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The Genetic Landscape of Cancer Cell Plasticity: Mechanisms, Implications for Therapy Resistance and Emerging Interventions

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Abstract

Cancer cell plasticity, the dynamic ability of tumor cells to switch phenotypic states, drives tumor progression, metastasis, and therapy resistance, posing a formidable challenge to effective cancer management. This review comprehensively explores the genetic and epigenetic mechanisms underlying plasticity, highlighting how oncogenic mutations, chromosomal instability, and pathways like PI3K/AKT and RAS/MAPK enable adaptive behaviors such as epithelial-mesenchymal transition and stemness. Epigenetic regulators, including DNA methylation, histone modifications, and non-coding RNAs, amplify this adaptability, allowing rapid responses to therapeutic pressures. We examine the profound clinical implications, with plasticity fueling relapse in breast, lung, and prostate cancers, exacerbated by tumor microenvironment interactions. Challenges in detecting plastic states due to intratumor heterogeneity underscore the need for advanced diagnostics like single-cell genomics. Emerging interventions, from CRISPR-based gene editing and epigenetic therapies to patient-derived organoids and AI-driven combination strategies, offer transformative potential to disrupt plasticity and overcome resistance. This review illuminates the intricate genetic landscape of cancer cell plasticity, advocating for integrated approaches to revolutionize personalized oncology and improve patient outcomes.

Keywords: Cancer Cell Plasticity; Tumor Heterogeneity; Therapy Resistance; Genetic Mechanisms; Epigenetic Regulation; Single-Cell Genomics; Targeted Therapies; Patient-Derived Organoids

1. Introduction

Cancer cell plasticity represents a fundamental attribute of malignant cells, enabling them to dynamically alter their phenotypic states in response to intrinsic genetic cues and extrinsic environmental pressures. This adaptability not only drives tumor heterogeneity but also underpins critical processes such as progression, metastasis, and resistance to therapeutic interventions. At the intersection of genetics and cellular behavior, plasticity allows cancer cells to evade immune surveillance, adapt to nutrient scarcity, and survive targeted therapies, posing significant challenges to effective cancer management. This review synthesizes recent insights into the genetic landscape of cancer cell plasticity,

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exploring its mechanisms, implications for therapy resistance, and promising emerging interventions to target this elusive trait.

1.1. Definition and Historical Context of Cancer Cell Plasticity in Oncology

Cancer cell plasticity is broadly defined as the capacity of tumor cells to reversibly switch between distinct phenotypic states, often mimicking developmental programs to enhance survival and proliferation. According to Bhat et al. [1], this phenomenon encompasses cellular, molecular, and genetic mechanisms that allow cancer cells to adapt to environmental stressors, leading to increased tumor heterogeneity and drug resistance. Such plasticity is not merely a passive response but an active process involving reprogramming of gene expression profiles, enabling cells to transition from proliferative to dormant states or acquire stem-like properties. This definition highlights the interplay between intrinsic factors, like oncogenic mutations, and extrinsic influences from the tumor microenvironment, which collectively shape the plastic behavior of cancer cells.

Historically, the concept of cell plasticity in cancer traces back to observations in developmental biology, where cells demonstrate remarkable flexibility in fate determination during embryogenesis. Early studies in the mid-20th century, inspired by phenomena like regeneration in lower organisms, began to apply similar principles to tumorigenesis. For instance, pioneering work on transdifferentiation in normal tissues laid the groundwork for understanding how cancer cells might hijack these pathways. As oncology evolved, the 1970s and 1980s saw the emergence of ideas around tumor heterogeneity, with researchers noting that not all cancer cells within a tumor behave identically, suggesting an underlying adaptability. This historical perspective underscores how plasticity was initially viewed through the lens of clonal evolution, where genetic mutations drive stable phenotypic changes, but later shifted to include reversible, non-genetic adaptations.

In a seminal study, Tata et al. [2] demonstrated that developmental transcription factor programs, when altered, can lead to tumor plasticity by enabling cells to adopt fates characteristic of adjacent organs, providing a roadmap for how historical developmental contexts influence cancer behavior. This work built on earlier findings from the 1990s, when the discovery of epithelial-mesenchymal transition (EMT) in cancer marked a key milestone, revealing plasticity as a driver of metastasis. Over the decades, technological advancements like single-cell sequencing have refined this understanding, showing that plasticity is not fixed but dynamic, influenced by both genetic drivers and epigenetic modifiers. These historical developments have transformed plasticity from a peripheral concept to a central paradigm in oncology.

Recent historical reviews emphasize the shift from rigid genetic models to inclusive frameworks incorporating plasticity. Findings from Yuan et al. [3] indicate that during cancer progression, tumor cells undergo molecular and phenotypic changes driven by microenvironmental cues and stochastic alterations, highlighting the evolution of plasticity as a response to therapy-imposed pressures. This context reveals how early dismissals of plasticity as artifactual have given way to its recognition as a hallmark of cancer, with implications for personalized medicine. The integration of historical insights with modern data continues to illuminate the adaptive strategies employed by cancer cells.

1.2. Intersection with Genetics: Overview of Genetic Drivers and Their Role in Phenotypic Adaptability

The genetic underpinnings of cancer cell plasticity involve key mutations and alterations that enable phenotypic switching, bridging somatic genetics with adaptive cellular behavior. Saha et al. [4] elucidate that intrinsic genetic factors, such as mutations and epigenetic changes, interact with extrinsic environmental cues to govern plasticity, influencing hallmarks like EMT and cancer stemness. Genetic drivers like oncogenic mutations in KRAS or TP53 can initiate plasticity by deregulating signaling pathways, allowing cells to adopt diverse states that enhance tumorigenicity. This intersection highlights how genetics not only initiates cancer but also sustains its adaptability through heritable changes that promote reversible phenotypes.

Further exploration reveals that copy number variations and chromosomal instabilities serve as genetic scaffolds for plasticity. In a novel investigation, Neftel et al. [5] integrated single-cell RNA-sequencing with bulk genetic analysis to show that malignant cells in glioblastoma exist in four main states, modulated by amplifications in CDK4, EGFR, and PDGFRA, which favor specific phenotypic adaptations. Such genetic drivers influence the relative frequency of plastic states, demonstrating how alterations in tumor suppressors like NF1 can bias cells toward more adaptable phenotypes. This genetic-phenotypic link underscores the role of driver mutations in enabling cells to navigate between states for survival advantage.

Epigenetic modifications, often intertwined with genetic drivers, amplify phenotypic adaptability. As noted by Gargiulo et al. [6], oncogenic driver aberrations shape cancer cell phenotypes alongside passenger mutations, but phenotypic cell states—classified as drivers, passengers, or trailers—can supersede genetics in dictating adaptability. For example, mutations cooperating with epigenetic regulators can induce dedifferentiation, allowing cancer cells to revert to stem-like states. This overview illustrates the complex genetic landscape where drivers not only initiate but also perpetuate plasticity through interactions with the cellular machinery.

Contemporary studies reinforce that genetic drivers facilitate adaptability by modulating transcriptional networks. Plass et al. [7] highlight epigenetic regulation across tumor types, where chromatin changes driven by genetic mutations enable transitions in cancer states, emphasizing the cooperative role in phenotypic shifts. This genetic intersection is crucial for understanding how adaptability emerges, providing a foundation for targeting these drivers to limit plasticity.

1.3. Significance in Tumor Progression, Metastasis, and Therapy Resistance

The significance of cancer cell plasticity in tumor progression lies in its ability to generate intratumor heterogeneity, fueling aggressive growth and adaptation. Pérez-González et al. [8] argue that plasticity enables cells to reprogram during progression, contributing to metastasis and drug tolerance by activating developmental programs. In progression, plastic cells can switch to invasive phenotypes, enhancing local invasion and systemic spread. This significance is evident in how plasticity allows evasion of apoptotic signals, promoting unchecked proliferation.

In metastasis, plasticity plays a pivotal role by enabling cells to detach, survive circulation, and colonize distant sites. Shi et al. [9] describe tumor cell plasticity as a mechanism for phenotypic switching, where cells adopt dormant or stem-like states to facilitate metastatic outgrowth and therapy evasion. Metastatic cells often undergo reversible transitions, such as EMT to disseminate and mesenchymal-epithelial transition to seed secondary tumors, underscoring plasticity's critical impact on disease dissemination.

Therapy resistance emerges as a major consequence of plasticity, where cells adapt to treatment pressures through state changes. Grimple et al. [10] posit that deeper insights into context-specific plasticity can reveal mechanisms underlying resistance, as seen in pediatric gliomas or prostate cancers where signaling pathways drive adaptive states. Plasticity allows subpopulations to persist as drug-tolerant persisters, leading to relapse. This significance highlights the need for therapies that address dynamic states rather than static genotypes.

Overall, the intertwined roles in progression, metastasis, and resistance position plasticity as a therapeutic target. As emphasized in recent analyses, targeting plastic transitions could disrupt these processes, improving outcomes in refractory cancers.

Scope of the Review: Mechanisms, Implications, and Emerging Interventions

This review comprehensively examines the genetic mechanisms driving cancer cell plasticity, including oncogenic mutations, epigenetic regulation, and pathway integrations that enable phenotypic shifts. We will delve into how these mechanisms contribute to adaptive behaviors observed across various cancer types. The scope includes an analysis of single-cell genomics data to uncover intratumor diversity, providing a foundation for understanding plasticity's molecular basis.

Implications for therapy resistance will be explored, highlighting how plasticity leads to evasion of targeted therapies, chemotherapy, and immunotherapy through reversible states. Clinical examples from breast, lung, and prostate cancers will illustrate relapse patterns driven by genetic plasticity, alongside challenges in biomarker development due to dynamic heterogeneity.

Emerging interventions, such as epigenetic therapies and combination strategies targeting key pathways, will be discussed as promising avenues to mitigate plasticity. The review aims to outline future directions, including AI-driven approaches for personalized oncology, to transform cancer treatment by addressing this adaptive landscape.

2. Conceptual Overview of Cancer Cell Plasticity

Cancer cell plasticity is a dynamic and multifaceted phenomenon that enables tumor cells to adapt their phenotypes in response to genetic, epigenetic, and environmental cues, significantly impacting tumor behavior and therapeutic outcomes. This section explores the conceptual framework of cancer cell plasticity, delineating its various forms, the interplay between genetic and non-genetic contributions, and the integration of recent paradigms that challenge traditional views of tumor evolution. By synthesizing insights from recent studies, we aim to provide a comprehensive understanding of how plasticity operates as a central mechanism in cancer progression and resistance.

2.1. Types of Plasticity: Lineage, Stem-Like, Epithelial-Mesenchymal Transition (EMT), and Dedifferentiation

Cancer cell plasticity manifests in multiple forms, each contributing to tumor heterogeneity and adaptability. Lineage plasticity allows cancer cells to switch between differentiated and undifferentiated states, often mimicking developmental programs. According to Quintanal-Villalonga et al. [11], lineage plasticity is a hallmark of aggressive cancers like small cell lung cancer, where cells transdifferentiate into neuroendocrine phenotypes, driven by genetic alterations such as RB1 and TP53 loss. This plasticity enables tumors to bypass lineage-specific therapies, complicating treatment strategies. For instance, prostate cancer cells can shift from androgen-dependent to neuroendocrine-like states, evading androgen receptor-targeted therapies.

Stem-like plasticity refers to the acquisition of cancer stem cell (CSC) properties, conferring self-renewal and tumor-initiating capabilities. In a pivotal study, Lytle et al. [12] demonstrated that pancreatic cancer cells exhibit stem-like plasticity through upregulation of stemness markers like SOX2, driven by microenvironmental signals and genetic mutations. This stem-like state enhances tumor propagation and resistance to chemotherapy, as CSCs often enter quiescent phases to survive treatment. The dynamic interplay between stem-like and non-stem states underscores the reversible nature of plasticity, allowing cells to adapt to therapeutic pressures.

Epithelial-mesenchymal transition (EMT) is a well-characterized form of plasticity where epithelial cancer cells adopt mesenchymal traits, enhancing motility and invasiveness. Pastushenko et al. [13] found that EMT in breast cancer involves hybrid states, were cells co-express epithelial and mesenchymal markers, enabling flexible adaptation during metastasis. This hybrid EMT state, regulated by transcription factors like ZEB1 and SNAIL, is genetically modulated by mutations in pathways such as TGF-β, highlighting the genetic basis of this plasticity. Similarly, dedifferentiation allows cancer cells to revert to less differentiated states, often resembling progenitor cells. Boumahdi et al. [14] reported that dedifferentiation in melanoma, driven by genetic alterations in BRAF and epigenetic reprogramming, promotes aggressive tumor behavior and therapy resistance.

Together, these forms of plasticity lineage, stem-like, EMT, and dedifferentiation—illustrate the diverse strategies cancer cells employ to adapt. Their reversible nature, governed by genetic and epigenetic mechanisms, enables tumors to navigate complex microenvironments and therapeutic challenges, underscoring the need for therapies targeting these dynamic states.

To provide a comprehensive overview of these plasticity types, their mechanisms, and implications, Table 1 summarizes key characteristics drawn from recent studies, highlighting their roles across different cancers.

Table 1 Types of Cancer Cell Plasticity and Their Characteristics

Type of Plasticity	Description	Key Mechanisms	Associated Cancers	Implications for Tumor Behavior	References
Lineage Plasticity	Reversible switching between differentiated and undifferentiated states, often mimicking developmental programs.	Genetic alterations like RB1 and TP53 loss leading to transdifferentiation; activation of developmental transcription factors.	Small cell lung cancer (neuroendocrine phenotypes); Prostate cancer (androgen-dependent to neuroendocrine-like).	Bypasses lineage-specific therapies; enhances aggressiveness and resistance.	Quintanal-Villalonga et al. [11]; Beltran et al. [25]
Stem-Like Plasticity	Acquisition of cancer stem cell properties, including self-renewal and tumor-initiating capabilities.	Upregulation of stemness markers (e.g., SOX2); microenvironmental signals and genetic mutations driving quiescence.	Pancreatic cancer; Glioblastoma; Medulloblastoma.	Promotes tumor propagation, chemotherapy resistance, and relapse through dormant states.	Lytle et al. [12]; Dirkse et al. [17]; Vanner et al. [44]
Epithelial-Mesenchymal Transition (EMT)	Epithelial cells adopt mesenchymal traits, enhancing motility and invasiveness; includes hybrid states.	Transcription factors like ZEB1, SNAIL, TWIST; regulated by TGF-β pathway and genetic mutations.	Breast cancer; Lung cancer; Melanoma.	Facilitates metastasis, immune evasion, and drug tolerance; reversible for colonization at distant sites.	Pastushenko et al. [13]; Pérez-González et al. [8]; Imodoye et al. [54]
Dedifferentiation	Reversion to less differentiated, progenitor-like states resembling embryonic cells.	Genetic alterations (e.g., BRAF); epigenetic reprogramming activating stem cell genes.	Melanoma; Leukemia; Colorectal cancer.	Drives aggressive behavior, therapy resistance, and tumor heterogeneity.	Boumahdi et al. [14]; Athanasoulis et al. [35]; Kumar et al. [45]
Drug-Tolerant Persister States	Temporary quiescence or altered phenotypes to survive therapeutic stress.	Epigenetic changes (e.g., histone modifications); pathway dysregulation like PI3K/AKT.	Breast cancer; Lung cancer; Ovarian cancer.	Leads to relapse post-treatment; amplifies resistance across modalities.	Sharma et al. [4]; Marine et al. [24]; Sharma et al. [63]
Phenotypic Switching	Stochastic transitions between proliferative, invasive, or dormant states.	Interplay of genetic heterogeneity and epigenetic regulators; influenced by TME cues.	Glioblastoma; Colorectal cancer; Head and neck squamous cell carcinoma.	Contributes to intratumor heterogeneity and adaptive evolution.	Gupta et al. [23]; Puram et al. [38]; Black et al. [21]
Hybrid States	Co-expression of multiple phenotypic markers (e.g., epithelial and mesenchymal).	Chromatin accessibility changes; transcription factor networks.	Breast cancer; Pancreatic cancer.	Enhances flexibility during metastasis and therapy evasion.	Pastushenko et al. [13]; Flavahan et al. [16]

To visually encapsulate the multifaceted forms of cancer cell plasticity discussed, figure 1 provides a schematic overview of CSC plasticity mechanisms, highlighting the interplay of genetic and epigenetic drivers with microenvironmental cues that enable phenotypic transitions.

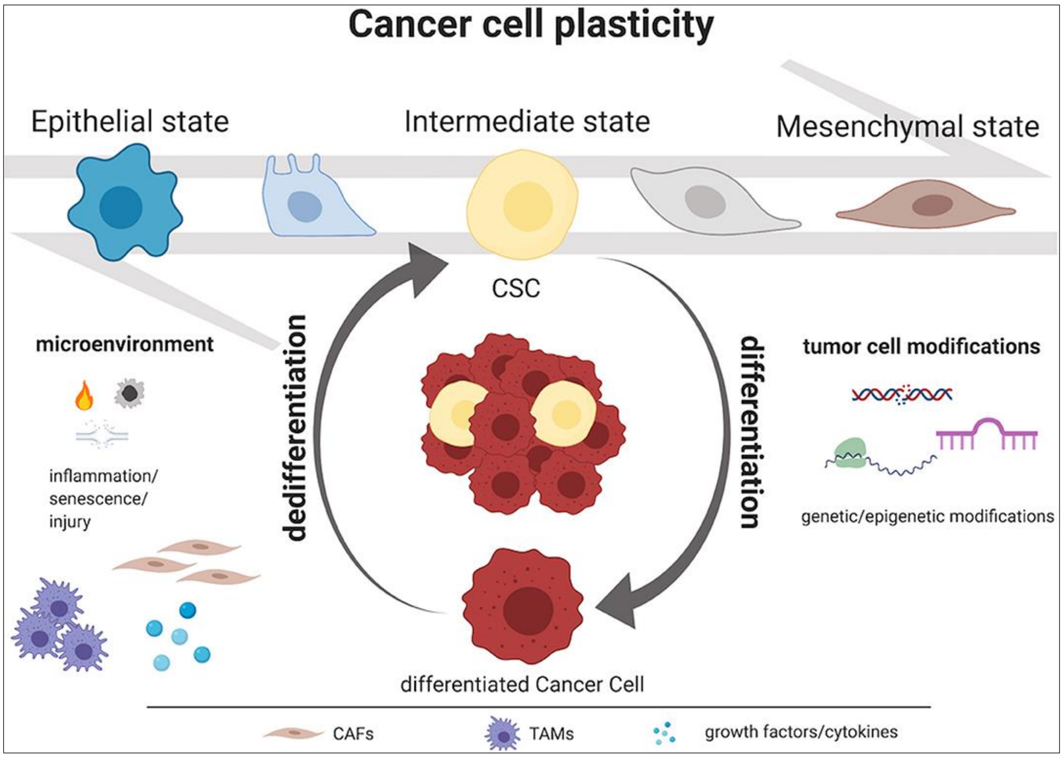

Figure 1 A schematic illustration of the dynamic shifts between cancer stem cell (CSC) and non-CSC states, driven by genetic, epigenetic, and microenvironmental factors, including epithelial-to-mesenchymal transition (EMT). Reproduced from Fanelli et al. [80] with permission

2.2. Genetic versus Non-Genetic Contributions, Including Tumor Heterogeneity and Microenvironment Influences

The balance between genetic and non-genetic contributions is central to understanding cancer cell plasticity. Genetic alterations, such as oncogenic mutations and copy number variations, provide the molecular foundation for plasticity. For example, Marjanovic et al. [15] elucidated that KRAS mutations in lung cancer drive plasticity by altering transcriptional networks, enabling cells to switch between epithelial and mesenchymal states. These genetic changes create a permissive landscape for phenotypic adaptability, often amplified by chromosomal instability, which introduces further heterogeneity.

Non-genetic factors, including epigenetic modifications and microenvironmental cues, play equally critical roles. According to Flavahan et al. [16], epigenetic reprogramming via histone modifications and DNA methylation can induce plastic states without altering the genetic code, allowing rapid adaptation to stressors like hypoxia or drug exposure. The tumor microenvironment (TME) further modulates plasticity by providing signals such as cytokines, growth factors, and extracellular matrix interactions. In a classic study, Dirkse et al. [17] showed that glioblastoma cells adopt stem-like states in response to TME-derived signals, such as TGF-β from stromal cells, independent of genetic changes. This interplay highlights how non-genetic factors amplify genetic predispositions.

Tumor heterogeneity, a hallmark of cancer, is both a cause and consequence of plasticity. Single-cell sequencing studies, like those by Patel et al. [18], reveal that intratumor heterogeneity arises from subpopulations with distinct genetic and epigenetic profiles, each capable of plastic transitions. These subpopulations contribute to tumor resilience, as some cells may adopt drug-tolerant states during therapy. The TME further exacerbates heterogeneity by creating niches that favor specific plastic phenotypes, such as hypoxic regions promoting stemness.

The synergy between genetic and non-genetic factors underscores the complexity of plasticity. As noted by Shen et al. [19], the convergence of genetic mutations and microenvironmental signals creates a feedback loop that sustains plasticity, driving tumor evolution and resistance. This dual contribution necessitates integrated therapeutic approaches targeting both genetic drivers and environmental modulators to disrupt plastic behavior effectively.

2.3. Key Models and Paradigms from Recent Studies, Such as Somatic Mutation Theory Challenged by Plasticity

The somatic mutation theory (SMT) has long dominated cancer research, positing that sequential genetic mutations drive tumor initiation and progression. However, recent studies challenge this paradigm by highlighting plasticity's role in tumor evolution beyond fixed genetic changes. Hanahan [20] argues that plasticity introduces a layer of adaptability that transcends SMT, as cancer cells can adopt phenotypes not strictly dictated by their mutational profile. This paradigm shift emphasizes dynamic, reversible changes over linear genetic progression.

A groundbreaking model proposed by Black et al. [21] integrates plasticity into tumor evolution, suggesting that non-genetic mechanisms, such as epigenetic reprogramming, allow cells to explore diverse phenotypic states within a genetically stable framework. Their work in breast cancer demonstrates how cells oscillate between proliferative and invasive states, driven by epigenetic regulators rather than new mutations. This model challenges the clonal dominance assumed by SMT, proposing instead a dynamic equilibrium of plastic states.

Another paradigm, the cancer stem cell model, has been refined to incorporate plasticity. Findings from Batlle et al. [22] indicate that non-stem cancer cells can acquire stem-like properties through plastic transitions, challenging the notion of a fixed CSC hierarchy. In colorectal cancer, genetic mutations in APC cooperate with microenvironmental signals to induce stemness, illustrating a plasticity-driven evolution model. Similarly, the concept of "phenotypic switching," as explored by Gupta et al. [23], describes how cancer cells stochastically transition between states, a process amplified by genetic heterogeneity but not solely dependent on it.

These paradigms collectively highlight that plasticity extends beyond SMT, integrating genetic, epigenetic, and environmental factors into a cohesive framework. As emphasized by Marine et al. [24], understanding plasticity requires moving beyond mutation-centric views to embrace dynamic models that account for reversible phenotypic states, paving the way for innovative therapeutic strategies.

3. Genetic mechanisms underlying cancer cell plasticity

The genetic mechanisms driving cancer cell plasticity form a cornerstone of tumor adaptability, enabling cells to dynamically switch phenotypes in response to therapeutic and environmental pressures. This section explores the intricate genetic alterations that underpin plasticity, including oncogenic mutations, chromosomal instability, and pathway dysregulation, as elucidated by recent genomic studies. By integrating findings from single-cell genomics and molecular biology, we aim to provide a comprehensive understanding of how genetic drivers facilitate the plastic behaviors that fuel tumor progression and resistance.

3.1. Oncogenic Mutations and Copy Number Variations Promoting Plasticity

Oncogenic mutations are pivotal in establishing the genetic foundation for cancer cell plasticity, enabling cells to adopt diverse phenotypic states. According to Beltran et al. [25], mutations in genes such as TP53 and RB1 in prostate cancer drive lineage plasticity, allowing cells to transition from luminal to neuroendocrine-like states, thereby evading targeted therapies. These mutations disrupt normal cellular checkpoints, creating a permissive environment for phenotypic switching. For instance, TP53 mutations often lead to the upregulation of transcription factors like SOX2, which promote stem-like plasticity and enhance tumor aggressiveness.

Copy number variations (CNVs) further amplify plasticity by altering gene dosages critical for cellular adaptability. In a landmark study, Ghandi et al. [26] analyzed genomic data across multiple cancer types and found that CNVs in oncogenes like MYC and EGFR are associated with increased plasticity, as they enhance signaling pathways that support stemness and EMT. MYC amplification, for example, has been linked to the activation of stem cell genes, enabling cancer cells to oscillate between proliferative and quiescent states. This genetic variability contributes to intratumor heterogeneity, allowing subpopulations to adapt to therapeutic challenges.

Moreover, oncogenic mutations and CNVs often cooperate to enhance plasticity. Lee J. [27] demonstrated in melanoma that BRAF mutations, combined with CNVs in MITF, drive dedifferentiation and resistance to MAPK inhibitors. This synergy creates a dynamic genetic landscape where cells can rapidly adapt to external pressures, such as drug exposure, by altering their transcriptional profiles. The interplay between mutations and CNVs underscores their role as genetic drivers of plasticity, providing a molecular basis for therapeutic resistance.

Recent genomic profiling has further clarified the role of these alterations. For instance, studies by Zhang et al. [28] revealed that CNVs in chromatin modifiers like KMT2D enhance epigenetic plasticity, enabling cells to switch phenotypes without additional mutations. This highlights how genetic alterations not only initiate but also sustain plastic states, posing challenges for precision oncology.

3.2. Chromosomal Instability and Aneuploidy as Drivers of Tumorigenesis

Chromosomal instability (CIN) and aneuploidy are critical genetic mechanisms that fuel cancer cell plasticity by introducing genomic variability. CIN, characterized by errors in chromosome segregation, leads to diverse karyotypes within a tumor, promoting adaptability. Bakhoum et al. [29] found that CIN in breast cancer cells enhances phenotypic heterogeneity by generating subpopulations with distinct genetic profiles, each capable of plastic transitions. This instability allows cells to explore a range of phenotypic states, increasing their resilience to therapies.

Aneuploidy, a consequence of CIN, further amplifies plasticity by altering gene expression on a chromosomal scale. According to Davoli et al. [30], aneuploidy in cancers like colorectal carcinoma disrupts gene dosage, upregulating oncogenes and downregulating tumor suppressors, which facilitates transitions to aggressive phenotypes. For example, aneuploidy-induced overexpression of genes like CCND1 can promote stem-like states, enabling cells to survive chemotherapy. This genetic chaos creates a fertile ground for plasticity, as cells adapt to environmental stressors through altered genomic landscapes.

The dynamic nature of CIN and aneuploidy also contributes to therapy resistance. In a novel study, Pinto et al. [31] showed that aneuploidy in glioblastoma cells drives plasticity by altering chromatin accessibility, allowing rapid adaptation to DNA-damaging agents. This adaptability is further enhanced by the activation of DNA repair pathways, which are often dysregulated in aneuploid cells. Such findings emphasize how chromosomal alterations provide a genetic scaffold for plasticity, enabling tumors to evade therapeutic pressures.

Moreover, CIN and aneuploidy interact with other genetic alterations to amplify plasticity. Sansregret et al. [32] demonstrated that CIN cooperates with oncogenic mutations like KRAS to enhance EMT and stemness in pancreatic cancer, illustrating a synergistic effect that drives tumor evolution. These mechanisms highlight the critical role of chromosomal alterations in sustaining plastic phenotypes, necessitating therapeutic strategies that target genomic instability.

3.3. Role of Specific Genes and Pathways in Enabling Reversible States

Specific genes and signaling pathways play a central role in enabling the reversible states characteristic of cancer cell plasticity. The PI3K/AKT pathway, frequently dysregulated in cancers, is a key regulator of plastic transitions. Hanker et al. [33] reported that PI3K/AKT activation in breast cancer promotes EMT and stem-like states by upregulating transcription factors like SNAIL and TWIST. This pathway, often activated by mutations in PIK3CA, enables cells to switch between proliferative and invasive phenotypes, contributing to metastasis and resistance.

The RAS/MAPK pathway similarly drives plasticity by modulating cellular responses to environmental cues. In a classic study, Maffeis et al. [34] found that RAS mutations in colorectal cancer enhance plasticity by activating ERK signaling, which promotes dedifferentiation and drug tolerance. This pathway's ability to integrate genetic and microenvironmental signals allows cells to adopt reversible states, such as dormancy, to survive therapeutic stress. These findings highlight the pathway's role in maintaining a dynamic phenotypic landscape.

Transcription factors like MYB and SOX2 are also critical for enabling reversible states. According to Wu et al. [35], MYB overexpression in leukemia drives stemness by regulating genes involved in self-renewal, allowing cells to oscillate between differentiated and progenitor-like states. Similarly, SOX2 activation in lung cancer, as shown by Boumahdi et al. [14], promotes plasticity by enhancing CSC properties, facilitating resistance to targeted therapies. These genes act as molecular switches, enabling rapid phenotypic transitions.

Recent studies also highlight the role of feedback loops in sustaining reversible states. For instance, Chakrabarti et al. [36] demonstrated that Wnt signaling, activated by genetic alterations in APC, creates a feedback loop that maintains stem-like plasticity in colorectal cancer. This pathway's dysregulation enables cells to adapt dynamically, underscoring the need for therapies targeting these genetic drivers to disrupt plasticity.

Table 2 compiles a detailed overview of key genetic alterations, their mechanisms, and implications for plasticity across various cancers, integrating insights from single-cell and genomic studies.

Table 2 Genetic Drivers of Cancer Cell Plasticity

Genetic Alteration	Specific Examples	Mechanisms Involved	Affected Pathways/ Genes	Cancer Types	Role in Plasticity and Resistance	References
Oncogenic Mutations	KRAS, TP53, RB1	Deregulation of signaling; upregulation of transcription factors like SOX2.	RAS/MAPK; PI3K/AKT; Stemness genes.	Lung cancer; Prostate cancer; Pancreatic cancer.	Enables EMT, stemness, and reversible states; drives resistance to targeted therapies.	Marjanovic et al. [15]; Beltran et al. [25]; Saha et al. [4]
Copy Number Variations (CNVs)	MYC amplification; EGFR, PDGFRA amplifications.	Gene dosage alterations enhancing signaling; chromatin modifier changes.	CDK4, NF1; Epigenetic regulators like KMT2D.	Glioblastoma; Multiple cancers (e.g., melanoma).	Promotes stemness, dedifferentiation, and intratumor heterogeneity.	Ghandi et al. [26]; Neftel et al. [5]; Zhang et al. [28]
Chromosomal Instability (CIN)	Errors in chromosome segregation leading to diverse karyotypes.	Genomic variability; altered chromatin accessibility.	DNA repair pathways; Oncogenes/tumor suppressors.	Breast cancer; Colorectal cancer; Glioblastoma.	Fuels phenotypic heterogeneity and adaptation to therapies.	Bakhoum et al. [29]; Sansregret et al. [32]; Pinto et al. [31]
Aneuploidy	Whole chromosome gains/losses altering gene expression.	Haploinsufficiency; triplosensitivity.	CCND1 overexpression; Tumor suppressors downregulation.	Colorectal carcinoma; Pancreatic cancer.	Enhances stem-like states and therapy evasion.	Davoli et al. [30]; Sansregret et al. [32]
Specific Gene Dysregulation	BRAF mutations; MITF CNVs.	Cooperation with epigenetic changes; transcriptional network modulation.	MAPK pathway; MITF/AXL expression.	Melanoma; Lung cancer.	Drives dedifferentiation and drug tolerance.	Lee J. [27]; Tirosh et al. [37]
Pathway Dysregulation	PI3K/AKT activation (e.g., PIK3CA mutations).	Upregulation of EMT factors like SNAIL, TWIST.	AKT-driven transcription.	Breast cancer; Colorectal cancer.	Facilitates phenotypic switches and resistance.	Hanker et al. [33]; Maffeis et al. [34]
Transcription Factor Alterations	SOX2, OCT4, MYB overexpression.	Regulation of self-renewal and progenitor states.	Stemness networks; Wnt signaling.	Medulloblastoma; Breast cancer; Leukemia.	Enables oscillation between states; sustains CSC properties.	Vanner et al. [44]; Kumar et al. [45]; Athanasoulis et al. [35]
Chromatin and Epigenetic Gene Mutations	KMT2D CNVs; APC alterations.	Feedback loops in signaling; chromatin accessibility.	Wnt pathway; Histone modifications.	Colorectal cancer; Multiple tumors.	Amplifies reversible transitions and adaptability.	Zhang et al. [28]; Chakrabarti et al. [36]

3.4. Integration of Single-Cell Genomics Data Revealing Intratumor Genetic Diversity

Single-cell genomics has revolutionized our understanding of intratumor genetic diversity, providing unprecedented insights into the genetic basis of plasticity. Tirosh et al. [37] utilized single-cell RNA sequencing in melanoma to identify distinct cellular states within tumors, driven by genetic heterogeneity in MITF and AXL expression. These states, ranging from proliferative to invasive, reflect the plastic nature of cancer cells, with genetic alterations dictating their frequency and stability.

The integration of single-cell data also reveals how genetic diversity fuels adaptability. In a pivotal study, Puram et al. [38] analyzed head and neck squamous cell carcinoma and found that genetic subpopulations with distinct mutational profiles exhibit unique plastic behaviors, such as EMT or stemness. These subpopulations, identified through single-cell sequencing, highlight how genetic diversity enables tumors to maintain a reservoir of adaptable cells, contributing to resistance.

Furthermore, single-cell genomics uncovers the role of rare subpopulations in driving plasticity. Neftel et al. [5] demonstrated in glioblastoma that rare cells with specific genetic alterations, such as EGFR amplifications, act as "plasticity hubs," seeding diverse phenotypic states within the tumor. This genetic diversity, coupled with dynamic transcriptional changes, allows tumors to adapt to therapeutic pressures rapidly.

The application of single-cell technologies also informs therapeutic strategies. As noted by Lim et al. [39], integrating single-cell genomic data with bulk sequencing can identify key genetic drivers of plasticity, guiding the development of targeted therapies. This approach highlights the power of single-cell genomics in dissecting the genetic landscape of plasticity, offering a path toward precision oncology.

4. Epigenetic and Transcriptional Regulation of Plasticity

Epigenetic and transcriptional regulation are pivotal in orchestrating cancer cell plasticity, enabling rapid and reversible phenotypic switches without altering the genetic code. These mechanisms allow cancer cells to adapt dynamically to therapeutic and environmental pressures, contributing to tumor heterogeneity and resistance. This section delves into the roles of epigenetic modifiers, transcriptional networks, mRNA translation, and therapy-induced epigenetic shifts in driving plasticity, drawing on recent studies to elucidate their molecular underpinnings and therapeutic implications.

4.1. Epigenetic Modifiers: DNA Methylation, Histone Modifications, and Non-Coding RNAs in Reprogramming Cancer Cells

Epigenetic modifiers, including DNA methylation, histone modifications, and non-coding RNAs, play a central role in reprogramming cancer cells to adopt plastic phenotypes. DNA methylation, which regulates gene expression by adding methyl groups to DNA, can induce reversible state changes. According to Easwaran et al. [40], hypermethylation of tumor suppressor genes in breast cancer promotes EMT and stem-like states, enabling cells to evade therapies. This methylation-driven plasticity is reversible, allowing cells to revert to proliferative states post-treatment, contributing to relapse.

Histone modifications, such as acetylation and methylation, further enhance plasticity by altering chromatin accessibility. In a seminal study, Suvà et al. [41] demonstrated that histone H3K27me3 demethylation in glioblastoma activates stemness genes like SOX2, driving dedifferentiation and therapy resistance. These modifications create an open chromatin state, facilitating rapid transcriptional shifts that underpin plasticity. Similarly, histone deacetylases (HDACs) modulate gene expression to promote aggressive phenotypes, as seen in pancreatic cancer where HDAC inhibition reverses plastic states.

Non-coding RNAs, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are critical epigenetic regulators of plasticity. Goodall et al. [42] found that miR-200 family members suppress EMT in lung cancer by targeting ZEB1, but their downregulation allows mesenchymal transitions, enhancing invasiveness. Conversely, lncRNAs like HOTAIR can promote plasticity by recruiting chromatin-modifying complexes, as shown by Gupta et al. [23]. These findings highlight how epigenetic modifiers orchestrate a complex regulatory network that enables cancer cells to navigate diverse phenotypic states.

The interplay of these epigenetic mechanisms creates a dynamic landscape for plasticity. As noted by Jones et al. [43], the reversible nature of epigenetic changes allows cancer cells to adapt rapidly to stressors, underscoring the potential of epigenetic therapies to disrupt plasticity and improve treatment outcomes.

4.2. Transcriptional Networks: Factors Like SOX2, OCT4, and MYB Driving Stemness and Plasticity

Transcriptional networks, driven by key factors like SOX2, OCT4, and MYB, are central to maintaining cancer cell plasticity and stemness. SOX2, a master regulator of stem cell identity, is frequently upregulated in cancers with high plasticity. According to Vanner et al. [44], SOX2 overexpression in medulloblastoma drives stem-like states, enabling cells to oscillate between proliferative and quiescent phenotypes, which contributes to chemotherapy resistance. This transcription factor activates genes involved in self-renewal, creating a reservoir of adaptable cells.

OCT4, another pluripotency factor, similarly promotes plasticity by reprogramming cancer cells to stem-like states. In a pivotal study, Kumar et al. [45] showed that OCT4 expression in breast cancer enhances CSC properties, allowing cells to survive targeted therapies through dormancy. This transcriptional reprogramming is often coupled with epigenetic changes, amplifying the plastic potential of tumor cells. OCT4's role in maintaining a dynamic equilibrium of cellular states underscores its significance in tumor progression.

MYB transcription factors also drive plasticity by regulating genes associated with stemness and differentiation. Athanasoulis et al. [35] demonstrated that MYB in leukemia activates a network of genes that promote progenitor-like states, facilitating resistance to differentiation therapies. This transcriptional control is dynamic, allowing cells to switch phenotypes in response to environmental cues. Recent studies further suggest that MYB cooperates with epigenetic modifiers to sustain plasticity, highlighting the interconnectedness of these regulatory mechanisms.

The synergy of these transcription factors creates robust networks that sustain plasticity. As emphasized by Boumahdi et al. [14], targeting these networks, such as through inhibitors of SOX2 or OCT4, could disrupt the transcriptional programs driving plasticity, offering a promising therapeutic avenue.

4.3. mRNA Translation and Post-Transcriptional Control as Modulators of Plasticity

mRNA translation and post-transcriptional control are emerging as critical modulators of cancer cell plasticity, enabling rapid adaptation to stress. Translational regulation allows cells to selectively prioritize protein synthesis, tailoring responses to environmental changes. According to Truitt et al. [46], activation of the mTOR pathway in pancreatic cancer enhances mRNA translation of stemness genes, promoting CSC-like plasticity. This rapid protein synthesis enables cells to adopt resistant phenotypes during therapy.

Post-transcriptional mechanisms, such as alternative splicing and RNA-binding proteins, further regulate plasticity. In a novel study, Oltean et al. [47] found that alternative splicing of EMT-related genes in prostate cancer generates isoforms that favor mesenchymal phenotypes, enhancing invasiveness. RNA-binding proteins like HuR stabilize mRNAs encoding plasticity drivers, as shown by Pereira et al. [48], amplifying the expression of genes like SNAIL in breast cancer. These mechanisms provide a layer of control that complements transcriptional regulation.

Moreover, miRNAs play a significant role in post-transcriptional regulation of plasticity. Bu et al. [49] reported that miR-34a suppresses stemness in colorectal cancer by targeting NOTCH1 mRNA, but its downregulation allows CSC expansion. This dynamic regulation enables rapid phenotypic switches without genetic alterations, highlighting the flexibility of post-transcriptional control.

The integration of translational and post-transcriptional mechanisms with genetic and epigenetic regulation creates a multifaceted system for plasticity. As noted by Silvera et al. [50], targeting mRNA translation pathways, such as mTOR inhibitors, could disrupt these rapid adaptations, offering a novel strategy to combat plasticity-driven resistance.

4.4. Therapy-Induced Epigenetic Shifts Contributing to Adaptive Resistance

Therapy-induced epigenetic shifts are a critical driver of adaptive resistance, as treatments often trigger epigenetic reprogramming that enhances plasticity. According to Sharma et al. [4], chemotherapy in lung cancer induces DNA hypomethylation, activating genes associated with stemness and EMT, which allows cells to enter drug-tolerant states. These epigenetic shifts are reversible, enabling cells to revert to sensitive states post-treatment, contributing to relapse.

Histone modifications also mediate therapy-induced plasticity. In a classic study, Knoechel et al. [51] showed that HDAC inhibition in leukemia triggers compensatory histone acetylation, promoting stem-like states that confer resistance. This adaptive response highlights how therapies can inadvertently enhance plasticity, necessitating strategies to counteract these shifts. Similarly, radiotherapy can induce epigenetic changes, as seen in glioblastoma where radiation promotes H3K27ac deposition, enhancing CSC properties.

Non-coding RNAs further contribute to therapy-induced resistance. According to Abdelmonem et al. [52], lncRNA MALAT1 is upregulated in response to chemotherapy in ovarian cancer, recruiting epigenetic complexes to promote EMT and resistance. These findings underscore the role of epigenetic plasticity in enabling tumors to adapt to therapeutic stress.

The clinical implications of therapy-induced epigenetic shifts are profound. As highlighted by Brown et al. [53], combining epigenetic therapies, such as DNA methyltransferase inhibitors, with standard treatments could prevent these adaptive shifts, reduce resistance and improve outcomes. This approach emphasizes the need to target epigenetic plasticity to overcome therapy-induced resistance.

5. Implications for Therapy Resistance

Cancer cell plasticity significantly contributes to therapy resistance, enabling tumor cells to evade the effects of targeted therapies, chemotherapy, and immunotherapy through dynamic phenotypic switches. This adaptability, driven by genetic and epigenetic mechanisms, allows cancer cells to adopt drug-tolerant states, survive treatment, and contribute to relapse. This section explores the mechanisms underlying plasticity-driven resistance, clinical examples across major cancer types, the role of tumor-educated immune cells and microenvironment interactions, and the challenges in detecting plastic states for effective biomarker development.

5.1. Mechanisms of Resistance: Plasticity Enabling Evasion of Targeted Therapies, Chemotherapy, and Immunotherapy

Cancer cell plasticity facilitates therapy resistance by enabling cells to transition into states that reduce drug efficacy. According to Boumahdi et al. [14], plasticity allows cancer cells to enter drug-tolerant persister (DTP) states, characterized by quiescence or stem-like properties, which protect them from targeted therapies. For instance, in EGFR-mutant lung cancer, cells can adopt a mesenchymal phenotype via EMT, rendering them insensitive to EGFR inhibitors. This reversible state, driven by epigenetic reprogramming, allows cells to survive initial treatment and later proliferate, leading to relapse.

Chemotherapy resistance is similarly influenced by plasticity. Sharma et al. [4] demonstrated that chemotherapy induces a subset of breast cancer cells to enter a dormant, stem-like state through epigenetic changes, such as histone modifications, enabling survival under cytotoxic stress. These DTP cells, often marked by high ALDH activity, can repopulate tumors post-treatment. The reversible nature of these states, as highlighted by Shen et al. [19], underscores how plasticity enables rapid adaptation to chemotherapeutic agents, complicating long-term disease control.

Immunotherapy resistance also involves plasticity-driven mechanisms. In a pivotal study, Imodoye et al. [54] showed that EMT in melanoma cells reduces their immunogenicity, allowing evasion of immune checkpoint inhibitors by downregulating MHC class I expression. Plasticity enables cells to toggle between immunogenic and non-immunogenic states, driven by transcription factors like ZEB1, which are activated by genetic mutations or microenvironmental cues. This adaptability poses a significant barrier to durable immunotherapy responses.

The convergence of these mechanisms highlights plasticity as a unifying driver of resistance across therapeutic modalities. As noted by Marine et al. [24], targeting plasticity requires addressing both genetic drivers and the epigenetic programs that enable rapid state transitions, emphasizing the need for combination therapies to overcome resistance.

5.2. Clinical Examples Across Cancers Where Genetic Plasticity Leads to Relapse

Genetic plasticity drives relapse in several cancers by enabling tumor cells to adapt to therapeutic pressures. In breast cancer, triple-negative subtypes exhibit high plasticity, with cells transitioning to CSC-like states post-chemotherapy. According to Creighton et al. [55], genetic alterations in MYC and epigenetic upregulation of EMT markers like TWIST1 allow these cells to survive treatment, leading to aggressive relapse. Clinical studies show that patients with high plasticity markers, such as CD44+/CD24-, have poorer progression-free survival.

In lung cancer, plasticity contributes to relapse following targeted therapies. A classic study by Sequist et al. [56] reported that EGFR-mutant non-small cell lung cancer (NSCLC) patients often relapse due to lineage plasticity, where cells acquire neuroendocrine features driven by RB1 loss and SOX2 upregulation. This phenotypic switch allows tumors to bypass EGFR inhibition, resulting in treatment failure. Similarly, ALK-rearranged NSCLC can develop resistance through EMT, as shown by Gower et al. [57], highlighting plasticity's role in clinical outcomes.

Prostate cancer provides another compelling example. Zhang et al. [28] found that castration-resistant prostate cancer (CRPC) frequently relapses due to lineage plasticity, with cells transitioning to androgen-independent, neuroendocrine-like states. Genetic alterations in TP53 and RB1, coupled with epigenetic reprogramming, drive this plasticity, enabling resistance to androgen receptor inhibitors. Clinical data indicate that patients with these genetic profiles have significantly reduced survival post-relapse.

These examples underscore the clinical impact of plasticity-driven relapse. As emphasized by Pérez-González et al. [8], understanding the genetic and epigenetic drivers of plasticity in these cancers is critical for developing strategies to prevent relapse and improve patient outcomes.

Table 3 below provides a detailed compilation of clinical examples across major cancers, outlining the plasticity mechanisms, drivers, and outcomes that contribute to therapy resistance.

Table 3 Clinical Examples of Plasticity-Driven Therapy Resistance Across Cancers

Cancer Type	Plasticity Mechanism	Genetic/ Epigenetic Drivers	Therapy Targeted	Resistance Outcome	Clinical Implications	References
Breast Cancer	EMT and stem-like transitions; DTP states.	MYC alterations; Epigenetic upregulation of TWIST1; CD44+/CD24- markers.	Chemotherapy; Targeted therapies.	Relapse in triple-negative subtypes; Reduced progression-free survival.	Poorer outcomes; Need for anti-plasticity combos.	Creighton et al. [55]; Sharma et al. [4]; Black et al. [21]
Lung Cancer	Lineage plasticity (neuroendocrine shift); EMT.	RB1 loss; SOX2 upregulation; EGFR mutations.	EGFR inhibitors; ALK inhibitors.	Relapse post-EGFR/ALK therapy; Acquired resistance.	Treatment failure; Shorter survival.	Sequist et al. [56]; Gower et al. [57]; Marjanovic et al. [15]
Prostate Cancer	Neuroendocrine-like transition; Dedifferentiation.	TP53, RB1 mutations; Epigenetic reprogramming.	Androgen receptor inhibitors.	Castration-resistant relapse; Androgen independence.	Reduced survival; Aggressive progression.	Beltran et al. [25]; Zhang et al. [28]; Quintanal-Villalonga et al. [11]
Melanoma	Phenotypic switching; Immune evasion via EMT.	BRAF mutations; MITF/AXL heterogeneity.	MAPK inhibitors; Immunotherapy.	Drug tolerance; Reduced immunogenicity.	Therapy failure; Metastatic spread.	Boumahdi et al. [14]; Tirosh et al. [37]; Imodoye et al. [54]
Glioblastoma	Stem-like plasticity; Hybrid states.	EGFR amplifications; Histone modifications.	Chemotherapy; Radiotherapy.	Rapid adaptation; Relapse.	Poor prognosis; Intratumor heterogeneity.	Neftel et al. [5]; Dirkse et al. [17]; Pinto et al. [31]
Colorectal Cancer	Stemness and EMT; Phenotypic switching.	APC mutations; Wnt signaling loops.	Chemotherapy; Targeted therapies.	Metastatic outgrowth; Resistance.	Increased relapse rates.	Maffeis et al. [34]; Chakrabarti et al. [36]; Batlle et al. [22]
Ovarian Cancer	Therapy-induced epigenetic shifts; lncRNA upregulation.	MALAT1; Histone acetylation.	Chemotherapy.	Drug-tolerant states; Relapse.	Challenges in long-term control.	Abdelmonem et al. [52]; Sharma et al. [63]
Pancreatic Cancer	CSC properties; Hypoxia-induced changes.	KRAS mutations; HIF1α-mediated epigenetics.	Chemotherapy.	Survival in nutrient-poor niches; Resistance.	Aggressive metastasis.	Lytle et al. [12]; Hirata et al. [59]

5.3. Role in Metastasis: Tumor-Educated Immune Cells and Microenvironment Interactions Amplifying Resistance

Plasticity plays a critical role in metastasis, where it facilitates tumor cell dissemination and amplifies resistance through interactions with the tumor microenvironment (TME). Tumor-educated immune cells, such as tumor-associated macrophages (TAMs), promote plasticity by secreting cytokines that induce EMT and stemness. According to Cassetta et al. [58], TAMs in breast cancer release TGF-β, which activates EMT programs, enabling cells to acquire invasive phenotypes and resist therapies. This interaction enhances metastatic potential and drug tolerance.

The TME also modulates plasticity through physical and biochemical cues. In a novel study, Hirata et al. [59] demonstrated that hypoxic microenvironments in pancreatic cancer induce HIF1α-mediated epigenetic changes, promoting stem-like plasticity and chemotherapy resistance. These plastic cells, capable of surviving in nutrient-poor niches, are primed for metastatic spread. Similarly, extracellular matrix stiffness, as shown by Levental et al. [60], enhances EMT in breast cancer, facilitating metastasis and resistance through integrin signaling.

Tumor-educated immune cells further amplify resistance by creating immunosuppressive niches. Wu et al. [9] found that myeloid-derived suppressor cells (MDSCs) in melanoma secrete IL-6, which induces stemness and EMT, allowing metastatic cells to evade immunotherapy. This interplay between plastic tumor cells and the TME creates a feedback loop that sustains resistance and metastatic progression.

The role of the TME in amplifying plasticity highlights the need for therapies targeting both tumor cells and their microenvironment. As noted by Quail et al. [61], disrupting these interactions, such as through TGF-β inhibitors, could reduce plasticity-driven metastasis and resistance, offering a promising therapeutic strategy.

5.4. Challenges in Detection: Intratumor Heterogeneity and Dynamic States Complicating Biomarkers

Detecting plasticity-driven resistance is challenging due to intratumor heterogeneity and the dynamic nature of plastic states. Intratumor heterogeneity, driven by genetic and epigenetic diversity, results in subpopulations with varying plastic potentials, complicating biomarker identification. According to Dagogo-Jack et al. [62], in NSCLC, single-cell sequencing reveals heterogeneous subpopulations with distinct EMT and stemness profiles, making it difficult to develop universal biomarkers for plasticity-driven resistance.

The dynamic nature of plastic states further hinders detection. As shown by Tirosh et al. [37], melanoma cells rapidly switch between proliferative and invasive states, driven by transient epigenetic changes, which evade static biomarker assays. This dynamism requires real-time monitoring approaches, such as liquid biopsies, to capture evolving phenotypes. However, current technologies struggle to detect low-frequency plastic subpopulations, as noted by Lim et al. [39].

Moreover, therapy-induced plasticity complicates biomarker development. In a pivotal study, Sharma et al. [63] found that chemotherapy in ovarian cancer induces transient epigenetic changes that promote drug-tolerant states, which are undetectable by conventional genomic profiling. This highlights the need for epigenetic biomarkers, such as histone modification signatures, to track plasticity.

Addressing these challenges requires advanced diagnostic tools. As emphasized by Navin et al. [64], integrating single-cell genomics with machine learning could improve the detection of plastic states, enabling the development of robust biomarkers to guide personalized therapies and overcome resistance.

6. Emerging Interventions and Therapeutic Strategies

The dynamic nature of cancer cell plasticity presents a formidable challenge to conventional therapies, necessitating innovative interventions that target its genetic and epigenetic underpinnings. Emerging therapeutic strategies aim to disrupt the mechanisms driving plasticity, from genetic alterations to microenvironmental influences, to overcome resistance and improve clinical outcomes. This section explores novel approaches, including gene editing technologies, epigenetic therapies, patient-derived models, and combination strategies, highlighting their potential to transform cancer treatment by addressing plasticity.

As we explore emerging interventions to mitigate cancer cell plasticity, Figure 2 provides a schematic framework for therapeutic strategies, illustrating approaches like subpopulation reprogramming and direct targeting of plasticity mechanisms to overcome resistance.

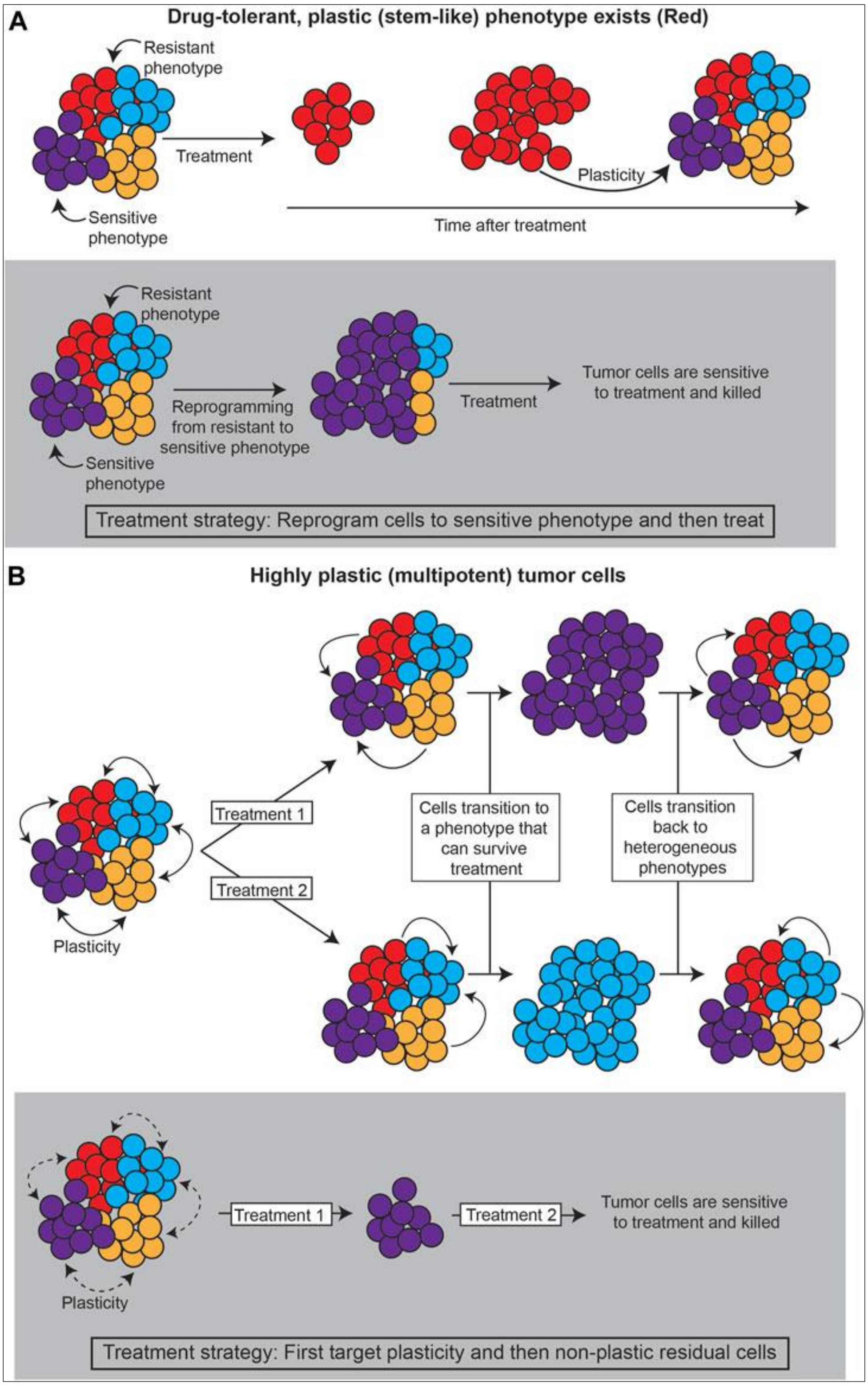

Figure 2 An outline of the therapeutic approaches to target plasticity, such as reprogramming subpopulations or reducing chromatin accessibility to limit phenotypic changes. Reproduced from Groves et al. [81] with permission

6.1. Targeting Genetic Drivers: CRISPR-Based Editing and Inhibitors of Key Pathways

CRISPR-based gene editing has emerged as a powerful tool to target genetic drivers of cancer cell plasticity, offering precision in disrupting oncogenic pathways. According to Konermann et al. [65], CRISPR/Cas9 can be used to knock out genes like MYC or SOX2, which drive stem-like plasticity in cancers such as glioblastoma. By targeting these genetic drivers, CRISPR disrupts the transcriptional networks that sustain plastic phenotypes, reducing tumor adaptability.

Preclinical studies demonstrate that CRISPR-mediated silencing of plasticity-associated genes enhances sensitivity to chemotherapy, suggesting a promising therapeutic avenue.

Inhibitors of key signaling pathways, such as PI3K/mTOR, also target plasticity by blocking pathways that enable phenotypic switches. Hanker et al. [33] showed that PI3K/mTOR inhibitors, like everolimus, reduce EMT and stemness in breast cancer by suppressing AKT-driven transcription of ZEB1 and SNAIL. Similarly, autophagy modulators, which intersect with mTOR signaling, have shown potential in overcoming plasticity-driven resistance. Amaravadi et al. [66] reported that hydroxychloroquine, an autophagy inhibitor, enhances the efficacy of MAPK inhibitors in melanoma by limiting plastic transitions to drug-tolerant states.

Combination strategies further enhance the efficacy of targeting genetic drivers. In a novel study, Engelman et al. [67] demonstrated that combining PI3K inhibitors with EGFR inhibitors in lung cancer prevents the emergence of plastic, resistant subpopulations driven by EGFR amplifications. These approaches highlight the potential of targeting genetic drivers to disrupt plasticity, though challenges like off-target effects and delivery remain critical hurdles.

Future directions include optimizing CRISPR delivery systems and developing next-generation inhibitors with higher specificity. As noted by Fellmann et al. [68], advancements in CRISPR screening technologies could identify novel genetic targets for plasticity, paving the way for personalized therapies that address tumor-specific drivers.

6.2. Epigenetic Therapies: HDAC Inhibitors, DNA Methyltransferase Blockers to Reverse Plastic States

Epigenetic therapies, such as histone deacetylase (HDAC) inhibitors and DNA methyltransferase (DNMT) inhibitors, offer promising strategies to reverse plastic states by targeting epigenetic reprogramming. HDAC inhibitors, like vorinostat, restore open chromatin states to suppress stemness and EMT. According to West et al. [69], HDAC inhibition in pancreatic cancer reduces the expression of plasticity drivers like SOX2, sensitizing cells to chemotherapy. This reversal of epigenetic plasticity disrupts the ability of cells to enter drug-tolerant states, improving treatment outcomes.

DNMT inhibitors, such as azacitidine, target DNA methylation to prevent therapy-induced plastic transitions. In a pivotal study, Baylin et al. [70] showed that azacitidine reverses hypermethylation of tumor suppressor genes in leukemia, inhibiting dedifferentiation and enhancing sensitivity to targeted therapies. These inhibitors are particularly effective in cancers with high epigenetic plasticity, such as acute myeloid leukemia, where methylation patterns drive resistance.

Combination epigenetic therapies show enhanced efficacy in targeting plasticity. Jones et al. [43] demonstrated that combining HDAC and DNMT inhibitors in lung cancer synergistically disrupts epigenetic programs that sustain stem-like states, reducing relapse rates. This approach leverages the reversible nature of epigenetic modifications to reprogram cancer cells into more vulnerable states.

Challenges remain, including toxicity and non-specific effects of epigenetic therapies. As highlighted by Berdasco et al. [71], developing selective epigenetic drugs and biomarkers to predict response could improve their clinical utility, making them a cornerstone of anti-plasticity strategies.

6.3. Novel Models: Patient-Derived Organoids for Studying and Targeting Plasticity in Real-Time

Patient-derived organoids (PDOs) have emerged as innovative models for studying and targeting cancer cell plasticity in real-time, offering a platform to mimic tumor heterogeneity and therapeutic responses. According to Sachs et al. [72], PDOs from colorectal cancer recapitulate the genetic and phenotypic diversity of the original tumor, including plastic states like EMT and stemness. These models enable researchers to study plasticity dynamics under controlled conditions, providing insights into resistance mechanisms.

PDOs also facilitate drug screening to identify anti-plasticity therapies. In a novel study, Vlachogiannis et al. [73] used PDOs from metastatic cancers to test responses to chemotherapy and targeted therapies, identifying drugs that inhibit plasticity-driven resistance. For example, PDOs revealed that MEK inhibitors reduce EMT in pancreatic cancer organoids, offering a strategy to target plastic phenotypes. This real-time analysis enhances the development of personalized treatment regimens.

Moreover, PDOs enable the study of microenvironmental influences on plasticity. Driehuis et al. [74] demonstrated that co-culturing PDOs with tumor-associated fibroblasts induces EMT and stemness, mimicking TME-driven plasticity. This model allows testing of therapies targeting TME-tumor interactions, such as TGF-β inhibitors, to disrupt plasticity.

The scalability and translational potential of PDOs make them a valuable tool. As noted by Tuveson et al. [75], integrating PDOs with genomic profiling could accelerate the discovery of plasticity-targeted therapies, bridging the gap between preclinical and clinical applications.

6.4. Combination Approaches: Integrating Immunotherapy with Plasticity Blockers and Future Directions

Combination approaches that integrate immunotherapy with plasticity blockers offer a promising strategy to overcome resistance by targeting both immune evasion and phenotypic adaptability. According to Dongre et al. [54], combining immune checkpoint inhibitors with EMT inhibitors, such as TGF-β blockers, enhances immunotherapy efficacy in melanoma by preventing immune-evasive plastic states. This synergy restores tumor immunogenicity, improving T-cell responses.

Plasticity blockers, such as inhibitors of stemness pathways, further enhance combination therapies. In a pivotal study, Huelsken et al. [76] showed that combining Wnt inhibitors with anti-PD-1 therapy in colorectal cancer reduces CSC-like plasticity, increasing immunotherapy sensitivity. Similarly, PI3K inhibitors combined with immunotherapy disrupt stemness-driven resistance, as shown by Spranger et al. [77], highlighting the potential of targeting genetic and epigenetic drivers alongside immune modulation.

AI-driven drug discovery is a promising future direction for developing combination therapies. As emphasized by Ho et al. [78], machine learning models can predict plasticity-associated gene networks and identify novel drug combinations to target dynamic tumor states. These approaches could accelerate the development of therapies that prevent plastic transitions, improving long-term outcomes.

Challenges include optimizing combination regimens to minimize toxicity and identifying biomarkers for patient selection. As noted by Ramos et al. [79], integrating single-cell genomics with AI could refine combination strategies, paving the way for personalized therapies that target the complex interplay of plasticity and immune evasion.

7. Conclusion

Cancer cell plasticity, driven by a complex interplay of genetic and epigenetic mechanisms, represents a critical challenge in oncology, underpinning tumor progression, metastasis, and therapy resistance. This review has elucidated how oncogenic mutations, chromosomal instability, and key signaling pathways, such as PI3K/AKT and RAS/MAPK, enable cancer cells to adopt dynamic phenotypic states, from stem-like to mesenchymal, facilitating their adaptability. Epigenetic modifications, including DNA methylation, histone alterations, and non-coding RNAs, further amplify this plasticity, allowing rapid responses to therapeutic pressures. The clinical implications are profound, as plasticity drives relapse in cancers like breast, lung, and prostate, while interactions with the tumor microenvironment exacerbate resistance and metastatic potential. The challenge of detecting plastic states, compounded by intratumor heterogeneity, underscores the need for advanced diagnostic tools like single-cell genomics.

Emerging interventions offer hope in addressing this adaptability. CRISPR-based gene editing and inhibitors targeting key pathways show promise in disrupting genetic drivers of plasticity, while epigenetic therapies, such as HDAC and DNMT inhibitors, aim to reverse plastic states. Patient-derived organoids provide a robust platform for real-time study and drug screening, bridging preclinical and clinical applications. Combination strategies integrating immunotherapy with plasticity blockers, enhanced by AI-driven drug discovery, pave the way for personalized approaches to overcome resistance. However, challenges remain, including optimizing specificity, minimizing toxicity, and developing reliable biomarkers to track dynamic states.

Looking forward, future research should focus on integrating multi-omics data to map the full spectrum of plasticity drivers, enabling the design of therapies that target both tumor cells and their microenvironment. Addressing open questions, such as the precise interplay between genetic and non-genetic factors or the role of rare subpopulations, will be crucial. Collaborative efforts leveraging advanced technologies, such as machine learning and organoid models, hold the potential to transform cancer treatment by dismantling the adaptive mechanisms of plasticity, ultimately improving patient outcomes in personalized oncology.

Compliance with ethical standards

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