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Review Article

Combating Resistance in Precision Oncology: Pathway-Centric Approaches Targeting RTKs, RAS/MAPK, PI3K/AKT, and CDK4/6

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Abstract

Precision oncology has improved cancer treatment by aligning therapies with the molecular drivers of tumor growth. However, resistance remains a major challenge in treatments targeting RTKs, Ras/MAPK, PI3K/AKT, and CDK4/6. This review presents these pathways as interconnected systems where adaptive feedback, signaling redundancy, and metabolic shifts enable tumors to evade inhibition. Resistance mechanisms include bypass signaling, RTK recycling, altered trafficking, and hypoxia-driven changes in the tumor microenvironment. To address these challenges, emerging strategies focus on combination approaches such as dual KRAS and MEK blockade, CDK4/6 and PI3K co-inhibition, integration with immune checkpoint therapies, and metabolic interventions targeting oxidative phosphorylation and lactate metabolism. The review highlights the importance of pathway-guided, combination-based strategies informed by genomic and proteomic profiling. By incorporating resistance adaptation into treatment design, precision oncology can advance beyond static molecular targeting toward dynamic and personalized approaches that improve long-term disease control.

Key words: Drug resistance, Neoplasm, Precision medicine, Signal transduction, Antineoplastic combined chemotherapy protocols, Molecular targeted therapy

Introduction

Despite significant progress in precision oncology, therapeutic resistance continues to be a major obstacle to achieving durable responses in solid tumors. Targeted treatments, including RTK inhibitors, Ras/MAPK pathway blockers, PI3K/AKT inhibitors, and CDK4/6 antagonists, frequently lose effectiveness due to adaptive signaling, pathway redundancy, and tumor heterogeneity. This review reconceptualizes these oncogenic pathways as interconnected systems, emphasizing how their flexibility enables both initial treatment success and the eventual emergence of resistance.

Resistance mechanisms fall into two broad categories: intrinsic (pre-existing) and acquired (developing during treatment). These often involve mutations in drug targets, activation of alternative signaling networks, or dynamic interactions within the tumor microenvironment (TME) [1]. For example, PI3Kα inhibitors in breast cancer frequently trigger MAPK pathway reactivation or AKT-independent survival signals via SGK1 and mTORC1 [2,3]. Similarly, CDK4/6 inhibitors face resistance due to RB1 loss, Cyclin E1 overexpression, and PI3K pathway crosstalk, leading to unchecked cell cycle progression [4].

Rather than attempting to cover every notable drug targeting these pathways, this review focuses on resistance mechanisms and emerging strategies to overcome them. These include vertical inhibition (e.g., dual KRAS and MEK blockade), synthetic lethality (e.g., PI3K and CDK4/6 co-inhibition), immune microenvironment modulation (e.g., CDK4/6 plus checkpoint blockade), and interventions targeting metabolic reprogramming. Together, these approaches shift the focus from single-pathway targeting to integrated strategies designed to prevent or reverse resistance.

By examining resistance mechanisms across RTK, Ras/MAPK, PI3K/AKT, and CDK4/6 signaling, this paper underscores the importance of precision oncology strategies that are both targeted and adaptable. It explores how feedback signaling, tumor microenvironment dynamics, and pathway redundancy reduce treatment durability, while rational combination approaches guided by genomic and proteomic profiling can help restore drug sensitivity and improve patient outcomes [5].

Methods

This review was based on a literature search using PubMed and Google Scholar. The focus was on peer-reviewed articles published between 2019 and 2025 that discussed resistance to therapies targeting RTK, Ras/MAPK, PI3K/AKT, and CDK4/6 pathways. Preference was given to studies that explored resistance mechanisms, combination treatments, pathway crosstalk, and tumor microenvironment changes. Clinical studies involving patients and preclinical studies using lab models (such as cell lines or animals) were included if they provided insight into why resistance happens or how it might be prevented or reversed. Review articles were used to support background information where appropriate.

Core Pathways in Resistance and Targeted Therapy

RTKs: Resistance mechanisms and therapeutic adaptation

Receptor Tyrosine Kinases (RTKs) play a critical role in regulating oncogenic signaling and are key targets in precision oncology.

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Therapies directed at RTKs, especially those targeting EGFR and HER2, have demonstrated initial effectiveness but often face widespread resistance. Tumors evade treatment through on-target mutations that alter drug binding, bypass signaling via alternative RTKs, and histological or phenotypic adaptations that sustain growth despite inhibition [6,7].

For example, first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) frequently fail due to secondary mutations like T790M and C797S, which hinder drug binding [8]. Even third-generation TKIs such as osimertinib, designed to counteract T790M resistance, eventually lose efficacy due to acquired C797S mutations or activation of bypass pathways like MET amplification or HER2 overexpression [9]. Similarly, HER2-positive cancers treated with monoclonal antibodies (e.g., trastuzumab) or small-molecule inhibitors (e.g., tucatinib) often develop resistance via truncated HER2 variants (p95HER2), which evade antibody binding [10].

Beyond genetic mutations and bypass signaling, RTK trafficking and recycling play a critical role in resistance. Cancer cells internalize RTKs via endocytosis, then recycle them back to the cell surface, allowing persistent signaling despite inhibitor presence. For example, EGFR recycling via Rab11-mediated trafficking can reactivate MAPK and PI3K pathways, sustaining oncogenic signaling even under tyrosine kinase inhibitor (TKI) therapy [11]. Similarly, HER2-positive tumors often evade Cbl-mediated ubiquitination, avoiding lysosomal degradation and enabling continued HER2-driven signaling despite therapeutic pressure [12].

To address these resistance mechanisms, researchers are investigating ways to block RTK recycling or promote receptor degradation. Endosome-targeting therapies, such as Rab protein inhibitors, dynamin blockers, and lysosomal trafficking disruptors, are designed to prevent receptor recycling and accelerate degradation, reducing RTK-driven resistance. Preclinical studies have shown that combining RTK inhibitors with trafficking disruptors can improve antitumor efficacy and enhance treatment durability in resistant cancer models [13].

To counter these adaptive mechanisms, researchers are focusing on rational combination therapy. Dual HER2 blockade—combining monoclonal antibodies with HER2-selective TKIs—has proven more effective in suppressing compensatory signaling than monotherapy [14]. Antibody–drug conjugates (ADCs), such as trastuzumab deruxtecan, offer another approach by delivering cytotoxic payloads directly to HER2-overexpressing cells, bypassing certain resistance mechanisms [15].

Another promising strategy involves co-targeting RTKs and downstream effectors. In PIK3CA-mutated breast cancers resistant to HER2 inhibition, adding PI3Kα inhibitors like alpelisib has improved efficacy by disrupting survival pathways activated via HER2 crosstalk [16]. These multidimensional approaches signal a shift from single-agent therapy to integrated treatment strategies aimed at blocking molecular escape routes.

Ultimately, RTK-targeted therapies must do more than inhibit the primary oncogenic driver—they must anticipate and neutralize emerging resistance. Future directions include real-time molecular monitoring to detect new mutations, feedback loops, and endocytic recycling patterns, enabling early therapeutic adjustments tailored to evolving resistance profiles [17].

Ras/MAPK Pathway: Targeting oncogenic drivers and overcoming resistance

The Ras/MAPK pathway is frequently altered in human cancers, primarily due to activating mutations in KRAS and BRAF. These mutations trigger persistent downstream signaling through MEK and ERK, fueling tumor growth, enhancing survival, and reducing susceptibility to cell death. While mutant-selective inhibitors such as KRAS G12C and BRAF V600E-targeted therapies represent significant advancements, resistance tends to emerge rapidly and remains a major challenge in treatment [18–20].

KRAS G12C inhibitors such as sotorasib and adagrasib initially show effectiveness by trapping mutant KRAS in its inactive GDP-bound form. However, resistance develops through secondary KRAS mutations like G12D and G13D, reactivation of receptor tyrosine kinases such as MET and HER3, or activation of alternative pathways including PI3K/AKT and YAP/Hippo signaling. Similarly, BRAF inhibitors like vemurafenib and dabrafenib, which target BRAF V600E-positive melanomas, encounter resistance due to RAF dimerization, MEK1/2 amplification, and feedback activation through RTKs such as EGFR [22].

To counteract this, vertical pathway inhibition has become a central strategy. Combining KRAS inhibitors with MEK or ERK inhibitors aims to block pathway reactivation through feedback loops and escape mutations. Preclinical and clinical data suggest that this layered approach enhances tumor regression and slows resistance development [23].

Another promising strategy includes pan-RAF inhibitors and SHP2 inhibitors. Pan-RAF inhibitors block both BRAF and CRAF dimers, preventing the unintended MAPK activation seen with selective BRAF inhibitors. SHP2 inhibitors act upstream by shutting down RTK-driven RAS activation, disrupting the cascade before resistance can take hold [24].

Immunotherapy is also being explored. Ras-mutant tumors often suppress immune responses, but early findings suggest that combining KRAS inhibitors with immune checkpoint blockers (e.g., anti–PD-1) may enhance tumor immunogenicity and improve treatment outcomes [25].

PI3K/AKT Pathway: Isoform-specific resistance and rational combination therapies

The PI3K/AKT pathway is essential for regulating metabolism, growth, and survival in various cancers. Genetic alterations such as PIK3CA mutations, PTEN loss, and AKT hyperactivation have driven the development of targeted inhibitors. However, therapeutic responses to these inhibitors are often limited, as tumors adapt through pathway redundancy, compensatory survival signaling, and feedback activation, reducing long-term efficacy [26].

Isoform-selective PI3K inhibitors, such as alpelisib (which targets p110α), have improved therapeutic outcomes in PIK3CA-mutated cancers. Still, resistance can emerge through AKT-independent mechanisms, including SGK1-driven activation of mTORC1 or reactivation of receptor tyrosine kinases (RTKs) such as HER3 and IGF1R [27]. Similarly, tumors with PTEN loss often evade PI3Kα inhibition by increasing p110β activity or activating the ERK pathway, reflecting the adaptability of downstream effectors [4].

To overcome these challenges, combination therapies are being developed to target multiple points within the PI3K pathway and its compensatory networks. Dual PI3K/mTOR inhibition has shown promise in preclinical studies, though toxicity remains a concern [28]. Another approach pairs PI3K inhibitors with CDK4/6 inhibitors, which has demonstrated efficacy in PIK3CA-mutant, endocrine-resistant breast cancers, especially those with PTEN deficiency [16].

RTK feedback is a common driver of resistance. PI3K inhibition can trigger upregulation of HER2, HER3, or MET, restoring PI3K or MAPK activity via alternative adaptors [1]. Combining PI3K inhibitors with RTK inhibitors (e.g., alpelisib + trastuzumab) is currently being tested in clinical trials to counteract this escape mechanism [29].

Additionally, metabolic adaptation allows tumors to survive despite PI3K inhibition. Cancer cells may shift toward glutaminolysis, fatty acid oxidation, or lactate metabolism to maintain ATP production and biosynthesis, bypassing PI3K-dependent signaling. These findings have spurred efforts to combine PI3K/AKT inhibitors with metabolic therapies targeting glutaminase, oxidative phosphorylation (OXPHOS), or monocarboxylate transporters (MCTs) [30].

CDK4/6 Inhibition: Resistance pathways and strategic combinations

Cyclin-dependent kinases 4 and 6 (CDK4/6) play a crucial role in controlling the G1-to-S phase transition in the cell cycle and are key targets in hormone receptor-positive breast cancer. Inhibitors such as palbociclib, ribociclib, and abemaciclib have demonstrated substantial clinical benefits when used alongside endocrine therapy, helping to slow disease progression in metastatic cases. Despite their effectiveness, resistance frequently develops through various molecular mechanisms, limiting long-term therapeutic success [31–33].

A major factor influencing CDK4/6 inhibitor sensitivity is the functional status of the retinoblastoma (RB) protein. Tumors lacking RB expression or carrying RB1 mutations fail to arrest in G1 despite CDK4/6 blockade, rendering treatment ineffective [34]. Other resistance mechanisms include Cyclin E1 (CCNE1) amplification, CDK2 activation, or CDK4/6 upregulation—all of which bypass CDK4/6 inhibition and restore cell cycle progression [35].

Beyond intrinsic resistance, acquired resistance frequently involves activation of alternative signaling pathways. The PI3K/AKT/mTOR and Ras/MAPK pathways can become hyperactive during CDK4/6 therapy, sustaining tumor growth through CDK-independent mechanisms [36]. For example, PTEN loss not only drives resistance to PI3K inhibitors but also reduces CDK4/6 inhibitor efficacy by activating downstream AKT [4]. These findings highlight the need for combination strategies that target both cell cycle and survival signaling.

Recent research has explored rational drug combinations to counteract resistance. Dual inhibition of CDK4/6 and PI3K has shown synergistic effects in PIK3CA-mutant breast cancers, particularly in cases with concurrent PTEN loss. Similarly, combining CDK4/6 inhibitors with endocrine agents and mTOR inhibitors has demonstrated enhanced tumor suppression and delayed resistance [37].

Immunotherapy is also being investigated. CDK4/6 inhibitors can increase antigen presentation, boost T cell infiltration, and sensitize tumors to immune checkpoint blockade. Ongoing trials are testing combinations of abemaciclib or palbociclib with PD-1/PD-L1 inhibitors to harness both cytostatic and immune-mediated effects [38].

In cases of resistance, shifting to CDK2 or CDK9 inhibitors may help reestablish cell cycle control, particularly in tumors with Cyclin E overexpression. Another potential strategy involves targeting upstream regulators of CDK4/6 activity, such as FGFR amplification or RAS pathway activation, which contribute to therapeutic escape mechanisms [39].

Emerging Themes in Resistance Management

Pathway crosstalk and adaptive signaling

A major challenge in precision oncology is the complex interaction between signaling pathways, which allows tumors to bypass inhibition through alternative routes. When one pathway is blocked, compensatory activation of another often occurs, such as MAPK upregulation following PI3K inhibition or CDK2/Cyclin E activation in response to CDK4/6 blockade [1,40]. These feedback loops reduce drug effectiveness but also create new vulnerabilities that can be addressed through strategic combination therapies.

Vertical inhibition approaches, including dual KRAS and MEK or ERK blockade, seek to prevent pathway reactivation by targeting multiple signaling levels [41]. Similarly, combining CDK4/6 inhibitors with PI3K inhibitors has shown synergistic effects in PIK3CA-mutant models, particularly in cases of PTEN loss where redundancy amplifies resistance [16]. These findings support the growing consensus that effective cancer control requires multi-targeted treatment strategies guided by molecular profiling.

Synthetic lethality and network disruption

Synthetic lethality occurs when the simultaneous disruption of two genes or pathways leads to cell death, whereas inhibiting either one alone does not. This approach has gained attention as a strategy to combat therapy resistance by targeting tumor-specific dependencies while minimizing effects on normal cells. Its effectiveness depends on accurate biomarker selection to identify patients whose tumors have exploitable vulnerabilities. Although best known for PARP inhibitors in BRCA-mutated cancers, researchers have now identified synthetic lethal interactions in Ras-driven and PI3K-activated tumors, expanding its potential applications in precision oncology [42].

For example, co-inhibition of CDK4/6 and PI3K can induce synthetic lethality in hormone receptor–positive, PIK3CA-mutated breast cancers. In these cases, CDK4/6 blockade activates survival pathways that PI3K inhibition then disrupts, pushing tumor cells toward apoptosis instead of dormancy [43]. Other promising synthetic lethal combinations include BCL-XL + MEK inhibition in KRAS-mutant cancers and SHP2 + KRAS blockade, both currently under clinical investigation [5, 55].

Emerging research is identifying additional synthetic lethal interactions that could further refine resistance-targeted therapies. One promising avenue involves STK11/LKB1 mutations, which disrupt AMPK signaling and render tumors vulnerable to metabolic stress. Dual inhibition of AMPK and mTOR has shown potential synthetic lethality in this context, selectively eliminating STK11-mutant tumors by exploiting their defective energy homeostasis [45].

Another developing strategy focuses on targeting the WRN helicase in microsatellite instability–high (MSI-H) tumors. WRN is

essential for resolving replication stress in MSI-H cancers, and its inhibition leads to catastrophic genomic instability and cell death. This vulnerability is currently being evaluated in early clinical trials, particularly for MSI-H colorectal and gastric cancers [46].

Tumor Microenvironment (TME) and resistance modulation

The tumor microenvironment (TME) plays a crucial role in resistance to targeted therapies. Components such as cancer-associated fibroblasts, myeloid-derived suppressor cells, and extracellular matrix proteins protect cancer cells from treatment by activating alternative signaling pathways or creating physical and immune barriers [47].

Growth factors like HGF and TGF-β released by fibroblasts can reactivate the MAPK and PI3K pathways, driving resistance to RTK and kinase inhibitors. Similarly, HER3 upregulation in response to neuregulin-1 secreted by stromal cells can restore PI3K/AKT signaling despite HER2 blockade [48].

Hypoxia is a significant but often overlooked factor in therapy resistance within the tumor microenvironment. Low oxygen conditions trigger hypoxia-inducible factors (HIFs), particularly HIF-1α, which drive resistance through multiple pathways. HIF-1α promotes VEGF expression, stimulating angiogenesis while simultaneously disrupting vascular architecture, leading to inefficient drug delivery and reduced interstitial perfusion [49]. Concurrently, hypoxia alters metabolic dependencies by shifting tumors toward glycolysis and enhancing RTK signaling, sustaining resistance to EGFR, HER2, and MET inhibitors despite kinase blockade [50]. To counter these effects, researchers are actively investigating therapeutic strategies such as HIF inhibitors and hypoxia-activated prodrugs to weaken these survival adaptations and improve drug sensitivity [51].

Beyond metabolic and signaling adaptations, hypoxia drives epithelial-to-mesenchymal transition (EMT), fostering phenotypic plasticity and the emergence of drug-tolerant cancer cell states. Hypoxic tumor niches also alter immune dynamics, as stromal and immune modulators upregulate checkpoint regulators like PD-L1, contributing to immune evasion and diminished immunotherapy efficacy [52].

Metabolic plasticity and therapy escape

Cancer cells exhibit remarkable metabolic flexibility, enabling them to shift energy production pathways under drug pressure. PI3K or CDK4/6 inhibition, which typically reduces glycolysis, may unintentionally drive increased oxidative phosphorylation (OXPHOS), glutaminolysis, or lipid metabolism as alternative fuel sources [62]. Beyond shifts toward glycolysis and lipid oxidation, mitochondrial reprogramming plays a critical role in therapy escape. Many drug-resistant tumors upregulate PGC-1α, a key regulator of mitochondrial biogenesis, leading to elevated oxidative phosphorylation (OXPHOS) and enhanced survival under targeted inhibition [54]. This adaptation provides an alternative energy source, enabling tumors to circumvent drug-induced metabolic stress and sustain growth despite pathway blockade.

Resistant cancer cells also exhibit altered mitochondrial dynamics, characterized by increased fusion and reduced fission, which improves energy efficiency and suppresses apoptotic signaling [55]. These mitochondrial adaptations have been directly linked to resistance in PI3K, CDK4/6, and KRAS-targeted therapies, highlighting mitochondria as a central hub in resistance biology.

To counteract these mechanisms, researchers are investigating OXPHOS inhibitors and mitochondrial uncouplers as adjuvant therapies to disrupt mitochondrial metabolism and restore drug sensitivity in resistant tumors [56]. Combining mitochondrial-targeting agents with traditional kinase inhibitors may offer a promising strategy to overcome metabolic plasticity and enhance treatment durability.

These metabolic adaptations are more than survival mechanisms—they can actively sustain resistance by ensuring ATP production and biosynthesis even when key signaling pathways are blocked. For example, lactate, once considered a metabolic byproduct, functions as an energy source in some tumors and is transported via monocarboxylate transporters (MCTs), whose upregulation is linked to therapy resistance [57].

Non-coding RNAs as resistance mediators

Although not yet widely used in clinical practice, non-coding RNAs, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are emerging as key regulators of therapy resistance. These RNAs impact pathways such as PI3K, Ras/MAPK, and CDK4/6 while modifying drug sensitivity through gene silencing and epigenetic remodeling [58].

Examples include miR-21–mediated resistance to EGFR inhibitors and lncRNA HOTAIR–driven modulation of CDK4/6 signaling. Additionally, tumor-derived exosomal miRNAs can modify the TME or distant tumor sites, priming them for drug insensitivity [59]. Although still an emerging field, RNA-based therapies hold promise as future tools for overcoming resistance through epigenetic and transcriptional modulation.

Conclusion

Therapeutic resistance remains the defining obstacle in precision oncology. As detailed across the RTK, Ras/MAPK, PI3K/AKT, and CDK4/6 pathways, resistance mechanisms are rarely driven by single mutations alone; rather, they emerge from the interplay of pathway crosstalk, tumor microenvironmental influences, metabolic reprogramming, and signaling redundancy. These pathways form a dynamic and adaptable network that tumors exploit to maintain growth and evade targeted therapies.

This review has emphasized that durable clinical responses will not result from targeting individual oncogenic nodes in isolation. Instead, effective resistance management requires pathway-centric strategies that combine vertical inhibition, synthetic lethality, metabolic interference, and immune modulation. The growing role of molecular profiling and predictive biomarkers further supports a transition toward personalized treatment adaptation, in which therapy is adjusted in response to early resistance signals rather than late-stage progression.

Importantly, future progress will depend not only on expanding the therapeutic toolkit, but on improving the logic that guides drug sequencing and combination design. By integrating insights into signaling adaptability, hypoxia-mediated resistance, mitochondrial dynamics, and synthetic vulnerabilities, the field can move toward more durable control of malignancy. Continued clinical and translational research will be essential to convert these insights into treatment frameworks that are not only precise, but pre-emptive.

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