Short Communication
Volume 17:04, 2025

Journal of Cancer Sciences and Therapy

ISSN: 1948-5956

Open Access

Multifaceted Cancer Relapse: Mechanisms, New Approaches

Patricia Torres *

Department of Cancer Epidemiology and Prevention, University of Chile, Santiago 8320000, Chile

Introduction

Cancer relapse is a formidable challenge in oncology, driven by a complex interplay of both cell-intrinsic mechanisms and cell-extrinsic factors. Intrinsic mechanisms involve genetic and epigenetic alterations within cancer cells that foster drug resistance and dormancy. Concurrently, extrinsic factors stemming from the tumor microenvironment (TME) are crucial in supporting residual disease and promoting tumor re-growth, highlighting a multifaceted challenge in preventing recurrence [1].

Understanding the diverse mechanisms underlying drug resistance and subsequent relapse is paramount. Resistance can be categorized into intrinsic and acquired forms, with genetic mutations, epigenetic changes, tumor microenvironment interactions, and cancer stem cell properties all contributing to therapy failure [9]. Specifically, immune evasion mechanisms significantly contribute to cancer relapse, particularly in the context of immunotherapy. Immunosuppressive cells, such as Myeloid-Derived Suppressor Cells and Regulatory T Cells, create an environment conducive to resistance against immune checkpoint blockade, demanding critical attention for improving long-term patient outcomes [2].

Dormant cancer cells play a critical role in initiating relapse, proving elusive to traditional detection methods. Single-cell technologies, including advanced single-cell sequencing, are emerging as powerful tools to identify these cells, revealing their unique characteristics, survival mechanisms, and the processes leading to their eventual reawakening. This knowledge is essential for developing targeted therapies aimed at eliminating dormant populations and preventing recurrence [3]. Furthermore, cancer stem cells (CSCs) exhibit significant metabolic plasticity, allowing them to adapt their metabolic pathways to survive therapeutic stress, remain dormant, and ultimately re-initiate tumor growth. Targeting these flexible metabolic programs in CSCs represents a promising strategy to prevent recurrence and enhance treatment efficacy [7].

Early detection of minimal residual disease (MRD) and accurate prediction of cancer relapse are crucial for timely intervention. Liquid biopsy techniques are gaining significant utility in this domain, leveraging circulating biomarkers such as Circulating Tumor DNA (ctDNA) and Circulating Tumor Cells (CTCs). These biomarkers are applied in monitoring treatment response and identifying patients at high risk for recurrence, thereby paving the way for personalized surveillance and intervention strategies [4]. Efforts to predict cancer recurrence also involve integrating clinical, pathological, and molecular biomarkers, including genomic and proteomic data. This comprehensive approach is steering towards more personalized predictive models, guiding adjuvant therapies and surveillance strategies to effectively prevent disease recurrence [8].

Epigenetic alterations in cancer cells are crucial drivers of therapeutic resistance and eventual relapse. Mechanisms like DNA methylation and histone modifications drive changes in gene expression, enabling cancer cells to evade treatment and re-establish growth. Emerging therapeutic strategies are now focusing on reversing these epigenetic changes to prevent recurrence [5]. Complementary to this, metabolic reprogramming is another critical facilitator of cancer relapse and metastasis. Cancer cells frequently alter key metabolic pathways, including glycolysis, oxidative phosphorylation, and fatty acid metabolism. These adaptations allow them to thrive in new microenvironments, evade therapeutic interventions, and fuel growth at distant sites. Therefore, targeting these altered metabolic dependencies offers a potent therapeutic avenue to prevent recurrence and metastasis [10].

The impact of the tumor microenvironment extends significantly to metastatic sites, where its unique cellular and molecular composition can dramatically foster the survival and outgrowth of disseminated tumor cells. This process directly contributes to secondary recurrence. Gaining a deeper understanding of these site-specific TME interactions is opening new avenues for both preventing and treating metastatic relapse, underscoring the dynamic role of the host tissue in disease progression [6].

Description

Cancer relapse is a complex biological phenomenon driven by a confluence of factors, making it a significant clinical challenge. At its core, recurrence involves both cell-intrinsic mechanisms, such as genetic and epigenetic alterations, and cell-extrinsic influences from the tumor microenvironment [1]. These intrinsic changes within cancer cells lead to the development of drug resistance and a dormant state, allowing them to persist despite therapy. Moreover, the tumor microenvironment actively supports the survival of residual disease and promotes re-growth, creating a fertile ground for recurrence [1]. The broader landscape of drug resistance, critical to understanding relapse, encompasses intrinsic and acquired forms, with genetic mutations, epigenetic modifications, TME interactions, and cancer stem cell properties all playing interconnected roles in therapy failure [9]. Overcoming these complex resistance pathways requires innovative strategies, often involving combination therapies [9].

One major contributor to cancer relapse, particularly in the context of advanced immunotherapies, is immune evasion. Immunosuppressive cells, notably Myeloid-Derived Suppressor Cells and Regulatory T Cells, are key players in fostering an environment that promotes resistance against immune checkpoint blockade. Ad-

dressing these immunosuppressive factors is essential for improving long-term patient outcomes [2]. Beyond immune mechanisms, the persistence of dormant cancer cells is a recognized initiator of relapse. These cells, often elusive, possess unique survival characteristics and mechanisms of reawakening. Advances in single-cell technologies, like single-cell sequencing, are providing unprecedented insights into these dormant populations, enabling the potential development of targeted therapies to eliminate them before recurrence can establish [3]. Furthermore, cancer stem cells (CSCs) demonstrate remarkable metabolic plasticity. This adaptability allows CSCs to modify their metabolic pathways, enabling them to survive therapeutic stress, maintain dormancy, and ultimately re-initiate tumor growth. Consequently, targeting these flexible metabolic programs in CSCs represents a promising avenue for preventing recurrence and enhancing overall treatment efficacy [7].

Detecting minimal residual disease (MRD) and accurately predicting cancer relapse are paramount for effective patient management. Liquid biopsy has emerged as a transformative tool in this regard, offering earlier detection than traditional imaging. It utilizes various circulating biomarkers, such as Circulating Tumor DNA (ctDNA) and Circulating Tumor Cells (CTCs), to monitor treatment response and identify patients at high risk for recurrence [4]. These insights are crucial for developing personalized surveillance and intervention strategies. Similarly, comprehensive predictive models for cancer recurrence integrate a range of clinical, pathological, and molecular biomarkers, including genomic and proteomic data. This holistic approach aims to identify high-risk patients more effectively, thereby guiding tailored adjuvant therapies and surveillance protocols to prevent disease recurrence [8].

Epigenetic alterations in cancer cells are pivotal drivers of therapeutic resistance and subsequent relapse. Mechanisms like DNA methylation and histone modifications lead to significant changes in gene expression, enabling cancer cells to evade existing treatments and re-establish their growth [5]. This highlights an opportunity for therapeutic intervention by developing strategies focused on reversing these specific epigenetic changes to prevent recurrence. In parallel, metabolic reprogramming is another critical process facilitating both cancer relapse and metastasis. Cancer cells skillfully alter their metabolic pathways—such as glycolysis, oxidative phosphorylation, and fatty acid metabolism—to adapt to new microenvironments, evade therapeutic pressures, and fuel their growth, even at distant sites. Targeting these altered metabolic dependencies thus presents a promising therapeutic strategy to inhibit both recurrence and metastatic spread [10].

The tumor microenvironment plays a profoundly influential role, not just at the primary site but critically at distant metastatic sites. The unique cellular and molecular composition of these remote organs can significantly foster the survival and outgrowth of disseminated tumor cells, directly leading to secondary recurrence [6]. This underlines that the environment surrounding cancer cells, whether at initial or distant locations, is not merely passive but an active participant in the disease's progression and resistance to therapy. Understanding and effectively targeting these site-specific TME interactions offer novel avenues for preventing and treating metastatic relapse, reinforcing the notion that recurrence is a systemic challenge influenced by local environmental cues [1, 6].

Conclusion

Cancer relapse is a multifaceted challenge in oncology, rooted in a complex interplay of intrinsic cellular mechanisms and extrinsic influences from the tumor microenvironment. Genetic and epigenetic alterations within cancer cells foster drug resistance and dormancy, contributing significantly to disease recurrence. Concurrently, the tumor microenvironment actively supports residual disease and promotes re-growth, underscoring its pivotal role. Immune evasion mechanisms, particularly those orchestrated by immunosuppressive cells like Myeloid-Derived Suppressor Cells and Regulatory T Cells, further complicate treatment, especially in the context of immunotherapy, by fostering resistance to immune checkpoint blockade.

Crucially, dormant cancer cells are increasingly recognized as primary initiators of relapse. Advanced single-cell technologies, including single-cell sequencing, are revealing the unique characteristics and survival mechanisms of these elusive cells, paving the way for targeted therapies to eliminate dormant populations. Detection of minimal residual disease (MRD) and early prediction of relapse are being revolutionized by liquid biopsy techniques. These methods utilize circulating biomarkers such as Circulating Tumor DNA (ctDNA) and Circulating Tumor Cells (CTCs) to monitor treatment response and identify high-risk patients, enabling more personalized surveillance and intervention strategies.

Beyond genetic shifts, epigenetic alterations like DNA methylation and histone modifications profoundly influence gene expression, allowing cancer cells to evade therapies. Developing strategies to reverse these epigenetic changes holds significant promise for preventing recurrence. The distinct cellular and molecular composition of the tumor microenvironment at distant metastatic sites further drives secondary recurrence by supporting disseminated tumor cells. Moreover, cancer stem cells (CSCs) exhibit remarkable metabolic plasticity, adapting their pathways to survive therapeutic stress and re-initiate growth. Targeting these flexible metabolic programs in CSCs is vital for improving treatment efficacy. The integration of diverse biomarkers, from clinical to genomic and proteomic data, is advancing the prediction of recurrence, guiding personalized adjuvant therapies. Ultimately, addressing the diverse mechanisms of drug resistance—encompassing genetic mutations, epigenetic shifts, TME interactions, and CSC properties—is paramount for developing effective combination therapies to overcome recurrence.

Acknowledgement

None.

Conflict of Interest

None.

References

1. Natalia K. Lytle, Kenneth Licon, Sarah Buechler, Taylor Tate, Daphne Mulder, Lindsy Vines. "Cell-intrinsic and extrinsic factors driving cancer relapse." *Nat Rev Cancer* 21 (2021):444-459.

2. Chengcheng Ma, Jie Li, Zhiyong Ding, Dai Wu, Hong Shen. "Immunosuppression and resistance to immune checkpoint blockade in cancer relapse." *Cancer Biol Med* 20 (2023):342-356.

3. Abdullah A. Al-Azri, Helle D. Møller, Line M. Schmidt, Rikke Thomsen, Mette Stougaard, Nanna Høi. "Single-Cell Approaches to Identify Dormant Cancer Cells and Understand Relapse." *Cancers* (Basel) 15 (2023):1184.

4. Xinyu Ma, Weijie Zhang, Haoran Yang, Junting Chen, Huiping Lu, Jie Li. "Liquid biopsy for molecular residual disease detection and early relapse prediction in cancer." *J Hematol Oncol* 16 (2023):100.

5. Nozomu Oishi, Sophia Chervin-Kozin, Melissa Mastroeni, Jennifer Kim, Jesse Mager. "Targeting epigenetic drivers of cancer therapy resistance and relapse." *Trends Cancer* 9 (2023):623-635.

6. So-Lim Park, Geongwon Jin, Hyo-Suk Kim, Kyoungseo Seo, Ki-Joong Ryu, Hayoung Noh. "The tumor microenvironment at distant metastatic sites drives cancer relapse." *Exp Mol Med* 55 (2023):1668-1678.

7. Ke Ma, Hao Yang, Jing Huang, Shengwu Chen, Rui Shi. "Metabolic plasticity of cancer stem cells in therapy resistance and tumor relapse." *Cell Death Discov* 8 (2022):172.

8. Kun Ma, Yang Shi, Jing Wang. "Prediction of cancer recurrence: current insights and future directions." *Front Oncol* 12 (2022):1069502.

9. Yong Huang, Hongbo Yuan, Jialin Xie, Ying Song. "Mechanisms of Drug Resistance and Relapse in Cancer." *Front Pharmacol* 14 (2023):1251347.

10. Yang Li, Fangfang Tian, Chen Wu, Zixuan Wang, Haiming Ding, Qiong Zhang. "Metabolic reprogramming in cancer relapse and metastasis." *Cell Death Dis* 13 (2022):1039.

How to cite this article: , Patricia Torres. "Multifaceted Cancer Relapse: Mechanisms, New Approaches." *J Cancer Sci Ther* 17 (2025):720.

Address for Correspondence: Patricia, Torres , Department of Cancer Epidemiology and Prevention, University of Chile, *Santiago* 8320000, Chile, E-mail: patricia.torres@uchile.cl

Received: 01-Jul-2025, Manuscript No. jcst-25-174957; **Editor assigned:** 03-Jul-2025, PreQC No. P-174957; **Reviewed:** 17-Jul-2025, QC No. Q-174957; **Revised:** 22-Jul-2025, Manuscript No. R-174957; **Published:** 29-Jul-2025, DOI: 10.37421/1948-5956.2025.17.720