Opinion

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Journal of Medical Oncology

2025
Vol.08 No.01:03

Molecular Mechanisms of Resistance to Targeted Cancer Therapy

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Received: February 01, 2025; **Accepted:** February 20, 2025; **Published:** February 28, 2025

Citation: Thieblemont W (2025) Molecular Mechanisms of Resistance to Targeted Cancer Therapy. J Med Oncol. Vol.08 No. 01: 03.

Introduction

The advent of targeted cancer therapy has transformed oncology, offering precision approaches that interfere with specific molecular alterations driving tumorigenesis. Unlike traditional chemotherapy, which exerts non-specific cytotoxic effects, targeted therapies selectively inhibit oncogenes, signaling pathways, or surface receptors that are aberrantly activated in cancer cells. Examples include tyrosine kinase inhibitors targeting the epidermal growth factor receptor, anaplastic lymphoma kinase, and BCR-ABL, monoclonal antibodies such as trastuzumab against HER2, and small molecules targeting angiogenesis or BRAF mutations. These therapies have produced unprecedented improvements in response rates and survival across various cancers, including non-small-cell lung cancer, breast cancer, melanoma, and chronic myeloid leukemia. However, the clinical benefits of targeted therapies are often limited by the emergence of resistance, which can occur either as primary resistance (intrinsic, where patients never respond) or secondary resistance (acquired, where initial response is followed by disease progression). Understanding the molecular mechanisms underlying resistance is crucial for the development of next-generation therapies and combination strategies that can overcome these barriers and improve long-term patient outcomes [1].

Description

Resistance to targeted therapies arises from a complex interplay of genetic, epigenetic, cellular, and microenvironmental factors that allow cancer cells to evade drug effects while sustaining proliferative signaling. These mechanisms can be broadly classified into on-target resistance, where mutations occur in the drug target itself, and off-target resistance, where compensatory pathways or alternative oncogenic drivers bypass the inhibited target. One of the best-studied examples of on-target resistance is found in EGFR-mutant NSCLC treated with first-generation TKIs such as gefitinib or erlotinib. While these drugs initially produce significant tumor regression, most patients relapse within a year due to secondary mutations such as T790M, which sterically hinders drug binding while maintaining kinase activity [2].

Off-target resistance mechanisms frequently involve the activation of alternative signaling pathways that restore proliferative and survival signals. For instance, in melanoma patients with BRAF V600E mutations treated with BRAF inhibitors like vemurafenib, resistance can occur through upregulation of MEK/ERK signaling, overexpression of receptor tyrosine kinases, or activation of parallel pathways such as PI3K/AKT. This has led to the clinical adoption of combination therapies targeting both BRAF and MEK to delay resistance. Similarly, in HER2-positive breast cancer, resistance to trastuzumab can result from PI3K mutations, PTEN loss, or shedding of HER2 extracellular domains, leading to persistent downstream signaling. Another critical layer of resistance involves epigenetic reprogramming and tumor plasticity. Cancer cells exhibit remarkable adaptability, often undergoing phenotypic changes that render them less dependent on the targeted pathway. In lung cancer, for example, resistance to EGFR inhibitors can be associated with epithelial-to-mesenchymal transition, which confers invasive potential and reduces sensitivity to apoptosis. In certain cases, histological transformation occurs, such as NSCLC converting to small-cell lung cancer following EGFR TKI treatment, accompanied by alterations in TP53 and RB1. Such lineage plasticity underscores the dynamic nature of resistance, extending beyond simple point mutations [3].

Emerging evidence also points to the role of cancer stem cells in resistance. CSCs represent a subpopulation of tumor cells with self-renewal and differentiation potential, often quiescent and inherently resistant to targeted therapies due to enhanced DNA repair capacity, expression of drug efflux pumps, and metabolic flexibility. Upon therapy, CSCs may survive and repopulate the tumor, driving relapse and progression. Understanding these diverse mechanisms has guided the development of novel therapeutic strategies. Combination therapies are increasingly employed to simultaneously block multiple signaling nodes, delay resistance, and improve durability of response. For example, combining EGFR TKIs with MET inhibitors or BRAF inhibitors with MEK inhibitors has demonstrated clinical benefit. Epigenetic therapies such as histone deacetylase inhibitors or DNA methyltransferase inhibitors are being tested to reverse resistance associated with EMT or lineage plasticity [4,5].

Conclusion

Resistance to targeted cancer therapy represents a formidable challenge that limits the long-term success of precision oncology. While targeted agents initially provide remarkable responses by selectively inhibiting oncogenic drivers, cancer cells inevitably evolve through genetic mutations, activation of bypass pathways, epigenetic plasticity, and microenvironmental support. The heterogeneity of resistance mechanisms underscores the adaptability of tumors and the need for multifaceted therapeutic strategies. Advances in next-generation inhibitors, rational drug combinations, and novel modalities such as PROTACs, cellular therapies, and immune-oncology approaches are paving the way to overcome resistance. Equally critical is the integration of precision diagnostics, including ctDNA monitoring and comprehensive molecular profiling, which enable dynamic treatment adaptation. Ultimately, a deeper understanding of the molecular underpinnings of resistance, coupled with innovative therapeutic strategies, will be essential to achieve durable and curative outcomes for patients. The battle against resistance is ongoing, but it also represents an unprecedented opportunity to refine cancer therapy into a truly personalized discipline.

Acknowledgement

None.

Conflict of Interest

None.

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