Gastric Cancer Treatment: A Survey on Chemotherapy Resistance and Targeted Therapy

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Abstract

Gastric cancer (GC) presents a formidable global health challenge, characterized by high incidence and mortality rates, largely due to late-stage diagnosis and chemotherapy resistance. This survey paper delves into the complex interplay between chemotherapy resistance and DNA damage repair (DDR) mechanisms in GC, highlighting the critical role of genomic instability in treatment outcomes. Chemotherapy resistance, exacerbated by tumor heterogeneity and cancer stem cell dynamics, remains a significant barrier to effective treatment. The paper explores the molecular underpinnings of resistance, including the role of cancer-associated fibroblasts and metabolic adaptations, which complicate therapeutic efforts. Crucially, DDR mechanisms, particularly those addressing double-strand breaks, are pivotal in maintaining genomic integrity and modulating chemotherapy sensitivity. The survey underscores the potential of targeted therapies that exploit specific DDR deficiencies to enhance treatment efficacy. Furthermore, the integration of genomic and epigenetic profiling with advanced drug delivery systems offers promising avenues for personalized treatment strategies. The paper also highlights the importance of multidisciplinary approaches and advanced predictive models, including AI, in overcoming the challenges of chemotherapy resistance. By synthesizing current research, this survey emphasizes the need for innovative therapeutic interventions that address the multifaceted nature of gastric cancer, ultimately aiming to improve patient outcomes through precision oncology.

1 Introduction

1.1 Prevalence and Challenges in Gastric Cancer Treatment

Gastric cancer (GC) represents a significant global health concern, with over one million new cases diagnosed annually, making it the fifth most prevalent cancer worldwide [1]. Despite advancements in therapeutic strategies, the mortality rate remains alarmingly high, with approximately 700,000 deaths reported in 2020 [1]. Late-stage diagnoses and the disease's inherent heterogeneity complicate efforts to improve survival rates [2]. Locally advanced gastric cancer (LAGC) is typically treated with neoadjuvant chemotherapy (NACT), yet the emergence of chemotherapy resistance poses a formidable barrier to successful outcomes [3, 1].

Chemotherapy resistance in gastric cancer is exacerbated by tumor heterogeneity and the complexity of cell death pathways, significantly influencing treatment efficacy. Cancer stem cells (CSCs) play a crucial role in this resistance by undergoing reprogramming that contributes to therapeutic failure and recurrence [4]. Both intrinsic and acquired drug resistance are major obstacles, paralleling challenges faced in infectious diseases where proliferative factors undermine treatment effectiveness [5].

Conventional therapies are hindered not only by severe side effects but also by their potential to foster treatment resistance, necessitating innovative approaches [6]. The low response rates and the impact of drug resistance considerably diminish the effectiveness of current gastric cancer treatments [7]. Addressing these challenges demands a thorough understanding of resistance mechanisms and

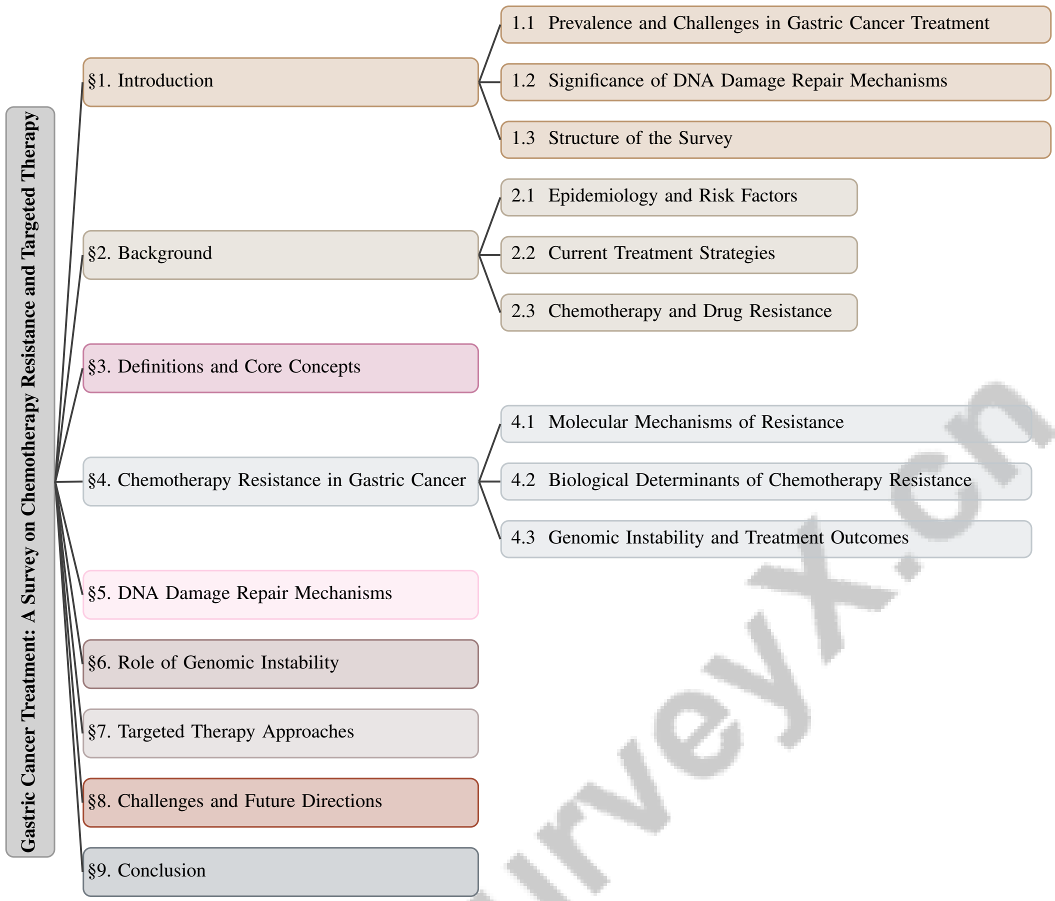


Figure 1: chapter structure

the development of targeted therapies. The DNA damage response (DDR) mechanisms are pivotal in maintaining genomic integrity and present a potential strategy for overcoming chemotherapy resistance [8]. Understanding genetic vulnerabilities associated with genomic instability is essential for developing effective targeted therapies [9]. The multifaceted etiology of gastric cancer, coupled with variability in treatment responses, complicates the formulation of effective prevention and treatment strategies [10]. Moreover, intra-tumoral heterogeneity and the limitations of existing chemotherapy methods further contribute to chemotherapeutic drug resistance, underscoring the urgent need for novel therapeutic strategies [11].

1.2 Significance of DNA Damage Repair Mechanisms

DNA damage response (DDR) mechanisms are essential for maintaining genomic stability and preventing tumorigenesis, serving as a cornerstone in cancer biology and therapy [12]. In gastric cancer, DDR critically influences treatment response, particularly concerning chemotherapy resistance [8]. Ineffective repair mechanisms can lead to increased mutagenesis and cancer progression, emphasizing the issue of genomic instability [13]. Insights into DDR pathways reveal genetic vulnerabilities that can be targeted for therapeutic benefit [14]. These pathways encompass a complex network responsible for detecting and repairing DNA lesions, such as double-strand breaks (DSBs), which are vital for maintaining genomic integrity [12]. The efficacy of these repair processes directly affects cancer progression and treatment outcomes [15].

Recent studies highlight the interplay between DNA repair pathways and cellular metabolism, indicating that metabolic changes can influence DNA repair efficacy and chemotherapy sensitivity. This relationship underscores the necessity of an integrated understanding of cancer biology that merges metabolic and genomic perspectives to devise effective therapeutic strategies [16]. Furthermore, the genomic instability characteristic of cancer cells, often exacerbated by defective DNA repair

AI-generated, for reference only.

mechanisms, presents both challenges and opportunities for targeted therapy [17]. Targeting specific repair pathways may enable selective sensitization of cancer cells to treatment while sparing normal tissues [8].

Addressing knowledge gaps in DNA damage and repair mechanisms is vital for advancing gastric cancer treatment [18]. This includes elucidating prevalent DNA damage types in cancer cells and identifying corresponding repair mechanisms that can be therapeutically targeted [18]. Additionally, understanding the genetic and epigenetic alterations underlying these processes is crucial for developing precision oncology approaches tailored to individual patient profiles [19]. As our comprehension of these mechanisms deepens, the potential for innovative therapeutic interventions that overcome drug resistance and enhance patient outcomes in gastric cancer becomes increasingly feasible [3].

1.3 Structure of the Survey

This survey is designed to provide a comprehensive analysis of gastric cancer treatment, emphasizing the challenges posed by chemotherapy resistance and the potential of targeted therapies. It begins with an introduction to the prevalence and challenges in gastric cancer treatment, particularly focusing on chemotherapy resistance and the significance of DNA damage repair mechanisms. The background section offers an overview of gastric cancer, discussing its epidemiology, risk factors, and current treatment strategies, with a specific emphasis on chemotherapy and its associated drug resistance.

Subsequent sections define key terms and core concepts, including chemotherapy resistance, DNA damage repair, genomic instability, and targeted therapy, establishing a foundational understanding for the analysis that follows. The section on chemotherapy resistance in gastric cancer delves into the molecular and biological mechanisms underlying resistance, highlighting genomic instability's role in treatment outcomes.

The discussion then transitions to DNA damage repair mechanisms, detailing the involved pathways and their potential as therapeutic targets. This analysis is enriched by an exploration of genomic instability, focusing on its causes—such as chromosomal instability (CIN) and environmental factors—and its implications for cancer progression, including the promotion of treatment resistance and intratumoral genetic heterogeneity, which complicate therapeutic strategies and influence patient prognosis [20, 15, 21, 9]. The survey further reviews current targeted therapy approaches, highlighting the importance of genomic and epigenetic profiling, the development of combination therapies, and innovative drug delivery and diagnostic systems.

The paper thoroughly examines the multifaceted challenges and future directions in developing effective targeted therapies for cancer. It emphasizes the necessity of integrating multidisciplinary approaches, including advances in precision oncology and mathematical modeling, to address issues such as drug resistance and tumor heterogeneity. Additionally, it underscores the critical role of advanced predictive models and artificial intelligence in enhancing treatment personalization, optimizing therapy selection, and potentially improving patient outcomes through more efficient screening and identification of novel therapeutic targets [22, 7, 23, 19]. The conclusion synthesizes the key findings, highlighting the importance of integrating knowledge of DNA damage repair and genomic instability in advancing gastric cancer treatment.The following sections are organized as shown in Figure 1.

2 Background

2.1 Epidemiology and Risk Factors

Gastric cancer (GC) poses a significant global health challenge, notably prevalent in East Asian countries such as Korea, Japan, and China, where Helicobacter pylori infections and dietary habits are primary contributors [10]. Analysis of the Korean population from the GEO database shows regional disparities in incidence [24]. The etiology of GC is multifactorial, involving both environmental and genetic determinants [10].

Environmental risk factors include high salt intake, smoked foods, low fruit and vegetable consumption, smoking, and alcohol use [10]. Chronic Helicobacter pylori infection is a well-known precursor to gastric inflammation and carcinogenesis. Additionally, Epstein-Barr virus (EBV) is linked to a subset of gastric cancers, although the molecular mechanisms remain poorly understood [25].

Genetically, the complexity of GC complicates the identification of specific mutations driving progression [19]. Recent genomic studies have identified differentially expressed circular RNAs (circRNAs) in GC tissues, indicating their potential as stable biomarkers for early diagnosis [26]. These insights are crucial for advancing precision oncology, enabling tailored early detection and personalized treatment strategies.

The interaction between epidemiological and genetic factors necessitates comprehensive research to elucidate GC mechanisms. Enhancing prevention, early diagnosis, and targeted therapy development is crucial to mitigate the global cancer burden, given the disease's complexity and heterogeneity. Advances in precision oncology, driven by genomic analyses, facilitate the identification of molecular alterations driving cancer progression, aiming to improve patient outcomes while minimizing resistance and recurrence. Innovations in genome editing and AI-driven biomarker screening are paving the way for personalized therapeutic strategies, enhancing cancer management efficacy [27, 19, 23, 28, 25].

2.2 Current Treatment Strategies

Gastric cancer management employs a multifaceted approach, integrating surgery, chemotherapy, and targeted therapies to address the disease's complexity [10]. Chemotherapy remains a cornerstone of treatment, though its effectiveness is often hindered by poor bioavailability and significant side effects [28]. Traditional chemotherapy regimens, administered in cycles, can allow for tumor regrowth between treatments, reducing overall efficacy [29].

Targeted therapies have emerged as crucial complements to conventional treatments, aiming to inhibit specific molecular pathways involved in GC progression. mTOR inhibitors, for instance, show potential in disrupting cancer cell proliferation and survival [30]. However, clinical application is challenged by patient response variability and resistance development, necessitating ongoing research to refine these approaches.

Innovative drug delivery systems, particularly nanomedicine, are being developed to enhance treatment precision and efficacy. Smart nanoparticles are engineered to improve drug targeting and minimize side effects, addressing limitations of traditional chemotherapy [31]. These advancements hold significant promise for overcoming challenges associated with conventional treatment strategies.

The influence of metabolic pathways on treatment resistance is gaining recognition, especially regarding glucose metabolism's impact on chemo- and radio-resistance mechanisms [32]. Understanding these metabolic interactions is crucial for devising strategies that sensitize tumors to existing therapies, thereby improving therapeutic outcomes.

2.3 Chemotherapy and Drug Resistance

Chemotherapy is fundamental in gastric cancer treatment, but its effectiveness is severely compromised by drug resistance, a multifaceted challenge that significantly affects treatment outcomes and contributes to recurrence and metastasis [33]. Resistance to agents like cisplatin arises from intrinsic and acquired mechanisms, including multi-drug resistance, apoptosis suppression, and alterations in drug metabolism [3].

Overcoming drug resistance is complicated by the genetic and epigenetic landscape of cancer cells, enabling adaptation and survival under chemotherapeutic stress. Tumor heterogeneity further complicates treatment responses, necessitating personalized therapeutic strategies [19]. Additionally, the tumor microenvironment plays a crucial role in mediating resistance, affecting drug delivery and efficacy [34].

Traditional chemotherapy methods, often characterized by severe side effects and inadequate drug delivery, exacerbate resistance issues [28]. Furthermore, slow-cycling subpopulations of cancer cells frequently evade treatment, contributing to disease persistence [11].

To address these challenges, innovative strategies such as dose-dense chemotherapy protocols are being explored to enhance treatment efficacy by optimizing dosing schedules and reducing tumor mass within critical timeframes. However, the complexity of tumor biology and resistance development necessitates ongoing research and the integration of precision oncology approaches [19]. Understanding resistance mechanisms, including DNA damage responses and repair pathway inefficiencies, is crucial for developing novel strategies that effectively target resistant cancer cells and improve clinical outcomes [13].

In recent years, the complexity of gastric cancer treatment has necessitated a comprehensive understanding of various interrelated factors. One of the critical areas of focus is the mechanisms underlying chemotherapy resistance, which significantly impacts treatment efficacy. As illustrated in Figure 2, the hierarchical organization of key concepts in gastric cancer treatment strategies is depicted, emphasizing the intricate relationships among chemotherapy resistance, DNA damage repair, genomic instability, and targeted therapy. This figure categorizes the types and mechanisms of resistance, the functions and pathways involved in DNA repair, the characteristics and contributions of genomic instability, and the precision approach of targeted therapy. By synthesizing these elements, we can better appreciate the multifaceted nature of treatment strategies and the importance of addressing each component in the management of gastric cancer.

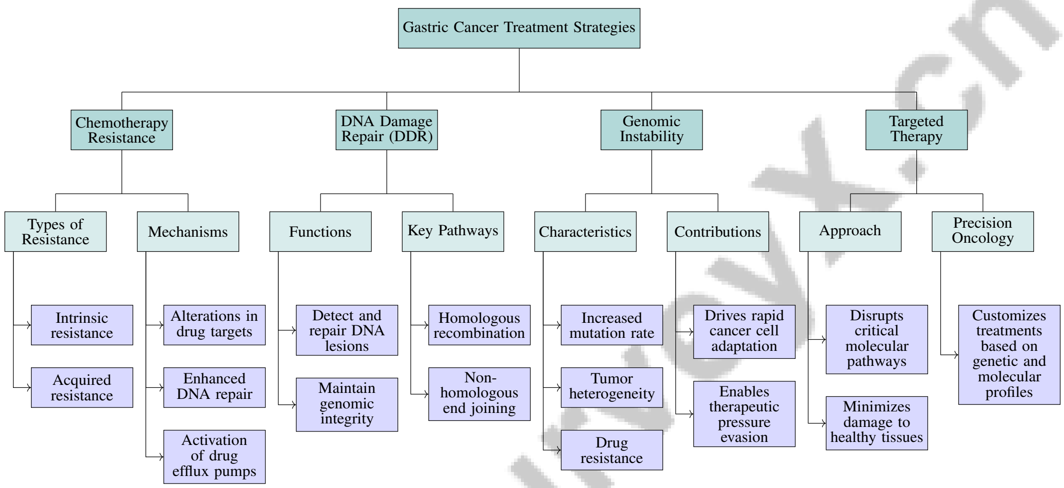


Figure 2: This figure illustrates the hierarchical organization of key concepts in gastric cancer treatment strategies, focusing on chemotherapy resistance, DNA damage repair, genomic instability, and targeted therapy. The diagram categorizes the types and mechanisms of resistance, functions and pathways of DNA repair, characteristics and contributions of genomic instability, and the approach and precision of targeted therapy.

3 Definitions and Core Concepts

3.1 Definitions

Chemotherapy resistance in gastric cancer refers to the diminished effectiveness of chemotherapeutic agents, leading to treatment failure and disease progression. This resistance can be intrinsic, present before treatment, or acquired during therapy [35]. Mechanisms include alterations in drug targets, enhanced DNA repair, and activation of drug efflux pumps [33]. Figure 3 illustrates the hierarchical structure of chemotherapy resistance in gastric cancer, highlighting key mechanisms such as intrinsic and acquired resistance, DNA damage repair pathways, and genomic instability factors that contribute to treatment challenges.

DNA damage repair (DDR) involves cellular processes that detect and repair DNA lesions to maintain genomic integrity [12]. DDR is crucial in preventing mutations that could drive cancer progression and affects cancer cell sensitivity to chemotherapy [8]. Key pathways include homologous recombination and non-homologous end joining, essential for repairing double-strand breaks [12].

Genomic instability, characterized by an increased mutation rate, often results from DNA repair pathway defects [13]. It is a hallmark of cancer, contributing to tumor heterogeneity and drug resistance [17], enabling rapid cancer cell adaptation to therapeutic pressures [9].

Targeted therapy employs agents designed to disrupt critical molecular pathways for cancer cell survival and proliferation [30]. Unlike traditional chemotherapy, which affects both cancerous and normal cells, targeted therapies focus on specific cancer-associated molecular targets, aiming to minimize damage to healthy tissues [31]. This approach is central to precision oncology, which customizes treatments based on individual genetic and molecular profiles [19].

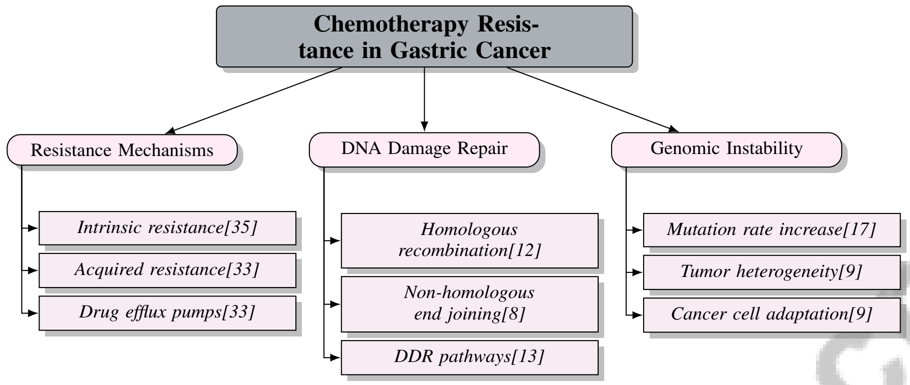


Figure 3: This figure illustrates the hierarchical structure of chemotherapy resistance in gastric cancer, highlighting key mechanisms such as intrinsic and acquired resistance, DNA damage repair pathways, and genomic instability factors contributing to treatment challenges.

3.2 Core Concepts

The interplay between chemotherapy resistance, DNA damage repair, genomic instability, and targeted therapy significantly shapes gastric cancer treatment strategies. Chemotherapy resistance often arises from cancer cells' proficient DNA repair, allowing evasion from chemotherapeutic cytotoxicity. Genomic instability, marked by frequent mutations and chromosomal abnormalities, drives genetic heterogeneity and rapid adaptation to therapy. The tumor microenvironment exacerbates this instability, fostering aggressive, treatment-resistant cell subpopulations [11, 21, 20, 9, 5].

DDR mechanisms, especially those repairing double-strand breaks, are vital for genomic integrity and determining chemotherapy sensitivity [12]. Inefficiencies or overactivity in these pathways can lead to increased mutagenesis and cancer progression, highlighting the significance of genomic instability [13]. Understanding these pathways reveals genetic vulnerabilities that can be targeted to improve therapeutic outcomes.

Targeted therapy offers promising solutions to traditional chemotherapy limitations by focusing on essential molecular pathways for cancer cell survival and proliferation [30]. By addressing specific genetic and molecular aberrations, these therapies seek to reduce collateral damage to healthy tissues and provide a more personalized treatment approach. This precision oncology strategy is crucial for overcoming challenges like chemotherapy resistance and genomic instability, ultimately improving gastric cancer treatment outcomes [19].

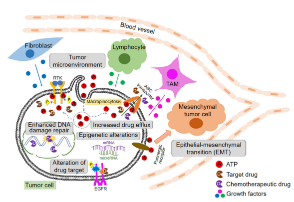
Incorporating concepts such as cMET signaling pathways and advanced multimodal data integration into therapeutic strategies is crucial for enhancing gastric cancer treatment efficacy, particularly in addressing resistance and optimizing patient selection for targeted therapies [1, 36]. By targeting the molecular bases of chemotherapy resistance and genomic instability, researchers and clinicians can develop more effective and personalized interventions, improving patient survival and quality of life.

4 Chemotherapy Resistance in Gastric Cancer

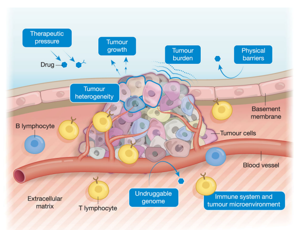
4.1 Molecular Mechanisms of Resistance

Chemotherapy resistance in gastric cancer stems from intricate interactions among genetic, cellular, and microenvironmental elements. Chromosomal instability (CIN) enhances tumor adaptability, enabling survival under therapeutic pressures [20, 15]. Dysregulation of the PI3K/AKT/mTOR pathway, prevalent in various cancers, further complicates resistance [37]. The tumor microenvironment, particularly cancer-associated fibroblasts (CAFs), mediates resistance by secreting factors like exosomal miR-522, which inhibit ferroptosis and promote chemoresistance [38]. Additionally, WNT signaling affects cancer stem cell (CSC) behavior, influencing their microenvironmental interactions and complicating treatment [4]. Metabolic adaptations, such as altered glucose metabolism, also contribute to resistance, presenting potential therapeutic targets [32]. The mTOR signaling pathway, involving mTORC1 and mTORC2, plays a critical role in cancer biology and resistance [30].

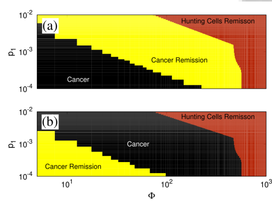
Gastric cancer's genetic landscape, characterized by low-frequency mutations and structural variants, influences tumor biology and resistance [39]. High-throughput AI-based methods, like HTAI-BS, are being developed to identify these genomic alterations, crucial for personalized treatment [23]. Addressing these mechanisms requires a comprehensive understanding of underlying biology and innovative, personalized therapeutic strategies. Targeting pathways involved in DNA repair, apoptosis, and metabolism, while considering genetic variability, could enhance chemotherapy efficacy and mitigate resistance. Challenges include achieving targeted chemotherapeutic delivery, overcoming resistance, and minimizing toxicity to healthy tissues [28].



(a) The image depicts a complex network of cells and molecules involved in cancer progression and drug resistance.[35]



(b) Factors Influencing Tumor Growth and Progression[5]



(c) Comparison of the Distribution of Cancer and Hunting Cells Remission in Two Different Conditions[40]

Figure 4: Examples of Molecular Mechanisms of Resistance

As shown in Figure 5, the visual exploration of "Chemotherapy Resistance in Gastric Cancer; Molecular Mechanisms of Resistance" illustrates the primary mechanisms contributing to chemotherapy resistance, categorized into genetic factors, microenvironmental influences, and therapeutic challenges. Each category highlights the intricate interactions and pathways involved, emphasizing the complexity of overcoming resistance and the need for innovative therapeutic strategies. The first image provides a schematic representation of the tumor microenvironment, emphasizing the roles of tumor cells and fibroblasts in sustaining tumor growth and survival. The second image details factors influencing tumor growth and progression, particularly the therapeutic pressures exerted by drugs. Finally, the third image compares the distribution of cancer and hunting cells under varying conditions, offering insights into how different parameters affect treatment outcomes. Together, these visualizations underscore the multifaceted nature of chemotherapy resistance and the necessity for a thorough understanding of the underlying molecular mechanisms to enhance therapeutic strategies in gastric cancer.

4.2 Biological Determinants of Chemotherapy Resistance

Chemotherapy resistance in gastric cancer is intricately linked to the interactions among cancer stem cells (CSCs), the tumor microenvironment, and cellular signaling pathways. CSCs, known for their self-renewal and differentiation capabilities, survive chemotherapeutic assaults, contributing to tumor recurrence [4]. Their heterogeneity and plasticity enable transitions between stem-like and differentiated states under therapeutic pressures [41], complicating conventional therapies as CSCs evade drug-induced apoptosis. The tumor microenvironment provides a protective niche for cancer cells, with CAFs secreting factors that enhance survival under chemotherapeutic stress [42]. The heterogeneity of CAFs across tumor types adds complexity to targeted therapies, as their interactions with cancer cells promote resistance [42]. Protein complexes, influenced by transcription factors, modulate cellular responses to chemotherapy, acting as biological determinants of resistance [43].

Regulating cell death pathways presents challenges in overcoming resistance. Targeting these pathways may improve outcomes, but off-target effects and difficulties in achieving selective targeting in heterogeneous tumor environments remain hurdles [44]. Complex signaling interactions within pathways like PI3K/AKT/mTOR can lead to resistance mechanisms, complicating therapeutic efforts

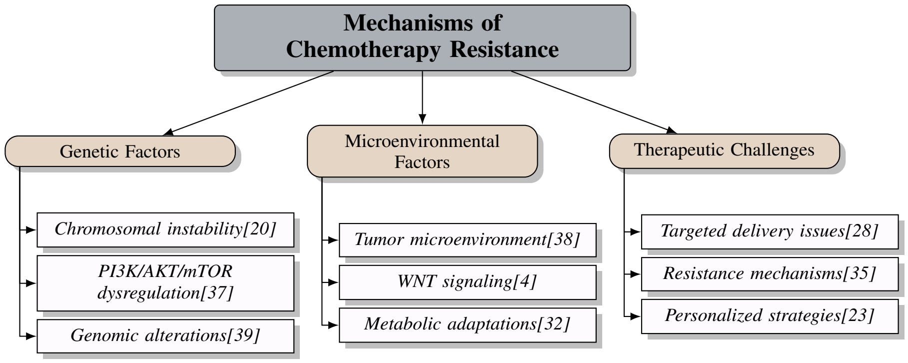


Figure 5: This figure illustrates the primary mechanisms contributing to chemotherapy resistance in gastric cancer, categorized into genetic factors, microenvironmental influences, and therapeutic challenges. Each category highlights the intricate interactions and pathways involved, emphasizing the complexity of overcoming resistance and the need for innovative therapeutic strategies.

[37]. Innovative approaches, such as dose-dense chemotherapy protocols, have been explored to increase chemotherapy cycles, potentially enhancing tumor reduction [29]. However, intrinsic and acquired resistance continues to pose substantial obstacles, necessitating strategies that effectively target inhibitors of apoptosis proteins (IAPs) without affecting healthy cells [45].

4.3 Genomic Instability and Treatment Outcomes

Genomic instability, a hallmark of cancer, critically influences gastric cancer progression and treatment outcomes. Characterized by frequent mutations and chromosomal alterations, genomic instability contributes to tumor heterogeneity and therapy resistance [20]. The failure of DNA repair mechanisms exacerbates this instability, allowing cancer cells to maintain high mutation rates and adapt swiftly to therapeutic pressures [17]. This complexity is further compounded by gastric cancer's heterogeneity, complicating treatment decisions and reducing the efficacy of targeted therapies [36].

The interplay between genomic instability and treatment outcomes is influenced by metabolic reprogramming and the tumor microenvironment. Metabolic changes can affect DNA repair processes, impacting genomic stability and cancer cell sensitivity to treatment [16]. CAFs within the tumor microenvironment interact with cancer cells, promoting therapeutic resistance and metastasis [42], highlighting the need for a comprehensive understanding of these influences.

Recent advances in high-throughput AI-based methods, such as HTAI-BS, provide insights into genomic instability metrics, including tumor mutation burden and microsatellite instability, crucial for predicting treatment responses in gastric cancer [23]. Identifying structural variants through systems like CIBRA underscores the substantial impact of genomic alterations on treatment outcomes, emphasizing the importance of targeting genomic instability in therapeutic strategies [39].

As illustrated in Figure 6, the hierarchical structure of genomic instability in gastric cancer highlights its impact on tumor heterogeneity, therapy resistance, and the role of DNA repair failure. This figure further depicts the influence of metabolic reprogramming and the tumor microenvironment on treatment outcomes, while outlining therapeutic strategies including AI-based methods, targeting KIF18A, and advanced drug delivery systems.

Targeting genomic instability presents a promising approach to enhance treatment efficacy. For example, KIF18A has emerged as a potential therapeutic target in CIN tumors, where its inhibition leads to significant mitotic errors and reduced cancer cell viability [9]. Strategies to increase mutation rates in unstable tumor cells may also reduce tumor populations, enhancing the effectiveness of mutagenic therapies [46]. Despite these advances, challenges persist in addressing the low solubility of many antitumor drugs, nonspecific distribution, and the development of drug resistance mechanisms by cancer cells [31]. These challenges underscore the need for innovative drug delivery systems and personalized therapeutic approaches that consider the unique genomic and microenvironmental characteristics of each tumor. By targeting the underlying mechanisms of genomic instability, it is possible to improve treatment outcomes and overcome barriers posed by tumor heterogeneity and resistance in gastric cancer.

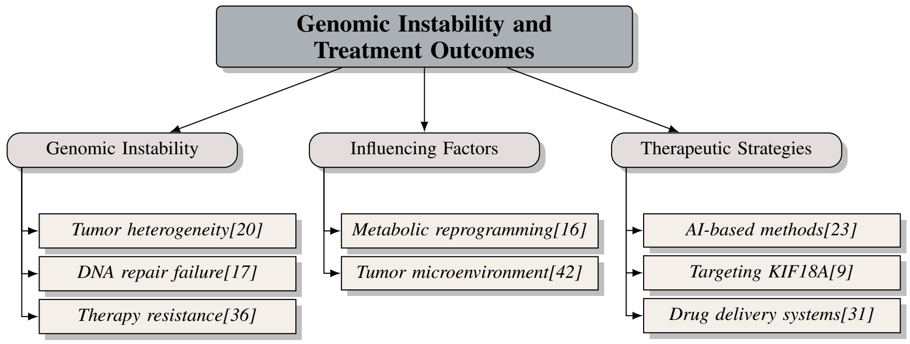


Figure 6: This figure shows the hierarchical structure of genomic instability in gastric cancer, highlighting its impact on tumor heterogeneity, therapy resistance, and the role of DNA repair failure. It also illustrates the influence of metabolic reprogramming and the tumor microenvironment on treatment outcomes, and outlines therapeutic strategies including AI-based methods, targeting KIF18A, and advanced drug delivery systems.

5 DNA Damage Repair Mechanisms

5.1 Overview of DNA Damage and Repair Pathways

DNA damage repair pathways are crucial for maintaining genomic stability and significantly impact gastric cancer progression and treatment outcomes. Key mechanisms include homologous recombination (HR), non-homologous end joining (NHEJ), base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR), each targeting specific DNA lesions. HR and NHEJ are essential for repairing double-strand breaks (DSBs), with HR using a homologous sequence as a template and NHEJ directly ligating DNA ends without a template [15]. These pathways modulate cancer cell sensitivity to DNA-damaging agents such as cisplatin, which induces DSBs through DNA crosslinking [15].

BER, NER, and MMR address single-strand breaks and minor lesions. BER repairs small base lesions from oxidation, alkylation, and deamination, while NER removes bulky DNA adducts from UV radiation. MMR corrects base mismatches and insertion-deletion loops during DNA replication [13]. The efficacy of these pathways is pivotal in preventing mutations that drive cancer progression and in modulating chemotherapy responses [15].

The intricate interplay between DNA repair pathways and cancer biology often results in genomic instability when repair mechanisms are defective, contributing to tumor heterogeneity and therapeutic resistance [13]. Identifying specific DNA repair deficiencies in gastric cancer can inform the development of targeted therapies that exploit these vulnerabilities, thereby enhancing treatment efficacy [35].

Next-generation sequencing is instrumental in precision oncology, identifying biomarkers for targeted therapies and enhancing our understanding of DNA repair pathways' implications for treatment strategies [19]. Comprehensive genomic testing is crucial for identifying patients who may benefit from specific targeted therapies, such as those against cMET, which is associated with various resistance mechanisms [36]. Additionally, integrating large-scale protein-interaction and gene-expression datasets provides insights into DNA damage repair mechanisms relevant to gastric cancer, facilitating the development of more effective therapeutic strategies [43].

Advanced computational models, including frameworks that categorize cancer-associated fibroblasts (CAFs) based on signaling pathways, highlight the bidirectional crosstalk between CAFs and cancer cells [42]. This approach illustrates the potential of combining bioinformatics with traditional cancer biology to create personalized therapeutic strategies addressing the challenges posed by DNA damage and repair pathways in gastric cancer.

5.2 Therapeutic Targeting of DNA Repair Pathways

Targeting DNA repair pathways offers a promising avenue for overcoming chemotherapy resistance in gastric cancer. By focusing on specific deficiencies within these pathways, it is possible to sensitize cancer cells to DNA-damaging agents, thereby enhancing treatment efficacy and improving patient outcomes [15]. Mechanisms such as homologous recombination and non-homologous end joining are pivotal for maintaining genomic integrity and serve as critical targets for therapeutic intervention [15].

Recent advancements in targeted drug delivery systems have significantly enhanced therapeutic indices while minimizing the side effects associated with conventional chemotherapy [28]. These innovations are vital for addressing chemotherapy resistance complexities, enabling precise delivery of therapeutic agents to cancer cells with defective DNA repair mechanisms, thus maximizing efficacy [34].

The integration of genomic alterations with transcriptomic responses, as demonstrated by CIBRA, identifies alterations with significant system-wide impacts that can serve as potential therapeutic targets [39]. This underscores the importance of leveraging molecular insights to develop targeted therapies capable of effectively overcoming drug resistance [34].

Furthermore, the application of mathematical models in combination cancer treatments offers innovative solutions for addressing the limitations of traditional therapies. These models optimize treatment protocols, enhance efficacy, and tackle drug resistance challenges [22]. Additionally, exploring combination therapies targeting the PI3K/AKT/mTOR (PAM) pathway highlights the potential for new therapeutic strategies informed by DNA repair mechanisms [37].

6 Role of Genomic Instability

Genomic instability, particularly chromosomal instability (CIN), is a hallmark of cancer, characterized by mitotic dysfunction, karyotypic abnormalities, and aneuploidy. CIN significantly impacts tumor evolution, prognosis, therapeutic resistance, and intratumoral heterogeneity, thereby affecting the efficacy of anti-cancer strategies [20, 9]. Understanding the mechanisms of genomic instability is crucial for exploring its implications in the tumor microenvironment and cancer progression.

6.1 Definition and Causes of Genomic Instability

Genomic instability is marked by increased mutation rates, chromosomal rearrangements, and aneuploidy, contributing to tumor heterogeneity and progression [39]. This instability often results from defects in DNA repair mechanisms crucial for genomic integrity [13]. Failures in these pathways allow genetic alterations that drive cancer development and therapeutic resistance [17].

In gastric cancer, genomic instability arises from both intrinsic genetic factors and extrinsic environmental conditions. The tumor microenvironment (TME) exacerbates instability through hypoxia, nutrient deprivation, and oxidative stress, promoting DNA damage and genomic alterations [21]. Biomarkers like H2AX are potential tools for early detection and therapeutic targeting, highlighting the clinical relevance of genomic instability as a prognostic biomarker across various cancer types [12, 9]. Despite advances, challenges remain in elucidating the roles of emerging biomarkers like circular RNAs (circRNAs) [26].

The paradox of cancer cells maintaining viability despite high mutation rates suggests adaptive mechanisms that exploit genomic instability for survival and proliferation [17]. Addressing genomic instability in gastric cancer requires a comprehensive approach incorporating genetic and environmental factors. Advanced technologies and integrative models like CIBRA enhance the identification of potential biomarkers and therapeutic targets [39].

Figure 7 illustrates the key aspects of genomic instability in cancer, highlighting its causes, implications, and the research technologies used to study it. This visual representation complements the discussion by providing a clear overview of the multifaceted nature of genomic instability, thereby enriching our understanding of its role in cancer biology.

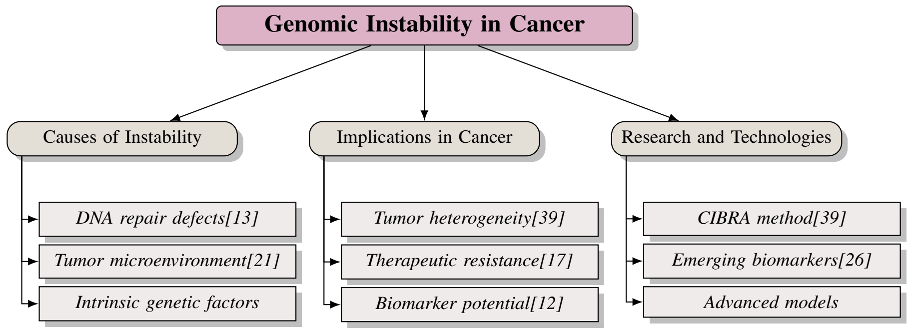


Figure 7: This figure illustrates the key aspects of genomic instability in cancer, highlighting its causes, implications, and the research technologies used to study it.

6.2 Impact of Tumor Microenvironment on Genomic Instability

The tumor microenvironment (TME) is pivotal in shaping genomic instability, a hallmark of cancer progression and treatment resistance. The TME consists of a complex network of non-cancerous cells, including fibroblasts, immune cells, and endothelial cells, along with extracellular matrix components that interact with cancer cells, aiding their survival and adaptation under therapeutic pressures [21].

Oxidative stress is a key mechanism through which the TME induces genomic instability. Reactive oxygen species (ROS) generated within the TME cause DNA damage, leading to mutations and chromosomal aberrations. This oxidative environment promotes genetic alterations and selects for cancer cells with enhanced DNA repair capabilities, contributing to therapeutic resistance and tumor progression [21]. Additionally, hypoxia within the TME stabilizes hypoxia-inducible factors (HIFs), altering gene expression related to angiogenesis, metabolism, and survival pathways, disrupting DNA repair processes and increasing mutation rates [21].

Furthermore, the TME modulates genomic instability through cytokines and growth factors that influence cancer cell behavior. Cancer-associated fibroblasts (CAFs) release factors enhancing cancer cell survival and proliferation, promoting a more unstable genomic landscape. This crosstalk between CAFs and cancer cells underscores the TME's complexity in genomic instability and highlights potential therapeutic targets [21].

6.3 Genomic Instability and Cancer Progression

Genomic instability significantly impacts cancer progression by facilitating genetic alterations and promoting tumor heterogeneity. This instability arises from ineffective DNA repair mechanisms essential for maintaining genomic integrity. Failures in these pathways lead to mutations, chromosomal rearrangements, and aneuploidy, driving the evolution of aggressive cancer phenotypes [8].

The relationship between genomic instability and cancer progression is further complicated by metabolic factors. Alterations in glucose metabolism, common in cancer cells, influence treatment resistance and interact with genomic instability. The precise pathways through which glucose metabolism affects treatment resistance and how different tumor microenvironments modulate these interactions remain unresolved [32]. These metabolic changes support the energy demands of rapidly proliferating cancer cells and contribute to resistance mechanisms, facilitating tumor progression.

As cancer evolves, genomic instability enables the selection of subclones with advantageous mutations that confer resistance to therapy and facilitate metastasis. This dynamic process illustrates the intricate nature of cancer evolution, wherein genomic instability fuels genetic diversity within tumors while posing significant challenges for effective treatment. Genomic instability, particularly CIN, is prevalent in most human cancers and contributes to intratumoral heterogeneity, enabling tumors to adapt and survive under therapeutic pressures. The TME exacerbates genomic instability, influencing mutation rates and treatment resistance, complicating the development of targeted therapies aimed at exploiting these vulnerabilities [21, 9]. Understanding the interplay between genomic instability and cancer progression is essential for devising therapeutic strategies targeting the underlying mechanisms of instability, potentially curbing tumor growth and improving patient outcomes.

7 Targeted Therapy Approaches

Category	Feature	Method
Development of Combination Therapies	Therapeutic Integration	OCS[47]

Table 1: This table summarizes the method of therapeutic integration utilized in the development of combination therapies for gastric cancer. The method referenced is the Optimal Control Strategy (OCS), which is instrumental in enhancing the efficacy of combined treatment modalities by strategically targeting multiple pathways.

Integrating molecular insights into treatment strategies is vital for developing targeted therapies in gastric cancer. Genetic and epigenetic profiling are instrumental in personalizing treatment modalities, providing a foundation for exploring combination therapies and innovative drug delivery systems. Table 1 presents a concise overview of the method employed in the development of combination therapies, highlighting the role of therapeutic integration in advancing treatment strategies for gastric cancer. Additionally, Table 2 presents a comprehensive comparison of various methodologies employed in the advancement of targeted therapies for gastric cancer, focusing on genomic profiling, combination therapies, and innovative delivery systems. This section examines how these profiling techniques guide targeted therapy decisions, enhancing patient outcomes in gastric cancer management.

7.1 Role of Genomic and Epigenetic Profiling

Genomic and epigenetic profiling are critical for advancing personalized medicine in gastric cancer by uncovering molecular biomarkers for targeted therapies. These techniques provide comprehensive insights into the genetic and epigenetic alterations driving cancer progression, enabling tailored therapeutic strategies that enhance treatment efficacy and patient outcomes [2]. Analyzing tumor genomic landscapes reveals specific mutations and aberrations linked to chemotherapy resistance and tumor heterogeneity, informing targeted therapy selection.

As illustrated in Figure 8, the interplay between genomic and epigenetic profiling plays a pivotal role in gastric cancer treatment. This figure highlights key areas such as molecular biomarkers, epigenetic modifications, and integrated approaches for personalized medicine, emphasizing the importance of these factors in developing effective treatment strategies.

Epigenetic modifications, such as DNA methylation and histone modification, significantly impact gene expression and treatment response. Profiling these modifications offers valuable insights for therapeutic interventions, facilitating the reversal of abnormal epigenetic states and enhancing tumor sensitivity to treatments. This aligns with precision oncology principles, advocating for individualized treatment strategies based on unique molecular alterations in each patient's tumor. Techniques like CIBRA integrate genomic and transcriptomic data to identify key alterations with system-wide effects on tumor biology, refining targeted therapy development and improving patient outcomes [39, 19].

Moreover, integrating genomic and epigenetic data with metabolic profiling can uncover novel therapeutic targets, particularly within dysregulated metabolic pathways in cancer [32]. Understanding the interplay among genetic, epigenetic, and metabolic factors is essential for devising effective treatment strategies addressing the complexities of gastric cancer.

7.2 Development of Combination Therapies

Combination therapies strategically enhance treatment efficacy in gastric cancer by integrating multiple modalities to overcome monotherapy limitations. Targeting different pathways simultaneously reduces resistance development and improves overall treatment outcomes, particularly given the significant tumor heterogeneity and complex cellular signaling pathways in gastric cancer, including MAPK and PI3K pathway activation by proto-oncogenes like cMET [22, 36, 19].

Advancements in targeted delivery systems facilitate precise co-delivery of chemotherapeutic agents and targeted therapies, ensuring effective delivery to tumor sites while minimizing off-target effects [6]. Refining these systems enhances the therapeutic index of combination treatments, maximizing efficacy while reducing toxicity.

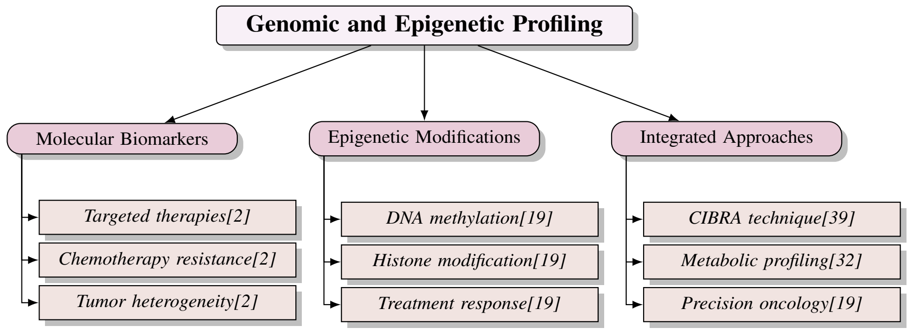


Figure 8: This figure illustrates the role of genomic and epigenetic profiling in gastric cancer treatment, highlighting key areas such as molecular biomarkers, epigenetic modifications, and integrated approaches for personalized medicine.

Emerging technologies, such as AI in radiomics and pathomics, offer opportunities to personalize combination therapies. AI-driven analyses identify patterns and biomarkers guiding optimal therapeutic combinations tailored to individual tumor characteristics [6]. This personalized approach ensures combination therapies are effective and specific to the cancer's molecular and phenotypic profiles.

Additionally, integrating radiotherapy with immuno- and chemotherapy in combination therapy models offers a more flexible and comprehensive treatment strategy, modulating immune responses and enhancing chemotherapeutic efficacy, ultimately improving patient outcomes [47].

7.3 Innovative Drug Delivery and Diagnostic Systems

Innovative drug delivery systems and diagnostic approaches are transforming targeted therapy in gastric cancer by improving treatment precision and efficacy. These advancements address conventional chemotherapy limitations, such as poor bioavailability, severe side effects, and drug resistance [28]. Cutting-edge technologies enable the development of novel delivery systems that enhance the targeting and delivery of therapeutic agents to tumor sites, minimizing off-target effects and improving therapeutic outcomes.

Nanotechnology-based delivery systems, such as smart nanoparticles, lead these innovations. They enhance the stability, solubility, and bioavailability of chemotherapeutic agents, allowing controlled and sustained drug release at tumor sites [31]. Engineering nanoparticles with specific surface modifications enables precise targeting of cancer cells, reducing systemic toxicity and improving the therapeutic index of anticancer agents [28].

Advancements in diagnostic systems are crucial for early detection and monitoring of gastric cancer. Integrating advanced imaging techniques with molecular diagnostics facilitates real-time assessment of tumor characteristics and treatment responses, essential for personalizing therapeutic strategies and allowing clinicians to adapt treatment regimens based on dynamic tumor microenvironment changes [6].

Furthermore, AI-powered radiomics and pathomics revolutionize diagnostics by providing comprehensive insights into tumor heterogeneity and molecular profiles [6]. AI-driven analyses identify patterns and biomarkers that inform the selection of optimal therapeutic combinations, ensuring treatment strategies are tailored to individual tumor characteristics.

Feature	Role of Genomic and Epigenetic Profiling	Development of Combination Therapies	Innovative Drug Delivery and Diagnostic Systems
Purpose	Personalized Treatment Strategies	Enhance Treatment Efficacy	Improve Treatment Precision
Key Techniques	Molecular Biomarker Analysis	Targeting Multiple Pathways	Nanotechnology-based Delivery
Innovations	Cibra Integration	Ai-driven Personalization	Ai-powered Diagnostics

Table 2: This table provides a comparative analysis of the roles and innovations in genomic and epigenetic profiling, combination therapy development, and drug delivery and diagnostic systems in gastric cancer treatment. It highlights the purpose, key techniques, and innovations associated with each approach, emphasizing their contributions to personalized medicine and treatment precision.

8 Challenges and Future Directions

8.1 Innovative Approaches and Future Directions

Innovative strategies are essential for addressing chemotherapy resistance and enhancing outcomes in gastric cancer treatment. Precision medicine, focusing on specific DNA repair deficiencies, requires further research into DNA repair pathway interactions and environmental influences on DNA damage, aiming to increase tumor sensitivity to treatments [13]. The tumor microenvironment (TME) plays a critical role in genomic instability, suggesting that targeting TME components, such as cancer-associated fibroblasts (CAFs), could provide new therapeutic opportunities, especially through pathways involving miR-522 [38]. Combining targeted therapies with dose-dense chemotherapy could further mitigate tumor regrowth and improve outcomes [11].

Emerging genome editing technologies, including the study of circular RNAs (circRNAs), offer transformative potential for cancer treatment. CircRNAs, due to their stability and expression specificity, are promising biomarkers for cancer diagnostics and targeted therapies [26, 44, 19, 39]. Future research should also focus on genetic dependencies related to chromosomal instability (CIN) and evaluate the therapeutic potential of inhibiting KIF18A in cancer [30]. Optimizing mTOR inhibitor dosing and exploring WNT-targeted therapies are crucial for improving patient outcomes [4].

Integrating therapies within a mathematically rigorous framework enhances personalized treatment potential [47]. Future studies should incorporate stochastic and spatial dynamics into predictive models to simulate tumor behavior more accurately, refining models to include detailed biological mechanisms validated with clinical data [11]. Validating AI models across diverse datasets and expanding their scope to include additional biomarkers and cancer types is vital for developing effective targeted therapies [23].

8.2 Integration of Multidisciplinary Approaches

The integration of multidisciplinary approaches is crucial for tackling the complexities of gastric cancer treatment, particularly in overcoming chemotherapy resistance driven by genetic alterations, tumor microenvironment adaptations, and cellular heterogeneity. Combination therapies and predictive modeling aim to enhance therapeutic outcomes and improve survival rates, especially in locally advanced gastric cancer, where neoadjuvant chemotherapy often shows variable effectiveness [36, 34, 1, 22, 2]. This integration necessitates collaboration across oncology, molecular biology, bioinformatics, and pharmacology to develop comprehensive strategies addressing the multifaceted nature of cancer.

A multidisciplinary approach enables diverse expertise to elucidate mechanisms underlying chemotherapy resistance. Collaboration between molecular biologists and oncologists aids in identifying novel biomarkers and therapeutic targets, leading to more effective targeted therapies [2]. Bioinformatics and computational modeling facilitate the analysis of large-scale genomic and transcriptomic data, providing insights into the genetic and epigenetic alterations driving cancer progression [23].

Advanced imaging techniques and molecular diagnostics enhance treatment precision by allowing real-time monitoring of tumor characteristics and responses, enabling clinicians to adapt therapeutic regimens according to dynamic changes within the tumor microenvironment [6]. Collaboration between pharmacologists and clinicians is vital for optimizing drug delivery systems and minimizing side effects associated with conventional chemotherapy. The development of innovative drug delivery technologies, such as nanomedicine and smart nanoparticles, relies on the expertise of both fields to enhance the targeting and delivery of therapeutic agents directly to tumor sites [31].

8.3 Advanced Predictive Models and AI

Advanced predictive models and AI are transforming gastric cancer treatment by providing sophisticated tools to enhance therapeutic strategies. These models offer quantitative insights into tumor population dynamics under varying conditions, informing therapeutic approaches and optimizing treatment regimens [46]. By integrating large-scale genomic, transcriptomic, and clinical data, AI-driven models facilitate the identification of novel biomarkers and therapeutic targets, supporting personalized medicine tailored to individual patients' unique molecular profiles.

AI applications in radiomics and pathomics allow for the extraction of high-dimensional data from medical images, providing comprehensive insights into tumor heterogeneity and treatment response. Such insights are crucial for refining treatment strategies to ensure that therapeutic interventions align with each tumor's specific characteristics. AI algorithms can analyze intricate datasets to predict treatment outcomes, identify potential mechanisms of drug resistance, and recommend optimal therapy combinations, addressing challenges posed by cell heterogeneity, drug target alterations, and microenvironmental adaptations. The use of combination cancer therapies (CCTs), which employ multiple therapeutic approaches, can significantly enhance the efficacy of existing treatment modalities and improve patient survival rates. Additionally, integrating mathematical modeling can streamline the development of effective treatment regimens by addressing the complexities of drug resistance and toxicity associated with various combinations [22, 48].

The synergy between AI and predictive modeling holds significant promise for simulating the effects of various therapeutic interventions in cancer treatment. This approach enables systematic exploration of treatment scenarios, including combination therapies that tackle drug resistance and tumor heterogeneity. By leveraging mathematical models and advanced statistical frameworks, AI can optimize treatment strategies, assess interactions among therapies, and enhance the identification of the most effective regimens. This innovative methodology not only streamlines the discovery of promising cancer treatments but also addresses the complexities of therapy-induced resistance, ultimately aiming to improve patient outcomes and survival rates [22, 47, 48, 41]. This capability is particularly valuable in gastric cancer, where tumor biology heterogeneity and resistance mechanism complexities pose significant treatment challenges.

9 Conclusion

The persistent issue of chemotherapy resistance in gastric cancer is intricately linked to the DNA repair mechanisms and genomic instability inherent in cancer cells. Delving into the relationship between cellular metabolism and DNA repair is crucial for the advancement of targeted therapies that address these core processes. A thorough investigation of the genetic and biochemical pathways responsible for drug resistance, especially in relation to cisplatin, is vital for improving treatment efficacy and exploring new metallodrugs. The application of innovative techniques, such as the random projection algorithm, has shown promise in enhancing predictive accuracy for peritoneal metastasis, highlighting the role of advanced methodologies in shaping therapeutic strategies. Additionally, the development of smart nanoparticles marks a significant leap forward in targeted drug delivery, offering the potential for improved treatment outcomes. Continued research is essential for identifying actionable targets within tumor genomes, thereby refining the precision of therapeutic interventions. Studies on EBV-associated carcinomas have revealed crucial biological processes and gene interactions, such as those involving the ABL1 gene, which may inform the creation of targeted therapies. The necessity for combinational and personalized treatment approaches, which consider ATP levels and tumor heterogeneity, is imperative for optimizing therapeutic results. Although targeted therapies against pathways like PAM show potential, resistance remains a significant hurdle, necessitating ongoing research to overcome these challenges. Personalized strategies, particularly those centered on mTOR-targeted therapies, require the identification of predictive biomarkers to enhance treatment efficacy. Factors such as early detection, dietary influences, and H. pylori infection, along with the effectiveness of combined treatment modalities, are pivotal in improving gastric cancer patient outcomes. Integrating knowledge of DNA damage repair and genomic instability is essential for developing effective targeted therapies, ultimately leading to better interventions and increased patient survival. A comprehensive understanding of cancer mechanisms at the systems level could facilitate the discovery of novel therapeutic targets, underscoring the importance of a holistic approach to treatment development.

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