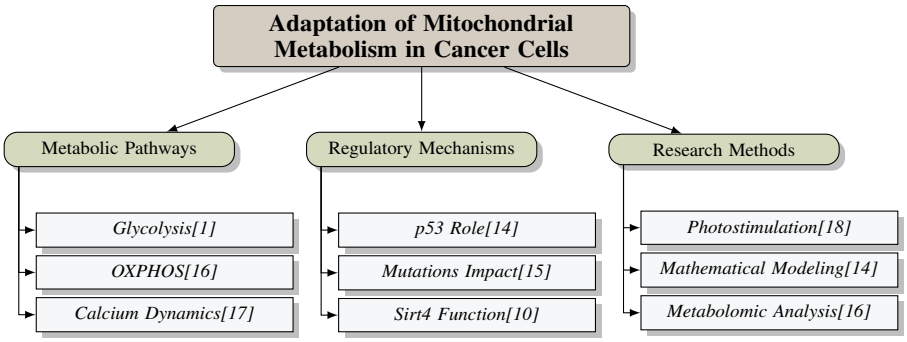


Figure 3: This figure illustrates the hierarchical categorization of key concepts related to the adaptation of mitochondrial metabolism in cancer cells, highlighting metabolic pathways, regulatory mechanisms, and research methods.

processes critical for cancer cell growth [19, 20, 21]. Such alterations favor glycolysis over OXPHOS, a hallmark of the Warburg effect, supporting rapid proliferation under hypoxic conditions. Mitochondrial dynamics, encompassing fission and fusion, are essential for maintaining function and homeostasis. In cancer cells, these dynamics are often disrupted, leading to altered morphology and function. Photostimulation techniques have enabled precise observation, revealing how cancer cells exploit dynamics for adaptability and survival [18].

The interplay between mitochondrial dynamics and chemoresistance is elucidated by frameworks categorizing chemoresistance mechanisms into distinct molecular pathways, highlighting interactions among proteins and signaling cascades contributing to drug resistance [22]. Alterations in fission and fusion can influence apoptotic pathways, modulating sensitivity to chemotherapeutic agents. Mitochondrial mutations also affect reactive oxygen species (ROS) production, which plays a dual role in cancer biology, promoting tumorigenesis through genomic instability and facilitating cell death via oxidative stress [19, 21]. Cancer cells adapt to maintain ROS at levels conducive to progression, partially through dynamics regulation.

The relationship between mitochondrial mutations and dynamics is crucial in cancer progression, impacting energy production, metabolic regulation, and processes like cell signaling and apoptosis [14, 23, 20, 24, 21]. Understanding these processes may reveal therapeutic targets to disrupt metabolic adaptations and resistance mechanisms.

3.3 Energy Production and Metabolic Pathways

Cancer cell metabolism involves a complex interplay of energy production mechanisms and metabolic pathways facilitating rapid growth and survival. The Warburg effect, where cancer cells prefer glycolysis over OXPHOS for ATP production, even with oxygen, supports biosynthetic and energetic demands [19]. The p53 protein, known for tumor suppression, regulates the balance between glycolysis and OXPHOS. Distinct metabolic profiles among p53 mutants influence active pathways, affecting glycolysis and respiration [19]. Genetic alterations in pathways like PI3K-AKT contribute to metabolic adaptations, promoting anabolic processes and enhancing glucose uptake and glycolysis [25].

Advanced computational models, such as the multi-agent system (MAS), simulate mitochondrial metabolism, providing insights into dynamic biochemical processes [26]. The interplay between glycolysis and mitochondrial metabolism is influenced by ROS production, regulating redox balance and impacting adaptation to stressors [27, 28, 23]. Cancer cells modulate ROS to promote proliferation while avoiding oxidative damage. This crosstalk highlights the complexity of energy production and potential therapeutic targeting.

Understanding energy production mechanisms and metabolic pathways is vital for identifying therapeutic targets. Studies demonstrate metabolic diversity and adaptability in response to nutrient availability and stress. Analysis of over 900 cell lines reveals distinct profiles linked to genetic alterations, while insights into glutamine metabolism underscore its role in proliferation and survival under stress. The tumor microenvironment's influence on metabolism suggests targeting specific

vulnerabilities could lead to effective strategies [29, 30, 31]. Elucidating metabolic adaptations can help devise strategies to disrupt flexibility enabling cancer cell survival.

4 Metabolic Reprogramming in Colorectal Cancer

4.1 Key Metabolic Pathways

Colorectal cancer (CRC) undergoes significant metabolic reprogramming, prominently featuring a shift towards aerobic glycolysis, known as the Warburg effect, where cancer cells favor glycolysis over oxidative phosphorylation (OXPHOS) for ATP production, even with sufficient oxygen. This adaptation supports rapid proliferation by providing energy and biosynthetic precursors, enabling survival in nutrient-limited environments, and promoting tumor progression. Metastatic cells often exhibit distinct metabolic profiles from primary tumors, highlighting potential therapeutic targets to counteract metastasis [32, 29, 33, 31, 30].

In CRC, the glycolytic pathway is upregulated, facilitating glucose conversion to lactate and contributing to an acidic tumor microenvironment. This metabolic shift is driven by mutations in oncogenes such as KRAS and tumor suppressor genes like TP53, which activate pathways including PI3K-AKT and MAPK, enhancing glucose uptake and glycolytic activity [25]. Beyond glycolysis, CRC cells alter the tricarboxylic acid (TCA) cycle and glutaminolysis, increasing glutamine uptake to fuel the TCA cycle, supporting biosynthesis and redox balance, and allowing adaptation to nutrient fluctuations [34, 35, 31].

The adaptability of cancer metabolism, as explored through surrogate relationships across treatment classes [36], is crucial for survival in the adverse tumor microenvironment and contributes to therapy resistance. Targeting these metabolic adaptations, such as the reliance on glucose and glutamine, enhanced glycolytic and glutaminolytic pathways, and altered fatty acid oxidation, offers a promising therapeutic avenue in CRC. Interventions in these pathways may restore chemotherapy sensitivity and inhibit processes like epithelial–mesenchymal transition (EMT), pivotal for metastasis and tumor aggressiveness, necessitating further exploration of metabolic mechanisms to develop effective CRC treatments [33, 2].

4.2 Role of Cellular Signaling in Metabolic Reprogramming

Cellular signaling pathways are pivotal in the metabolic reprogramming of colorectal cancer (CRC), linking extracellular cues to intracellular metabolic processes and shaping cancer cell phenotypes for growth and survival. The PI3K-AKT-mTOR pathway is frequently activated in cancer, promoting anabolic processes by increasing glucose uptake, glycolysis, and lipid and protein synthesis [25]. Oncogenic mutations, such as KRAS activation and TP53 loss, further enhance the influence of signaling pathways on metabolism, disrupting cascades like MAPK and Wnt/-catenin, which regulate glycolysis and mitochondrial function [19].

Signaling pathways also impact OXPHOS and the TCA cycle, as interactions between signaling molecules and metabolic enzymes enable cancer cells to adjust energy production to environmental changes, ensuring ATP supply and essential intermediates for proliferation. Oncogenic pathways like PI3K/AKT and Myc drive metabolic gene expression and enzyme activity, facilitating tumor growth, metastasis, and therapy resistance [1, 32]. Transcriptional regulators like YAP/TAZ mediate signaling effects on metabolism, controlling genes related to glycolysis and glutaminolysis, illustrating the complexity of signaling-mediated metabolic reprogramming [8].

Integrating cellular signaling with metabolic reprogramming is vital for cancer cells to adapt to the tumor microenvironment, supporting survival under stress and enhancing resistance to therapies. This adaptation involves changes in glycolysis, glutaminolysis, and lipid metabolism, contributing to tumor aggressiveness and therapy evasion. Targeting these metabolic changes offers a strategy to overcome therapeutic resistance and improve treatment efficacy [33, 37, 2]. Understanding these molecular mechanisms can aid in developing therapies targeting signaling pathways that drive metabolic reprogramming, potentially enhancing colorectal cancer treatment outcomes.

Category	Feature	Method
Mechanisms of Drug Resistance in Colorectal Cancer	Microenvironmental Factors	HMM[38], gFMMR[39], SPM[40]
Targeting Metabolic Pathways to Overcome Chemoresistance	Machine Learning Approaches	CD[41]
	Environmental and Biological Modeling	ESL[42]
	Data Integration Techniques	ADS[43]

Table 1: This table provides a comprehensive summary of the methods employed to study drug resistance mechanisms and strategies to overcome chemoresistance in colorectal cancer. It categorizes the features and methods involved in understanding microenvironmental factors and targeting metabolic pathways, including machine learning approaches, environmental and biological modeling, and data integration techniques.

5 Drug Resistance and Chemoresistance

Understanding drug resistance in colorectal cancer involves examining the intricate mechanisms that contribute to this phenomenon. Table 1 presents a detailed summary of the methods and features associated with the mechanisms of drug resistance in colorectal cancer and strategies to target metabolic pathways to overcome chemoresistance. Additionally, Table 2 presents a comprehensive comparison of the mechanisms and therapeutic strategies associated with drug resistance in colorectal cancer, elucidating the complex interplay of molecular and environmental factors that hinder effective treatment. The following subsection will explore these mechanisms, focusing on how molecular, cellular, and environmental factors converge to create a challenging landscape for effective treatment. This exploration lays the groundwork for understanding the complexity of resistance and its implications for therapeutic strategies.

5.1 Mechanisms of Drug Resistance in Colorectal Cancer

Drug resistance in colorectal cancer is driven by a complex interplay of molecular, cellular, and microenvironmental factors. The rapid emergence of drug-resistant cancer cells poses a significant challenge, limiting the efficacy of single and multi-drug therapies and often resulting in multidrug resistance [44]. This resistance is exacerbated by the toxic side effects of cytotoxic drugs, which can lead to the survival and proliferation of resistant clones [40].

Cancer stem cells (CSCs) are pivotal in mediating drug resistance due to their enhanced drug efflux capabilities, primarily mediated by ATP-binding cassette (ABC) transporters, and their superior DNA repair mechanisms [45]. These properties enable CSCs to survive chemotherapy and contribute to tumor relapse. Additionally, slow-cycling subpopulations within tumors complicate treatment, as these cells are less sensitive to conventional chemotherapy, allowing them to persist and eventually repopulate the tumor [38].

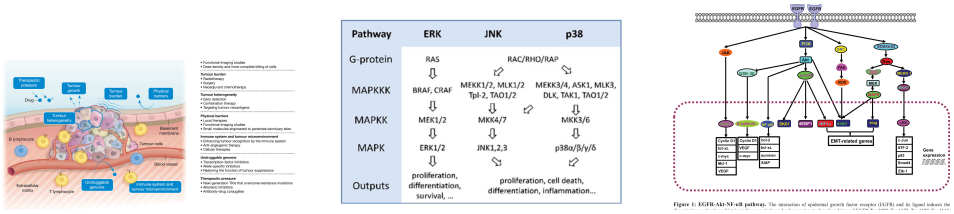
The tumor microenvironment significantly influences drug resistance through the secretion of survival-promoting factors and the establishment of physical barriers by the extracellular matrix, which impede drug penetration [45]. Hypoxic conditions within the tumor microenvironment, characterized by elevated levels of hypoxia-inducible factor-1 alpha (HIF-1), induce adaptive responses that enhance cancer cell survival and contribute to chemoresistance.

Intracellular signaling pathways, particularly the PI3K/AKT pathway, drive resistance by modulating downstream targets such as c-myc and p53, influencing cell cycle progression and apoptosis [46]. The activation of these pathways promotes survival and proliferation, enhancing resistance to chemotherapeutic agents.

The challenge of predicting effective drug combinations to combat resistance is highlighted by the need for accurate computational models, given the extensive number of possible combinations [43]. Models like the gFMMR, which handle overlapping clusters and jointly model multiple drugs, improve predictive accuracy and offer potential solutions to overcome resistance [39].

The complexity of drug resistance mechanisms in colorectal cancer underscores the need for comprehensive strategies addressing diverse resistance factors. By elucidating these mechanisms and interactions within cancer therapies, innovative therapeutic strategies can be developed, such as combination cancer therapies (CCTs) targeting multiple pathways. These approaches aim to enhance treatment efficacy and improve patient outcomes by overcoming molecular and pathophysiological

challenges, leading to more personalized treatment regimens informed by advanced computational methods and omics data analysis [12, 47].



(a) Therapeutic Strategies for Cancer Treatment[48]

(b) Cellular Pathways and Signaling[49]

(c) EGFR-Akt-NF-B pathway[22]

Figure 4: Examples of Mechanisms of Drug Resistance in Colorectal Cancer

As shown in Figure 4, drug resistance and chemoresistance in colorectal cancer involve complex cellular mechanisms and therapeutic challenges. The first image, "Therapeutic Strategies for Cancer Treatment," illustrates the tumor microenvironment's roles in influencing tumor growth and progression. The second image, "Cellular Pathways and Signaling," showcases molecular pathways like ERK, JNK, and p38, highlighting the intricate network of signaling molecules mediating cellular responses and survival. The "EGFR-Akt-NF-B pathway" image underscores how aberrant signaling can lead to altered gene expression and resistance to apoptosis. These visual representations provide a comprehensive overview of the multifaceted mechanisms driving drug resistance, underscoring the need for innovative therapeutic strategies [48, 49, 22].

5.2 Role of ABC Transporters and Cancer Stem Cells

ABC transporters and cancer stem cells (CSCs) are significant contributors to drug resistance in colorectal cancer, presenting challenges for effective treatment. ABC transporters actively pump chemotherapeutic agents out of cancer cells, reducing drug accumulation and efficacy, a well-established contributor to multidrug resistance [50]. Their roles extend beyond drug efflux, involving interactions with signaling pathways and the tumor microenvironment, complicating their impact on drug resistance [50].

CSCs, a subpopulation of cancer cells with stem-like properties, are inherently resistant to conventional treatments due to their quiescent nature, efficient DNA repair mechanisms, and expression of ABC transporters [51]. CSCs adapt to changes in the tumor microenvironment, maintaining their stemness and driving tumor progression under therapeutic pressure [51]. The plasticity of CSCs and their interaction with the tumor microenvironment create a dynamic and resilient niche supporting their survival and resistance to treatment.

The impact of ABC transporters and CSCs on drug resistance highlights the complexity of targeting these mechanisms in therapy. Understanding the interplay between tumor cells and their microenvironment is essential for developing innovative strategies aimed at improving treatment outcomes. By targeting the pathways and mechanisms underlying ABC transporters and CSC resilience, novel strategies can be developed to enhance treatment efficacy and reduce resistance likelihood [29, 13, 52, 44].

5.3 Spatial Heterogeneity and Drug Resistance

Spatial heterogeneity within tumors critically affects drug resistance by creating diverse microenvironments that influence cellular behavior and treatment response. Tumors comprise various cell types with distinct genetic and phenotypic profiles, leading to differential chemotherapy responses. Heterogeneity arises from genetic mutations and variations in the tumor microenvironment, including differences in oxygen availability, nutrient gradients, and extracellular matrix composition [45].

Hypoxic tumor regions induce adaptive responses enhancing cell survival and chemoresistance, often stabilizing hypoxia-inducible factors (HIFs) that promote angiogenesis, alter metabolism, and enhance drug efflux transporter expression [45]. Uneven blood vessel distribution within tumors can result in limited drug penetration, reducing chemotherapeutic effectiveness.

CSCs in specific tumor niches complicate treatment, exhibiting inherent chemotherapy resistance and the capacity to repopulate tumors post-treatment. CSCs reside in protective niches within the tumor microenvironment, maintaining their stem-like properties [51]. Their interaction with the microenvironment contributes to tumor spatial heterogeneity, complicating eradication efforts.

Mathematical and computational models studying spatial heterogeneity's impact on drug resistance provide insights into how cell density and microenvironmental variations influence treatment outcomes [12]. These models emphasize the importance of considering spatial heterogeneity in therapeutic strategy design, as targeting diverse tumor microenvironments may enhance treatment efficacy.

Spatial heterogeneity complicates effective therapy by fostering drug resistance and enhancing tumor survival. Variations in drug penetration and concentration across tumor regions can lead to resistant cancer cell emergence, especially in areas with lower drug exposure. Mathematical modeling studies show spatial differences can accelerate resistance evolution, highlighting the necessity for novel strategies targeting both tumor cells and their microenvironments to combat cancer effectively [52, 53, 54, 40]. Understanding these heterogeneity mechanisms can help develop more targeted and effective treatment strategies addressing cancer cells' diverse needs within the tumor microenvironment.

5.4 Targeting Metabolic Pathways to Overcome Chemoresistance

Targeting metabolic pathways to overcome chemoresistance in colorectal cancer offers a promising avenue for enhancing therapeutic efficacy. Cancer cells exhibit unique metabolic adaptations, such as the Warburg effect, characterized by increased glycolytic activity even in the presence of oxygen, supporting their survival and proliferation under chemotherapeutic stress [32].

The tumor microenvironment plays a critical role in chemoresistance, and targeting its components may offer new avenues for overcoming resistance [52]. Interactions within the tumor microenvironment, including those involving cancer-associated adipocytes (CAAs) and lipid metabolism, can be modulated to enhance therapy efficacy, suggesting a need for combination approaches [55].

Emerging research indicates that inducing ferroptosis, a form of regulated cell death driven by iron-dependent lipid peroxidation, can effectively reverse drug resistance, offering a novel approach to enhance cancer treatment efficacy [56]. This strategy targets cancer cells' metabolic dependencies, disrupting their ability to manage oxidative stress and maintain cellular homeostasis.

The AKT signaling pathway, frequently dysregulated in cancer, plays a significant role in mediating chemoresistance. Targeting AKT and associated pathways, particularly through ion channels, presents a promising therapeutic strategy to overcome resistance [46]. Inhibiting key components of this pathway can sensitize cancer cells to chemotherapeutic agents, improving treatment outcomes.

Mathematical and computational models have been developed to understand tumor growth and drug resistance dynamics better. For instance, a mathematical model based on the environmental stress level (ESL) describes the collective influence of oxygen levels and tissue stiffness on tumor cell response to chemotherapy [42]. Additionally, the CelluDose model employs deep reinforcement learning for adaptive drug dosing, targeting stochastic and heterogeneous cell proliferation [41].

The integration of advanced computational methods, such as AuDNNsynergy, which predicts synergistic drug combinations by integrating gene expression, mutation, copy number variation, and drug physicochemical properties, can enhance chemotherapeutic response prediction [43]. This approach, combined with developing combination therapies targeting multiple pathways simultaneously, holds promise for sensitizing resistant cancer cells and improving treatment outcomes.

Feature	Mechanisms of Drug Resistance in Colorectal Cancer	Role of ABC Transporters and Cancer Stem Cells	Spatial Heterogeneity and Drug Resistance
Resistance Mechanism	Multidrug Resistance	Drug Efflux	Microenvironmental Diversity
Key Factors	Cancer Stem Cells	Abc Transporters	Hypoxic Conditions
Therapeutic Strategy	Combination Therapies	Targeting Pathways	Mathematical Modeling

Table 2: This table provides a comparative overview of the mechanisms of drug resistance in colorectal cancer, focusing on multidrug resistance, drug efflux, and spatial heterogeneity. It highlights the role of cancer stem cells, ABC transporters, and hypoxic conditions in contributing to resistance, and outlines therapeutic strategies such as combination therapies, targeting specific pathways, and mathematical modeling to overcome these challenges.

6 Mitochondrial Dynamics and Cancer Progression

6.1 Impact of Mitochondrial Dynamics on Cancer Cell Adaptability

Mitochondrial dynamics, encompassing fission and fusion processes, are vital for cancer cell adaptability and survival under stress. These processes allow cancer cells to adjust mitochondrial morphology and function to meet metabolic demands. Mitofusin 1 (Mfn1) and Mitofusin 2 (Mfn2) are pivotal in mitochondrial fusion, merging membranes to maintain mitochondrial integrity and function [57]. This fusion is crucial for stabilizing mitochondrial DNA (mtDNA) and optimizing metabolism during stress.

Mitochondrial dynamics enhance cellular resilience by redistributing components, supporting bioenergetic efficiency, and enabling mitophagy to remove damaged mitochondria [58]. This adaptability is essential for cancer cells facing fluctuating microenvironmental conditions and therapeutic pressures. Spatial heterogeneity and cancer cell migration amplify their ability to modulate mitochondrial dynamics, influencing drug resistance evolution in metastatic cancers [54]. The interplay of fission and fusion optimizes metabolic states, aiding rapid proliferation and survival in diverse environments.

Techniques like photostimulation with femtosecond laser pulses have elucidated mitochondrial dynamics' roles in energy production and apoptotic regulation, impacting cancer cell survival [18]. The clonal diversity in cancer recurrence, driven by mutations rather than single clone expansion, underscores mitochondrial dynamics' importance in cancer adaptability [59]. The interaction between mitochondrial dynamics and cellular signaling pathways can refine treatment strategies based on pre-existing resistance levels, as shown in models of cell competition and drug resistance [4].

6.2 Mitochondrial Dynamics and Chemoresistance

Mitochondrial dynamics significantly influence chemoresistance development in cancer cells by enabling adaptation to metabolic and environmental stresses from chemotherapy. Fission, mediated by proteins like Drp1 and Fis1, is crucial for mitochondrial distribution and quality control, facilitating damaged mitochondria's segregation and removal via mitophagy [57]. This quality control is vital for maintaining mitochondrial function and cellular homeostasis during chemotherapeutic stress.

The relationship between mitochondrial dynamics and chemoresistance is further complicated by phenotypic switching, a non-genetic resistance mechanism affecting treatment outcomes [60]. This allows cancer cells to transiently alter their phenotype in response to environmental changes, including drug exposure, without genetic mutations, evading chemotherapy's cytotoxic effects and contributing to drug-resistant populations' persistence.

Mitochondrial fusion, facilitated by Mitofusin 1 and 2, complements fission by optimizing metabolic function and enhancing cellular resilience against stress [57]. The fission-fusion balance is critical for maintaining mitochondrial integrity and function necessary for cancer cell survival and proliferation amid chemotherapeutic challenges.

The interplay between mitochondrial dynamics and chemoresistance underscores the complexity of targeting these processes for therapeutic intervention. Modulating the balance between fission and fusion could enhance cancer cells' susceptibility to chemotherapy, potentially overcoming drug resistance mechanisms that lead to treatment failure. This approach is essential for addressing cancer drug resistance's multifaceted nature, driven by mechanisms like metabolic reprogramming and evasion of cell death pathways [56, 61, 45, 62, 21]. Understanding molecular mechanisms underlying mitochondrial dynamics and their role in chemoresistance offers insights for developing novel therapeutic strategies to improve cancer treatment outcomes.

7 Therapeutic Implications and Future Directions

7.1 Therapeutic Targets and Implications

Targeting mitochondrial metabolism and dynamics offers promising strategies for colorectal cancer treatment, particularly in overcoming drug resistance. The tumor suppressor protein p53 plays a critical role in modulating cancer cell metabolism by reversing the Warburg effect, thus enhancing oxidative phosphorylation and treatment efficacy [14, 33, 19, 2]. Targeting pathways involved in

ferroptosis can further disrupt cancer cells' oxidative stress management, improving therapeutic outcomes.

Cancer stem cells (CSCs) significantly contribute to therapy resistance, and identifying key CSC markers and pathways provides potential therapeutic targets [51]. Disrupting these pathways could mitigate CSC survival during chemotherapy, addressing tumor relapse. The tumor microenvironment, including tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs), is crucial in mediating chemoresistance through interactions with cancer cells [63, 52]. Strategies targeting both tumor cells and their microenvironment, coupled with metabolic interventions and immunotherapy, could enhance treatment efficacy.

Adaptive therapies, informed by continuous monitoring, are vital for managing resistance, and research should incorporate non-chemical methods to enhance treatment efficacy [44]. Mathematical models simulating tumor dynamics under drug influences can optimize therapy [40], while stability analyses of mitochondrial models can identify conditions ensuring stability in complex biological interactions [64].

Combination therapies, including epigenetic drugs, are critical for preventing drug-resistant cancer cell formation [45]. Advanced computational models, such as AuDNNsynergy, enhance drug combination predictions, improving personalized cancer therapy [43].

7.2 Future Directions in Combating Drug Resistance

A comprehensive approach integrating advanced detection techniques, therapeutic monitoring, and innovative strategies is necessary to address drug resistance in colorectal cancer. Future research should develop specific ferroptosis inducers targeting cancer cells while minimizing systemic effects and identify reliable biomarkers for clinical monitoring [56]. Exploring circular RNAs (circRNAs) offers potential for understanding drug resistance mechanisms and identifying therapeutic targets [65].

Combination therapies targeting multiple CSC-associated pathways are crucial for improving treatment efficacy and preventing relapse [51]. Personalized combination therapies based on individual epigenetic profiles should be considered to optimize drug dosages and explore new targets [45].

Understanding metabolic crosstalk between cancer and immune cells is vital for enhancing immunotherapy outcomes. Future research should focus on metabolic interventions to improve immunotherapy efficacy, revealing vulnerabilities that enhance effectiveness by targeting cancer progression and modulating immune responses [66, 29, 67, 31, 30].

Refining SMAC mimetic designs and their combination with other therapies could improve treatment effectiveness. Investigating IAP modulation across various cancer types may provide insights into overcoming resistance [68]. These directions can deepen understanding of drug resistance mechanisms, leading to more effective therapeutic strategies for colorectal cancer.

7.3 Emerging Molecular Targets

Recent advancements have identified promising molecular targets for therapeutic intervention in colorectal cancer. The Bcl-2 protein family, crucial in apoptosis regulation, is implicated in chemoresistance. Inhibitors targeting Bcl-2 proteins, such as BH3 mimetics, have shown potential in sensitizing cancer cells to chemotherapy by promoting apoptosis [68].

The PI3K/AKT/mTOR signaling pathway, frequently dysregulated in colorectal cancer, contributes to tumor growth and survival. Inhibitors targeting this pathway have demonstrated efficacy in preclinical models, and dual inhibitors targeting both PI3K and mTOR may enhance therapeutic outcomes [25].

Epigenetic regulators, such as histone deacetylases (HDACs) and DNA methyltransferases (DNMTs), offer potential therapeutic targets. Inhibitors of these enzymes can modulate gene expression and reverse aberrant epigenetic modifications, offering a novel approach to sensitize tumors to chemotherapy [45].

The Wnt/-catenin signaling pathway, often activated in colorectal cancer, represents another promising target. Small molecule inhibitors disrupting -catenin interactions have shown potential in preclinical studies, underscoring the therapeutic value of targeting this pathway [19].

These molecular targets highlight the potential for developing targeted therapies to enhance existing treatments and overcome resistance in colorectal cancer. By focusing on emerging targets and leveraging precision oncology advancements, researchers can devise innovative strategies to improve patient outcomes [13, 12, 69, 47, 39].

7.4 Innovative Computational Models

Innovative computational models are crucial for identifying and testing new therapeutic strategies for colorectal cancer, offering frameworks to simulate complex biological systems and predict treatment outcomes. The structured population model, accounting for spatial organization and phenotypic variability, provides a nuanced understanding of tumor dynamics compared to traditional models [40]. This approach explores spatial heterogeneity's impact on drug resistance and tumor progression, informing targeted therapy development.

These models incorporate diverse biological data, including genetic, epigenetic, and metabolic profiles, to simulate interactions between cancer cells and their microenvironment comprehensively. Leveraging extensive datasets from resources like the Cancer Cell Line Encyclopedia enables detailed analyses of how metabolic diversity and genomic features influence tumor behavior and therapeutic responses, aiding in identifying potential drug targets and improving patient stratification [29, 70, 71, 11]. Capturing tumor biology's complexity, computational models identify therapeutic targets and predict drug combination efficacy, facilitating personalized treatment strategy design.

Integrating machine learning algorithms with computational models enhances the ability to analyze large datasets and identify patterns not apparent through traditional methods. This fusion accelerates the discovery of novel therapeutic targets and optimizes treatment regimens, contributing to more effective cancer therapies. By harnessing advanced computational models, researchers can significantly enhance understanding of cancer biology, particularly in predicting drug resistance, clonal evolution, and identifying therapeutic biomarkers. These models facilitate the development of combination cancer therapies (CCTs) to address tumor heterogeneity and microenvironmental adaptations, translating insights into more effective clinical applications and personalized treatment strategies for cancer patients [11, 12, 69, 72, 39].

8 Conclusion

This survey highlights the pivotal influence of mitochondrial metabolism and dynamics in the therapeutic landscape of colorectal cancer. Mitochondria serve as central bioenergetic platforms, crucially affecting metabolic reprogramming and contributing to drug resistance, thereby emerging as promising targets for therapeutic intervention. The identification of mitochondrial ClpP as a significant target for imipridones underscores the potential of targeting mitochondrial functions to improve treatment efficacy.

Metabolic reprogramming, exemplified by the Warburg effect and alterations in glycolytic pathways, plays a crucial role in facilitating epithelial-mesenchymal transition and tumor metastasis. A comprehensive understanding of these metabolic shifts is vital for enhancing therapeutic strategies. Future investigations should focus on elucidating the regulatory mechanisms of metabolic reprogramming across various cancer types, potentially leading to combination therapies that simultaneously target glycolysis and mitochondrial metabolism.

The inherent adaptability of cancer cells, driven by their plastic nature and influenced by intercellular communication and tissue-specific constraints, presents a formidable challenge to effective therapy. This adaptability is further complicated by mitochondrial involvement in immune responses, posing additional hurdles for treatment strategies.

Adopting principles from integrated pest management (IPM) in oncology could offer a novel framework for managing cancer as a chronic condition, prioritizing prolonged survival and improved quality of life over an exclusive focus on curative approaches. Furthermore, the development of innovative computational methods, such as APPM, promises to enhance the efficiency and personalization of cancer therapies, paving the way for more effective treatment paradigms.

References

[1] Jae Hyung Park, Woo Yang Pyun, and Hyun Woo Park. Cancer metabolism: phenotype, signaling and therapeutic targets. *Cells*, 9(10):2308, 2020.

[2] Xun Chen, Shangwu Chen, and Dongsheng Yu. Metabolic reprogramming of chemoresistant cancer cells and the potential significance of metabolic regulation in the reversal of cancer chemoresistance. *Metabolites*, 10(7):289, 2020.

[3] Ming Li, Bingjie Hao, Menghuan Zhang, Russel J Reiter, Shumeng Lin, Tiansheng Zheng, Xiangyun Chen, Yanbei Ren, Liduo Yue, Baigenzhin Abay, et al. Melatonin enhances radiofrequency-induced nk antitumor immunity, causing cancer metabolism reprogramming and inhibition of multiple pulmonary tumor development. *Signal transduction and targeted therapy*, 6(1):330, 2021.

[4] Heyrim Cho and Doron Levy. The impact of competition between cancer cells and healthy cells on optimal drug delivery, 2018.

[5] Neuro-oncology.

[6] Lisa Vettore, Rebecca L Westbrook, and Daniel A Tennant. New aspects of amino acid metabolism in cancer. *British journal of cancer*, 122(2):150–156, 2020.

[7] Bo Yu, Jing Ma, Jing Li, Dazhi Wang, Zhigao Wang, and Shusheng Wang. Mitochondrial phosphatase pgam5 modulates cellular senescence by regulating mitochondrial dynamics. *Nature Communications*, 11(1):2549, 2020.

[8] Xiaodong Zhang, Haiying Zhao, Yan Li, Di Xia, Liang Yang, Yingbo Ma, and Hangyu Li. The role of yap/taz activity in cancer metabolic reprogramming. *Molecular cancer*, 17:1–10, 2018.

[9] Xiaohong Yi, Xianwen Zhang, Claire H. Zhao, Yuhui Chen, Lijun Huang, Hua Zhong, and Yumei Wang. Sowaha as a cancer suppressor gene influence metabolic reprogramming, 2024.

[10] Daniela Tomaselli, Clemens Steegborn, Antonello Mai, and Dante Rotili. Sirt4: a multifaceted enzyme at the crossroads of mitochondrial metabolism and cancer. *Frontiers in Oncology*, 10:474, 2020.

[11] Daniele Ramazzotti. A model of selective advantage for the efficient inference of cancer clonal evolution, 2016.

[12] Joseph Malinzi, Kevin Bosire Basita, Sara Padidar, and Henry A. Adeola. Prospect for application of mathematical models in combination cancer treatments, 2021.

[13] Narges Ramezani and Erfan Mohammadi. The role of public health in the fight against cancer: Awareness, prevention, and early detection, 2023.

[14] Roba Abukwaik, Elias Vera-Siguenza, Daniel Tennant, and Fabian Spill. P53 orchestrates cancer metabolism: Unveiling strategies to reverse the warburg effect, 2024.

[15] Sara Sommariva, Giacomo Caviglia, and Michele Piana. Gain and loss of function mutations in biological chemical reaction networks: a mathematical model with application to colorectal cancer cells, 2020.

[16] Reika Shiratori, Kenta Furuichi, Masashi Yamaguchi, Natsumi Miyazaki, Haruna Aoki, Hiroji Chibana, Kousei Ito, and Shigeki Aoki. Glycolytic suppression dramatically changes the intracellular metabolic profile of multiple cancer cell lines in a mitochondrial metabolism-dependent manner. *Scientific reports*, 9(1):18699, 2019.

[17] Valérie Voorsluijs, Francesco Avanzini, Gianmaria Falasco, Massimiliano Esposito, and Alexander Skupin. Nonequilibrium calcium dynamics optimizes the energetic efficiency of mitochondrial metabolism, 2023.

[18] Yintao Wang, Hao He, Shaoyang Wang, Yaohui Liu, Minglie Hu, Youjia Cao, and Chingyue Wang. Photostimulation activates restorable fragmentation of single mitochondrion by initiating oxide flashes, 2015.

[19] Matilda Eriksson, Gorbatchev Ambroise, Amanda Tomie Ouchida, Andre Lima Queiroz, Dominique Smith, Alfredo Gimenez-Cassina, Marcin P Iwanicki, Patricia A Muller, Erik Norberg, and Helin Vakifahmetoglu-Norberg. Effect of mutant p53 proteins on glycolysis and mitochondrial metabolism. *Molecular and cellular biology*, 37(24):e00328–17, 2017.

[20] Ling He, Karl Johan Tronstad, and Akhil Maheshwari. Mitochondrial dynamics during development. *Newborn (Clarksville, Md.)*, 2(1):19, 2023.

[21] Paolo Ettore Porporato, Nicoletta Filigheddu, José Manuel Bravo-San Pedro, Guido Kroemer, and Lorenzo Galluzzi. Mitochondrial metabolism and cancer. *Cell research*, 28(3):265–280, 2018.

[22] Hua-Chuan Zheng. The molecular mechanisms of chemoresistance in cancers. *Oncotarget*, 8(35):59950, 2017.

[23] Shamir Cassim, Milica Vučetić, Maša Ždralević, and Jacques Pouyssegur. Warburg and beyond: the power of mitochondrial metabolism to collaborate or replace fermentative glycolysis in cancer. *Cancers*, 12(5):1119, 2020.

[24] Marta Giacomello, Aswin Pyakurel, Christina Glytsou, and Luca Scorrano. The cell biology of mitochondrial membrane dynamics. *Nature reviews Molecular cell biology*, 21(4):204–224, 2020.

[25] Gerta Hoxhaj and Brendan D Manning. The pi3k–akt network at the interface of oncogenic signalling and cancer metabolism. *Nature Reviews Cancer*, 20(2):74–88, 2020.

[26] Charles Lales, N. Parisey, Jean-Pierre Mazat, and Marie Beurton-Aimar. Simulation of mitochondrial metabolism using multi-agents system, 2009.

[27] Jessica B Spinelli and Marcia C Haigis. The multifaceted contributions of mitochondria to cellular metabolism. *Nature cell biology*, 20(7):745–754, 2018.

[28] Lucas C Wollenman, Matthew R Vander Ploeg, Mackinzie L Miller, Yizhu Zhang, and Jason N Bazil. The effect of respiration buffer composition on mitochondrial metabolism and function. *PLoS One*, 12(11):e0187523, 2017.

[29] Haoxin Li, Shaoyang Ning, Mahmoud Ghandi, Gregory V Kryukov, Shuba Gopal, Amy Deik, Amanda Souza, Kerry Pierce, Paula Keskula, Desiree Hernandez, et al. The landscape of cancer cell line metabolism. *Nature medicine*, 25(5):850–860, 2019.

[30] Inmaculada Martínez-Reyes and Navdeep S Chandel. Cancer metabolism: looking forward. *Nature Reviews Cancer*, 21(10):669–680, 2021.

[31] Yeon-Kyung Choi and Keun-Gyu Park. Targeting glutamine metabolism for cancer treatment. *Biomolecules & therapeutics*, 26(1):19, 2017.

[32] Gabriele Bergers and Sarah-Maria Fendt. The metabolism of cancer cells during metastasis. *Nature Reviews Cancer*, 21(3):162–180, 2021.

[33] Hyunkoo Kang, Hyunwoo Kim, Sungmin Lee, HyeSook Youn, and BuHyun Youn. Role of metabolic reprogramming in epithelial–mesenchymal transition (emt). *International Journal of Molecular Sciences*, 20(8):2042, 2019.

[34] Elizabeth L Lieu, Tu Nguyen, Shawn Rhyne, and Jiyeon Kim. Amino acids in cancer. *Experimental & molecular medicine*, 52(1):15–30, 2020.

[35] Ahmad A Cluntun, Michael J Lukey, Richard A Cerione, and Jason W Locasale. Glutamine metabolism in cancer: understanding the heterogeneity. *Trends in cancer*, 3(3):169–180, 2017.

[36] Tasos Papanikos, John Thompson, Keith Abrams, Nicolas Staedler, Oriana Ciani, Rod Taylor, and Sylwia Bujkiewicz. A bayesian hierarchical meta-analytic method for modelling surrogate relationships that vary across treatment classes using aggregate data, 2019.

[37] Jinguan Lin, Longzheng Xia, Jiaxin Liang, Yaqian Han, Heran Wang, Linda Oyang, Shiming Tan, Yutong Tian, Shan Rao, Xiaoyan Chen, et al. The roles of glucose metabolic reprogramming in chemo-and radio-resistance. *Journal of Experimental & Clinical Cancer Research*, 38(1):218, 2019.

[38] Gibin G Powathil, Mark AJ Chaplain, and Maciej Swat. Investigating the development of chemotherapeutic drug resistance in cancer: A multiscale computational study, 2014.

[39] Hongmei Liu and J. Sunil Rao. Precision therapeutic biomarker identification with application to the cancer genome project, 2017.

[40] Alexander Lorz, Tommaso Lorenzi, Jean Clairambault, Alexandre Escargueil, and Benoît Perthame. Effects of space structure and combination therapies on phenotypic heterogeneity and drug resistance in solid tumors, 2013.

[41] Dalit Engelhardt. Dynamic control of stochastic evolution: A deep reinforcement learning approach to adaptively targeting emergent drug resistance, 2020.

[42] Sabrina Schönfeld, Laura Scarabosio, Alican Ozkan, Marissa Nichole Rylander, and Christina Kuttler. Using systemic modeling and bayesian calibration to investigate the role of the tumor microenvironment on chemoresistance, 2023.

[43] Tianyu Zhang, Liwei Zhang, Philip R. O. Payne, and Fuhai Li. Synergistic drug combination prediction by integrating multi-omics data in deep learning models, 2018.

[44] Sareh Seyedi, Valerie K. Harris, Stefania E. Kapsetaki, Daniel Saha, Zachary Compton, Rezvan Yousefi, Alexander May, Efe Fakir, Amy M. Boddy, Marco Gerlinger, Christina Wu, Lida Mina, Silvie Huijben, Dawn H. Gouge, Luis Cisneros, Peter C. Ellsworth, and Carlo C. Maley. Resistance management for cancer: Lessons from farmers, 2023.

[45] Meghan Leary, Sarah Heerboth, Karolina Lapinska, and Sibaji Sarkar. Sensitization of drug resistant cancer cells: a matter of combination therapy. *Cancers*, 10(12):483, 2018.

[46] Rédoane Daoudi. Understanding akt-mediated chemoresistance: the relationship between ion channels and akt activation, 2023.

[47] Patrick J. Lawrence and Xia Ning. Enhancing drug and cell line representations via contrastive learning for improved anti-cancer drug prioritization, 2023.

[48] Neil Vasan, José Baselga, and David M Hyman. A view on drug resistance in cancer. *Nature*, 575(7782):299–309, 2019.

[49] Shannon Lee, Jens Rauch, and Walter Kolch. Targeting mapk signaling in cancer: mechanisms of drug resistance and sensitivity. *International journal of molecular sciences*, 21(3):1102, 2020.

[50] Romana-Rea Begicevic and Marco Falasca. Abc transporters in cancer stem cells: beyond chemoresistance. *International journal of molecular sciences*, 18(11):2362, 2017.

[51] Yuan Li, Zhenning Wang, Jaffer A Ajani, and Shumei Song. Drug resistance and cancer stem cells. *Cell Communication and Signaling*, 19:1–11, 2021.

[52] Dimakatso Alice Senthebane, Arielle Rowe, Nicholas Ekow Thomford, Hendrina Shipanga, Daniella Munro, Mohammad AM Al Mazeedi, Hashim AM Almazyadi, Karlien Kallmeyer, Collet Dandara, Michael S Pepper, et al. The role of tumor microenvironment in chemoresistance: to survive, keep your enemies closer. *International journal of molecular sciences*, 18(7):1586, 2017.

[53] Jana L. Gevertz, Zahra Aminzare, Kerri-Ann Norton, Judith Perez-Velazquez, Alexandria Volkening, and Katarzyna A. Rejniak. Emergence of anti-cancer drug resistance: Exploring the importance of the microenvironmental niche via a spatial model, 2014.

[54] Feng Fu, Martin A. Nowak, and Sebastian Bonhoeffer. Spatial heterogeneity in drug concentrations can facilitate the emergence of resistance to cancer therapy, 2014.

[55] Yihai Cao et al. Adipocyte and lipid metabolism in cancer drug resistance. *The Journal of clinical investigation*, 129(8):3006–3017, 2019.

[56] Chen Zhang, Xinyin Liu, Shidai Jin, Yi Chen, and Renhua Guo. Ferroptosis in cancer therapy: a novel approach to reversing drug resistance. *Molecular cancer*, 21(1):47, 2022.

[57] Yi-Han Chiu, Shu-Chuan Amy Lin, Chen-Hsin Kuo, and Chia-Jung Li. Molecular machinery and pathophysiology of mitochondrial dynamics. *Frontiers in Cell and Developmental Biology*, 9:743892, 2021.

[58] Verónica Eisner, Martin Picard, and György Hajnóczky. Mitochondrial dynamics in adaptive and maladaptive cellular stress responses. *Nature cell biology*, 20(7):755–765, 2018.

[59] Kevin Leder and Zicheng Wang. Clonal diversity at cancer recurrence, 2023.

[60] Einar Bjarki Gunnarsson, Subhajyoti De, Kevin Leder, and Jasmine Foo. Understanding the role of phenotypic switching in cancer drug resistance, 2020.

[61] Dauren Alimbetov, Sholpan Askarova, Bauyrzhan Umbayev, Terence Davis, and David Kipling. Pharmacological targeting of cell cycle, apoptotic and cell adhesion signaling pathways implicated in chemoresistance of cancer cells. *International journal of molecular sciences*, 19(6):1690, 2018.

[62] José Pedro Friedmann Angeli, Dmitri V Krysko, and Marcus Conrad. Ferroptosis at the crossroads of cancer-acquired drug resistance and immune evasion. *Nature Reviews Cancer*, 19(7):405–414, 2019.

[63] Lucy V Ireland and Ainhoa Mielgo. Macrophages and fibroblasts, key players in cancer chemoresistance. *Frontiers in cell and developmental biology*, 6:131, 2018.

[64] Pete Donnell, Murad Banaji, and Stephen Baigent. Stability in generic mitochondrial models, 2007.

[65] Tao Yu, Yanfen Wang, Yu Fan, Na Fang, Tongshan Wang, Tongpeng Xu, and Yongqian Shu. Circrnas in cancer metabolism: a review. *Journal of hematology & oncology*, 12:1–10, 2019.

[66] Longzheng Xia, Linda Oyang, Jinguan Lin, Shiming Tan, Yaqian Han, Nayiyuan Wu, Pin Yi, Lu Tang, Qing Pan, Shan Rao, et al. The cancer metabolic reprogramming and immune response. *Molecular cancer*, 20:1–21, 2021.

[67] Robert D Leone and Jonathan D Powell. Metabolism of immune cells in cancer. *Nature reviews cancer*, 20(9):516–531, 2020.

[68] Rama Rathore, Jennifer E McCallum, Elizabeth Varghese, Ana-Maria Florea, and Dietrich Büsselberg. Overcoming chemotherapy drug resistance by targeting inhibitors of apoptosis proteins (iaps). *Apoptosis*, 22(7):898–919, 2017.

[69] Edwin Wang, Naif Zaman, Shauna Mcgee, Jean-Sébastien Milanese, Ali Masoudi-Nejad, and Maureen O'Connor. Predictive genomics: A cancer hallmark network framework for predicting tumor clinical phenotypes using genome sequencing data, 2014.

[70] Davide Maspero, Claudio Isella, Marzia Di Filippo, Alex Graudenzi, Sara Erika Bellomo, Marco Antoniotti, Giancarlo Mauri, Enzo Medico, and Chiara Damiani. Metabolic enrichment through functional gene rules, 2017.

[71] Andrew Teschendorff, Peter Sollich, and Reimer Kuehn. Signalling entropy: a novel network-theoretical framework for systems analysis and interpretation of functional omic data, 2014.

[72] Salim Chowdhury, Yanjun Qi, Alex Stewart, Rachel Ostroff, and Renqiang Min. Cancer diagnosis with quire: Quadratic interactions among informative features, 2013.

Disclaimer:

SurveyX is an AI-powered system designed to automate the generation of surveys. While it aims to produce high-quality, coherent, and comprehensive surveys with accurate citations, the final output is derived from the AI's synthesis of pre-processed materials, which may contain limitations or inaccuracies. As such, the generated content should not be used for academic publication or formal submissions and must be independently reviewed and verified. The developers of SurveyX do not assume responsibility for any errors or consequences arising from the use of the generated surveys.