Cancer signaling networks in tumor progression and drug resistance: Crosstalk, adaptive reprogramming and therapeutic targeting (Review)

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Abstract. Cancer signaling networks, highly dynamic with interconnected systems, regulate tumor initiation, its progression, therapeutic response and drug resistance. Rather than functioning as isolated pathways, these networks integrate extracellular and intracellular signals through coordinated interactions among membrane receptors, intracellular transducers and downstream effectors. Increasing evidence suggests that pathway crosstalk, feedback regulation and adaptive reprogramming are central to tumor phenotypic plasticity, microenvironmental adaptation and resistance to therapy. In this review, the core architecture of cancer signaling networks and the major oncogenic pathways embedded within them were summarized with a particular focus on PI3K/Akt/mTOR, MAPK/ERK and Wnt/β-catenin signaling. The dynamic network properties that shape cancer behavior, including compensatory activation, context-dependent signaling outputs and interactions with the tumor microenvironment, were further discussed. These features provide insights into why single-pathway inhibition often produces only a limited and transient clinical benefit. Importantly, a network-level understanding of cancer signaling has major translational implications. Therapeutic resistance frequently arises through pathway reactivation, bypass signaling and adaptive reprogramming, necessitating rational combination strategies and multi-target interventions. Advances in multi-omics, single-cell and spatial technologies and computational modeling are crucial for characterizing signaling network dynamics and identifying clinically relevant vulnerabilities.

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Contents

1. Introduction

Cancer cell signaling networks are highly complex and dynamically regulated systems that play key roles in tumor initiation, its progression, metastasis, therapeutic response and drug resistance (1). Rather than functioning as isolated pathways, these networks operate through extensive crosstalk and feedback among multiple signaling cascades, thereby regulating key malignant behaviors such as proliferation, apoptosis, invasion, metabolic reprogramming and immune evasion (2). Advances in multi-omics and systems biology have offered deeper insights into the organization and regulatory principles of these networks (3,4). Such insights have improved the current understanding of tumor heterogeneity and evolutionary dynamics, while also identifying new therapeutic targets and more individualized treatment strategies (5,6). Although several oncogenic pathways overlap across cancers, their functional roles and clinical relevance remain highly context dependent.

In this review, the core architecture of cancer signaling networks, the major oncogenic pathways embedded within them and the dynamic properties that shape their biological and clinical effects were summarized. Particular emphasis

was placed on pathway crosstalk, feedback regulation and adaptive reprogramming, and it was discussed how these dynamic features influence tumor phenotypes, therapeutic resistance and clinical outcomes. Rather than providing a static summary of individual signaling pathways, this review adopts a network-level perspective that integrates structural organization, dynamic regulation and translational implications within a unified conceptual framework. Because several oncogenic signaling pathways display context-dependent outputs for different tumor types, this review revolves around common network principles while incorporating representative tumor-specific examples. By linking pathway architecture with adaptive network behavior, the present study aimed to elucidate how signaling interactions (not as isolated pathways) drive tumor progression and mediate therapeutic responses.

Previous reviews have summarized major cancer-related signaling pathways and their crosstalk, particularly focusing on canonical pathways such as MAPK, PI3K/Akt/mTOR and Wnt/β-catenin signaling (7,8). A recent review has also discussed how signaling networks influence cancer metabolism and therapeutic response (2). The present review aimed to take a broader perspective by emphasizing how these pathways interact within a dynamic network. This perspective may provide a more integrated understanding of signaling networks in tumor progression and therapeutic resistance. Compared with previous reviews focusing mainly on individual signaling pathways and selected crosstalk mechanisms, the present review emphasizes the hierarchical organization of cancer signaling networks, adaptive responses under therapeutic pressure, microenvironment-mediated resistance and their translational implications for network-based therapeutic strategies. Fig. 1 presents a simplified conceptual framework of cancer signaling networks, showing the hierarchical flow of signaling from membrane receptors through intracellular transducers and downstream effectors to drive diverse tumor phenotypes. It also highlights major dynamic interactions among oncogenic pathways, including crosstalk, feedback regulation and adaptive reprogramming.

2. Core architecture of cancer signaling networks

Membrane receptors. Membrane receptors serve as the initiating nodes of cancer signaling networks by sensing extracellular and microenvironmental cues and transmitting signals intracellularly to drive tumor cell proliferation, migration, survival and other malignant behaviors. Major receptor classes include receptor tyrosine kinases [e.g., EGFR, human EGFR 2 (HER2)], G protein-coupled receptors, integrins, immune checkpoint receptors [e.g., programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1)] and cytokine receptors (e.g., TNF and Wnt receptors). Upon ligand binding, these receptors activate downstream cascades, particularly the MAPK, PI3K/Akt and JAK/STAT pathways, thereby promoting tumorigenesis and disease progression (9-12). Aberrant EGFR and HER2 activation is frequently observed across multiple cancers (13,14), while increased PD-1/PD-L1 signaling contributes to tumor immune evasion (15). As central regulatory nodes, membrane receptors are primary targets in precision oncology, with targeted inhibitors and monoclonal antibodies demonstrating substantial clinical benefit across diverse malignancies (16).

Signal transducers. Signal transducers act as critical intermediates between membrane receptors and downstream effectors; they integrate, amplify and diversify signaling inputs to dictate cellular responses to extracellular stimuli (17). These molecules fall into four major categories.

G proteins and their family members. G proteins are categorized as heterotrimeric G proteins, which couple to G protein-coupled receptors, and small GTPases, including members of the Ras and Rho families (18). Heterotrimeric G proteins regulate intracellular second messengers such as cAMP, inositol 1,4,5-trisphosphate and diacylglycerol (19), thereby modulating cellular metabolism, ion channel activity and gene expression (20-23). Small GTPases are central nodes in cancer signaling: Ras proteins act as key signaling hubs, where oncogenic mutations often trigger constitutive MAPK/ERK and PI3K/Akt activation, promoting proliferation, survival and metastasis (24,25). By contrast, Rho family proteins primarily regulate cytoskeletal dynamics and cell motility, contributing to cancer invasion and metastatic potential (26).

Kinase cascades. Kinase cascades, particularly the MAPK and PI3K/Akt/mTOR pathways, amplify and diversify signaling through sequential phosphorylation events (27,28). These pathways regulate key biological processes, with MAPK being primarily involved in proliferation, differentiation and stress responses (29,30), and PI3K/Akt in cell survival, metabolism and therapeutic resistance (31-33). Their multi-layered structure and extensive branching not only confer flexibility in signal processing but also foster tumor heterogeneity and treatment resistance when persistently activated.

Signal integration proteins. Signal integration proteins organize signaling pathways in space and time, including scaffold proteins such as receptor for activated C kinase 1, A-kinase anchoring proteins and IQ motif-containing GTPase-activating protein 1, as well as adaptor proteins such as growth factor receptor-bound protein 2 (Grb2), Src homology 2 domain-containing transforming protein and Grb2-associated binder 1/2 (34-36). By assembling signaling complexes, these molecules enhance signal transduction efficiency and facilitate pathway crosstalk. Certain proteins, such as β-arrestin and Grb2 (Table I), function as both scaffolds and adaptors to coordinate signaling (37,38). Dysregulated proteins disrupt signaling homeostasis, triggering malignancy. Representative scaffold and adaptor proteins involved in signaling integration, together with their associated pathways and tumor-related functions, are summarized in Table I (39-48).

Regulatory enzymes and negative regulators. Regulatory enzymes and negative regulators critically balance signaling. These include phosphatases such as phosphatase and tensin homolog (PTEN), as well as ubiquitin ligases and SUMOylation enzymes (49,50). These molecules limit persistent pathway activation and preserve network homeostasis. Loss or inactivation of PTEN leads to uncontrolled amplification of oncogenic signaling and represents a key event in cancer progression (51,52).

Downstream effectors. Downstream effectors are the final mediators that execute the biological consequences of signaling activation. They include transcription factors, cell cycle and apoptosis regulators, metabolic enzymes, cytoskeletal proteins

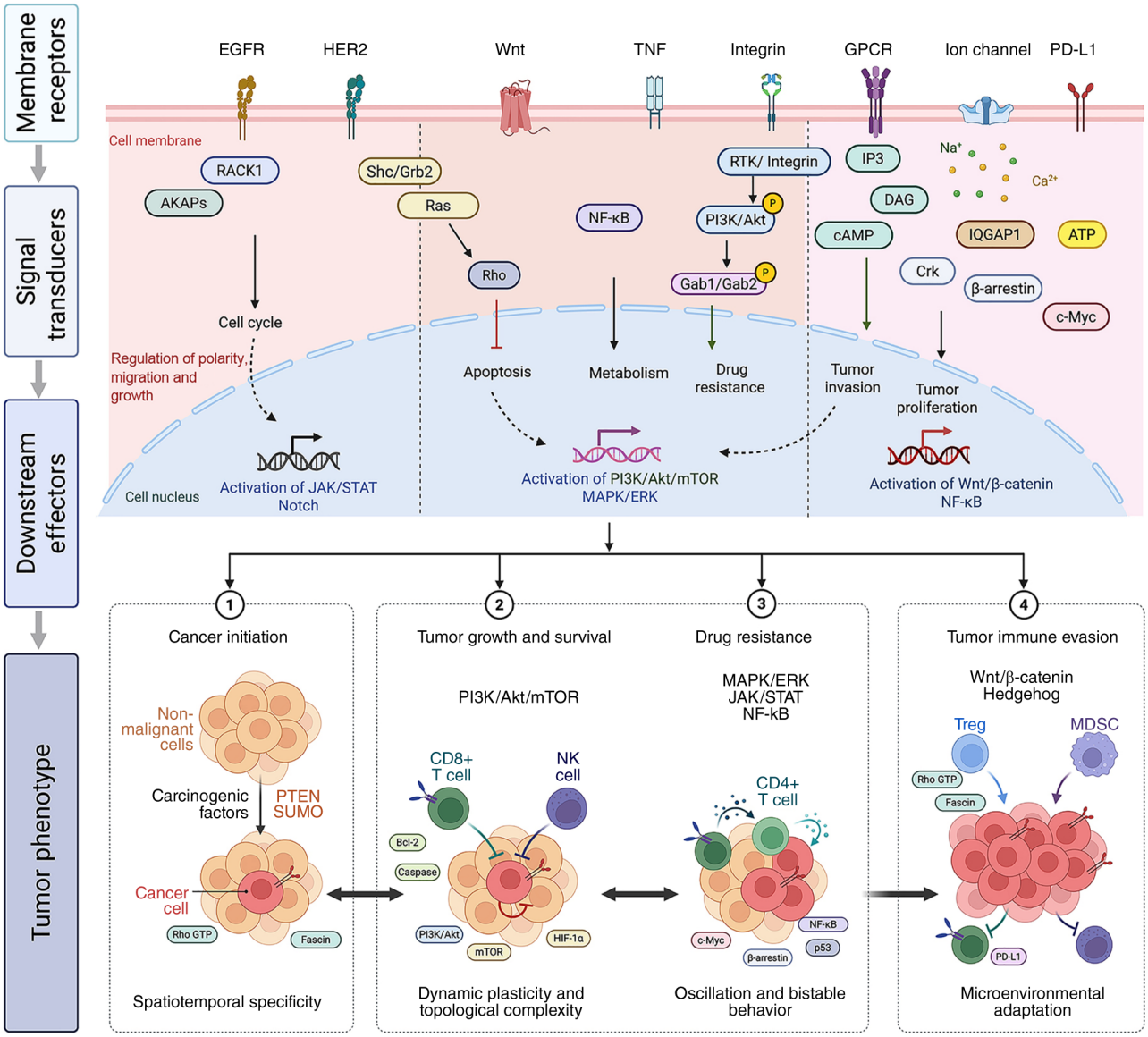

Figure 1. Conceptual framework of cancer signaling networks driving tumor phenotypes and therapeutic resistance. Schematic representation of cancer signaling networks, illustrating the hierarchical flow of signal transduction from membrane receptors through intracellular transducers to core oncogenic pathways, including PI3K/Akt/mTOR, MAPK/ERK and Wnt/β-catenin. These pathways regulate key cellular processes such as proliferation, apoptosis, metabolism and drug resistance. The framework highlights directional signal flow and pathway integration, illustrating how signaling networks collectively shape tumor phenotypes, including tumor initiation, growth, immune evasion and therapeutic resistance. Dynamic features such as crosstalk, feedback regulation and adaptive reprogramming are shown alongside a signal integration layer of scaffold and adaptor proteins that ensure signaling specificity, efficiency and pathway coordination within the network. EGFR, epidermal growth factor receptor; HER2, human EGFR 2; TNF, tumor necrosis factor; GPCR, G protein-coupled receptor; PD-L1, programmed death ligand 1; RACK1, receptor for activated C kinase 1; AKAPs, A-kinase anchoring proteins; Shc, Src homology 2 domain-containing transforming protein; Grb2, growth factor receptor-bound protein 2; Ras, rat sarcoma viral oncogene homolog; Rho, Ras homolog family member; NF-κB, nuclear factor-κB; RTK, receptor tyrosine kinase; IP3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; cAMP, cyclic adenosine monophosphate; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; Gab1/2, Grb2-associated binder 1/2; Crk, CT10 regulator of kinase; IQGAP1, IQ motif-containing GTPase-activating protein 1; ATP, adenosine triphosphate; JAK, Janus kinase; STAT, signal transducer and activator of transcription; mTOR, mechanistic target of rapamycin; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; PTEN, phosphatase and tensin homolog; SUMO, small ubiquitin-like modifier; CD8, cluster of differentiation 8; NK, natural killer; HIF-1α, hypoxia-inducible factor-1α; CD4, cluster of differentiation 4; p53, tumor protein p53; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell.

and immune modulators. They collectively control processes such as proliferation, apoptosis, differentiation, metabolism, migration and immune responses (7). Specifically, transcription factors including NF-κB, c-Myc and β-catenin regulate tumor-associated gene expression (53,54), while proteins such as Bcl-2 family members, caspases and p53 control apoptosis and cell cycle progression (55-57). Metabolic regulators such as mTOR and HIF-1α support cellular adaptation (58), while Rho GTPases and Fascin mediate cytoskeletal remodeling and invasion (59,60). Additionally, PD-L1 plays a pivotal role in tumor immune evasion (61). Dysregulated effectors generate malignant phenotypes, drive therapeutic resistance and often yield poor clinical outcomes (62,63). These downstream consequences arise not from isolated signaling events but from the coordinated activation of oncogenic pathways operating within interconnected networks.

Table I. Representative scaffold and adaptor proteins in cancer signaling networks and their roles in signaling integration and tumor phenotypes.

Protein	Functional category	Representative cancer types	Associated signaling pathways	Molecular function in signaling integration	Tumor-related functional role	Representative (Refs.)
RACK1	Scaffold protein	Breast, gastric and hepatocellular cancers	PKC/Src/FAK, MAPK, PI3K/Akt	Scaffolds adhesion-and growth factor-related signaling complexes and facilitates signal convergence	Context-dependent regulation of proliferation, migration and invasion	(39,40)
β-arrestin	Scaffold/ adaptor protein	Breast cancer, ovarian cancer, lung cancer	GPCR, MAPK/ERK, PI3K/Akt, NF-κB	Couples receptor desensitization to oncogenic signaling	Regulates proliferation, survival, migration and drug resistance	(34,35,37)
Grb2	Adaptor protein	Breast cancer, lung cancer, leukemia	RTK/Ras/MAPK, PI3K/Akt	Links activated RTKs to Ras and PI3K cascades	Promotes mitogenic signaling, proliferation and survival	(36,38)
Shc	Adaptor protein	Breast cancer, prostate cancer, lung cancer	RTK/Ras/MAPK, PI3K/Akt	Recruits Grb2/SOS and amplifies receptor-derived signaling	Promotes proliferation, survival, and tumor progression	(41)
IQGAP1	Scaffold protein	Colorectal, gastric and hepatocellular cancers	Rac1/Cdc42, MAPK, Wnt/β-catenin	Coordinates cytoskeletal remodeling and signaling complex assembly	Promotes migration, invasion and metastasis	(42)
Crk	Adaptor protein	Lung cancer, glioma, breast cancer	Integrin/Src/FAK, small GTPase pathways	Couples adhesion and growth factor signaling to motility pathways	Promotes migration, invasion and metastasis	(43)
AKAPs	Scaffold protein	Breast cancer, ovarian cancer, melanoma	cAMP/PKA, MAPK	Spatially organizes kinase complexes and restricts signaling to specific subcellular compartments	Regulates proliferation, survival and stress adaptation	(44)
Gab1/ Gab2	Adaptor protein	Breast cancer, leukemia, gastric cancer	RTK, PI3K/Akt, MAPK	Functions as a docking platform that amplifies receptor signaling and recruits multiple downstream effectors	Promotes proliferation, survival and oncogenic signaling	(45)
Nck	Adaptor protein	Breast cancer, pancreatic cancer, melanoma	RTK, actin remodeling pathways	Links activated receptors to cytoskeletal regulators and motility pathways	Promotes invasion and migratory behavior	(46)
14-3-3 proteins	Regulatory adaptor protein	Breast, lung, liver and other solid tumors	Cell cycle, apoptosis, PI3K/Akt, MAPK	Bind phosphorylated signaling proteins and modulate their localization, stability, and signaling output	Regulates cell survival, cell cycle progression and therapeutic response	(47)
p130Cas	Scaffold/ adaptor protein	Breast cancer, lung cancer, ovarian cancer	Integrin/Src/FAK, Rac1	Integrates adhesion-dependent signaling and links it to motility and invasion-associated pathways	Promotes migration, invasion and metastasis	(48)

The cancer types listed are representative examples and are not intended to be exhaustive, as many of these proteins function across diverse malignancies. RTK, receptor tyrosine kinase; GPCR, G protein-coupled receptor; FAK, focal adhesion kinase; PKA, protein kinase A; Rac1, Ras-related C3 botulinum toxin substrate 1; Cdc42, cell division cycle 42.

3. Core oncogenic signaling pathways

Although the major oncogenic pathways described below are broadly involved in cancer biology, their activation patterns, biological functions and clinical relevance vary across tumor types. In certain cancers, specific pathways act as dominant drivers of tumor growth and therapeutic response, while in others, they coordinate with additional signaling modules. Importantly, these pathways are embedded within dynamic networks where crosstalk and feedback regulation shape their functional output. Interactions with parallel pathways and microenvironmental cues further modulate these signals, underscoring the necessity of a network-level perspective to understand tumor behavior and therapeutic response. Such a framework accounts for adaptive reprogramming that ultimately dictates clinical effects.

PI3K/Akt/mTOR pathway. The PI3K/Akt/mTOR pathway centrally regulates cancer cell proliferation, survival, metabolic reprogramming and therapeutic resistance. Activated downstream of receptor tyrosine kinases and G protein-coupled receptors, sequential activation of PI3K, Akt and mTOR promotes cell growth while suppressing apoptosis (64-68). Aberrant activation of this pathway is frequent in cancer and is often driven by PTEN loss or activating mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (PIK3CA), resulting in constitutive output that supports tumor progression and resistance to therapy (69-71). Its clinical relevance is particularly notable in breast cancer, endometrial cancer and glioblastoma, where PI3K alterations are prevalent. Given its central role, the PI3K/Akt/mTOR pathway has become a major target in precision oncology and its mechanistic inhibition may relieve negative feedback on upstream receptor tyrosine kinases, thereby triggering compensatory activation of parallel signaling cascades, particularly MAPK/ERK (72). This adaptive reprogramming sustains tumor survival, limits the durability of single-pathway inhibition and drives therapeutic resistance (73).

MAPK/ERK pathway. The MAPK/ERK cascade, organized around the Ras-Raf-MEK-ERK kinase axis, regulates multiple biological processes, including proliferation, differentiation, apoptosis and migration (74,75). Oncogenic alterations, particularly mutations in Ras or BRAF, frequently trigger constitutive MAPK/ERK signaling, thereby driving tumor growth, metastasis and therapeutic resistance; accordingly, the clinical importance of this pathway is especially evident in melanoma and colorectal cancer, where Ras or BRAF mutations often function as primary oncogenic drivers (76-81).

Notably, the MAPK/ERK and PI3K/Akt/mTOR pathways are intimately interconnected. Their extensive crosstalk coordinates control of proliferation, survival and stress responses. In numerous tumor contexts, inhibiting one pathway can induce compensatory activation of the other, thereby maintaining downstream signaling output and reducing therapeutic efficacy (82). This reciprocal regulation is a key mechanism of treatment resistance, providing a strong rationale for pharmacological combination therapies targeting both axes. Often, this compensatory response is mediated by the relief of ERK-dependent negative feedback on upstream nodes, which restores signaling after targeted inhibition (83).

Wnt/β-catenin pathway. The Wnt/β-catenin pathway is a vital regulator of cancer cell stemness, self-renewal and metastatic potential. Upon signaling, β-catenin accumulates in the cytoplasm and translocates to the nucleus to drive the expression of genes involved in proliferation and epithelial-mesenchymal transition (EMT) (84-88). Aberrant Wnt activation has been implicated in colorectal cancer and other tumor contexts, where it contributes to tumor initiation, progression and the maintenance of stem-like and aggressive phenotypes (89,90). Beyond its tumor-intrinsic effects, the Wnt/β-catenin axis modulates the tumor microenvironment and immune responses, further supporting tumor progression (91,92). Mechanistically, stabilized nuclear β-catenin promotes the transcription of EMT-related genes, such as Snail and c-Myc, enhancing tumor invasion, metastasis and therapeutic resistance (93). These features position the pathway as a key candidate for combination-based therapeutic strategies.

Other crucial signaling pathways. In addition to the major pathways described, several other signaling cascades regulate cancer progression, including the JAK/STAT, Notch, Hippo/Yes-associated protein (YAP), NF-κB and Hedgehog pathways. These regulate diverse processes, such as inflammation, immune modulation, cell fate determination and stemness, in a context-dependent manner. For instance, JAK/STAT and NF-κB signaling link inflammation, immune responses to therapeutic resistance (94-98), whereas Notch and Hippo/YAP primarily influence cell fate decisions and cellular plasticity (99,100). Aberrant Hedgehog signaling further promotes tumor proliferation and metastasis, particularly in cancers reactivating developmental programs (101-103). Importantly, these pathways are integrated through extensive crosstalk and feedback regulation, forming a dynamic network with context-dependent outputs. Such interactions, mediated by shared signaling intermediates and transcriptional programs, coordinate regulation of inflammation, immune evasion and tumor cell plasticity (104).

4. Dynamic network properties: Crosstalk, feedback and adaptive reprogramming

Cancer signaling pathways operate within adaptive network systems rather than as isolated modules. These networks are characterized by crosstalk, feedback regulation and adaptive reprogramming that yield context-dependent signaling outputs (105). Such dynamic properties drive phenotypic plasticity, allowing cancer cells to respond to environmental and therapeutic stresses. Consequently, it is essential to understand how these signaling networks drive tumor phenotypes, adapt to therapeutic pressure and shape clinical outcomes.

Spatiotemporal specificity. Signaling events are tightly regulated spatiotemporally, with their activation, propagation and termination restricted within specific cellular compartments and temporal windows. For example, receptor tyrosine kinases frequently localize to membrane microdomains or lipid rafts for activation (106), while the subcellular localization and

nucleo-cytoplasmic shuttling of proteins such as NF-κB, β-catenin and STAT critically influence downstream gene expression and cellular phenotypes. Furthermore, signaling pathways may display transient or sustained activation patterns, as exemplified by the MAPK/ERK cascade (107-110), triggering distinct cellular outcomes ranging from proliferation to differentiation or apoptosis.

Dynamic plasticity and network reprogramming. A defining feature of cancer signaling networks is their capacity for dynamic adaptation under stress. In response to environmental changes or therapeutic pressure, cancer cells can reprogram signaling activity to sustain survival. Inhibiting dominant pathways, such as PI3K/Akt, often triggers compensatory activation of alternative cascades, including MAPK, Wnt or JAK/STAT (111-113). This adaptive reprogramming may arise from altered protein expression, pathway switching or regulatory mutations (114), representing a central mechanism for drug resistance, metastasis and tumor heterogeneity (115,116). In addition, resistance emerges from pathway reactivation, activation of parallel signaling routes or microenvironment-mediated survival signals (117).

Fig. 1 outlines the signaling hierarchy and directionality from membrane receptors to downstream effectors, while Fig. 2 illustrates the mechanistic basis of pathway crosstalk, therapeutic inhibition and adaptive responses under treatment pressure. Specifically, inhibiting dominant hubs such as PI3K/Akt/mTOR can induce compensatory activation of parallel routes, notably MAPK/ERK and Wnt/β-catenin, maintaining downstream signaling and promoting therapeutic resistance. These adaptive responses often stem from pathway reactivation, bypass signaling or microenvironment-derived cues such as cytokines and growth factors, which collectively shield signaling activity from therapeutic inhibition (118).

Topological complexity and redundancy. Cancer signaling networks possess substantial topological complexity, incorporating branched pathways, positive and negative feedback loops, feedforward regulation and redundant signaling routes. Key nodes such as Ras, Akt and β-catenin serve as central hubs that integrate and distribute signals across multiple axes (8,119). While this complex architecture enhances cellular adaptability under stress, it also enables compensatory signaling and therapeutic escape (120).

Oscillation and bistable behaviors. Certain signaling circuits exhibit oscillatory or bistable behaviors in response to external stimuli, as seen in the p53-MDM2 and NF-κB-IκB regulatory loops (121,122). These dynamic patterns trigger switch-like responses or periodic signaling activity, enabling flexible transitions between cellular states. Such behaviors drive tumor heterogeneity, cellular adaptability and the development of therapeutic resistance.

Epigenetic memory and microenvironmental adaptation. Signaling activation is closely linked to epigenetic regulation, including chromatin remodeling, histone modification and DNA methylation (123,124). These processes can encode prior signaling events, generating a form of epigenetic 'memory' that stabilizes tumor phenotypes even after the initial stimulus dissipates (125).

Simultaneously, cancer signaling networks continuously engage with the tumor microenvironment (104). Immune cells, fibroblasts and other stromal components can modulate pathway activity, while tumor cells reciprocally remodel their surroundings. These bidirectional interactions further promote tumor progression, immune evasion and adaptive responses to therapy (126). Tumor microenvironment-mediated resistance is also an important cause of treatment failure. In addition to tumor cells themselves, fibroblasts, immune cells, endothelial cells, extracellular matrix components, hypoxia and soluble cytokines can all influence pathway activity during therapy (117,127). For instance, cancer-associated fibroblasts may release hepatocyte growth factor, which activates MET signaling and downstream PI3K/Akt and MAPK pathways, thereby reducing the efficacy of EGFR tyrosine kinase inhibitors (128). Cytokines such as IL-6 and TGF-β can also activate JAK/STAT3, SMAD or EMT-related signaling, promoting tumor cell survival, immune escape and drug resistance (95,97,129). Furthermore, extracellular matrix remodeling may strengthen integrin-FAK/Src signaling (130), while hypoxia can induce HIF-1α-dependent programs related to angiogenesis, metabolic adaptation and treatment resistance (131). These findings suggest that effective treatment may need to target both tumor-intrinsic oncogenic pathways and protective signals from the surrounding microenvironment.

5. Signaling networks, tumor phenotypes and therapeutic implications

Tumor phenotypes and microenvironmental remodeling. The biological relevance of cancer signaling networks lies in their coordinated ability to shape malignant phenotypes and remodel the tumor microenvironment. Dysregulation of these networks drives key features of cancer, including uncontrolled proliferation, resistance to apoptosis, invasion, metastasis and metabolic reprogramming (132,133). Beyond these tumor-intrinsic effects, these networks reconfigure surrounding stromal and immune components through cytokines, exosomes and other mediators (134).

For example, persistent PI3K/Akt/mTOR and MAPK/ERK activation promotes tumor growth and therapeutic resistance (135-137), while Wnt/β-catenin signaling enhances stemness and metastatic potential (138,139). These alterations can upregulate immunosuppressive molecules, notably PD-L1 (140), and reprogram tumor-associated stromal cells to reinforce immune evasion, angiogenesis and tumor aggressiveness (141). Notably, although many signaling principles are shared across cancers, the phenotypic and therapeutic consequences of dysregulation are highly context-dependent, shaped by lineage, genomic background and the microenvironment. These differences ultimately regulate the efficacy, durability and resistance patterns of targeted therapies.

Therapeutic targeting and clinical implications. From a clinical perspective, the significance of cancer signaling networks lies in their coordinated behavior, rather than in isolated oncogenic drivers. Traditional approaches targeting single signaling nodes such as EGFR, PI3K or BRAF have yielded substantial clinical benefits in selected patient populations (142,143). Representative examples include EGFR

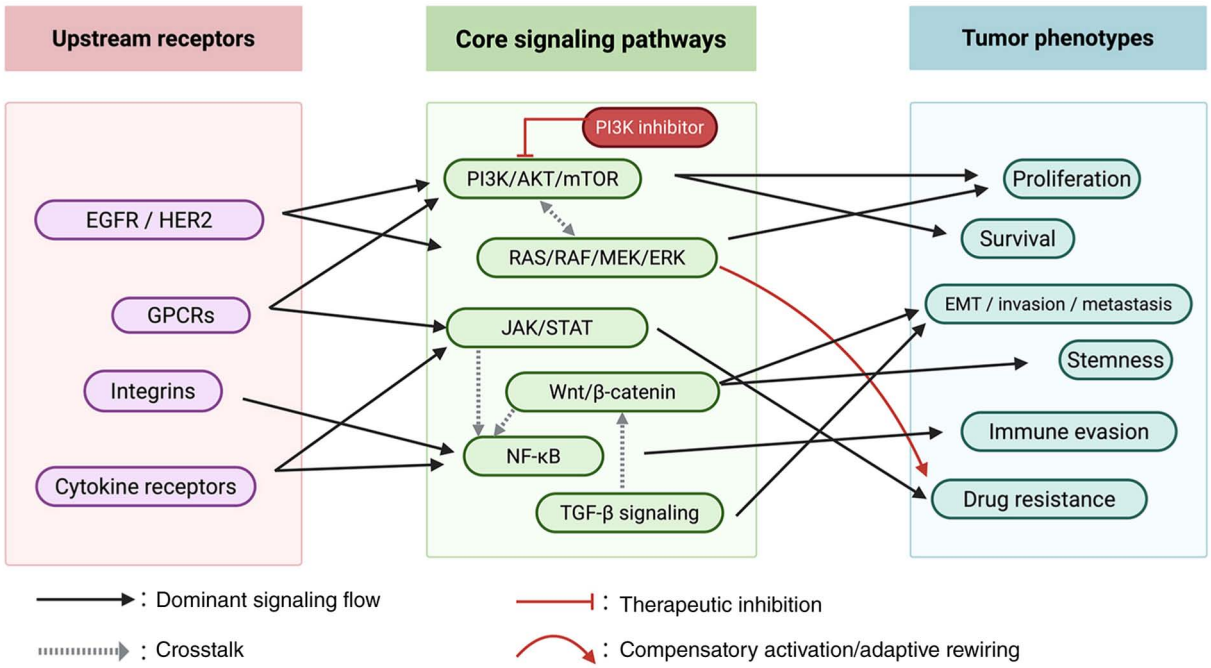

Figure 2. Network-based signaling crosstalk and therapeutic resistance mechanisms in cancer. Schematic illustrating how inhibition of a dominant oncogenic pathway (e.g., PI3K/Akt/mTOR) triggers compensatory activation of parallel signaling pathways, such as MAPK/ERK and Wnt/β-catenin, through network crosstalk. These adaptive responses help sustain downstream signaling outputs to promote tumor cell survival and drive therapeutic resistance. The figure underscores the interconnected nature of cancer signaling networks, suggesting that effective treatment strategies may require multi-target or network-level interventions rather than single-pathway inhibition alone. GPCR, G protein-coupled receptor.

tyrosine kinase inhibitors for EGFR-mutant non-small cell lung cancer, BRAF/MEK inhibitors for BRAF-mutant melanoma and colorectal cancer, PI3K pathway inhibitors for biomarker-selected tumors and immune checkpoint inhibitors for tumors with specific immune-related biomarkers. In the case of PI3K pathway inhibitors, patients are usually selected according to molecular alterations in the PI3K/Akt/mTOR axis, such as activating PIK3CA mutations, PTEN loss, or other evidence of pathway activation (144). For example, PI3K inhibitors have been used in hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer (145). For immune checkpoint therapy, 'high immune regulatory signaling' mainly refers to clinically used biomarkers, including increased PD-L1 expression, microsatellite instability-high status, mismatch repair deficiency, high tumor mutational burden or an inflamed tumor microenvironment (146). However, these biomarkers are not perfect predictors, and their clinical value may differ among tumor types and treatment settings (147).

However, the clinical benefit of single-target inhibition is often limited by the adaptive nature of cancer signaling networks (148). In many tumor contexts, suppression of a dominant node fails to fully extinguish oncogenic output, as parallel pathways are reactivated or newly engaged. A representative example is the reciprocal crosstalk between the PI3K/Akt/mTOR and MAPK/ERK axes, where inhibition of one axis can relieve negative feedback or trigger bypass signaling through the other, sustaining proliferation and survival (149,150). Furthermore, intratumoral heterogeneity and microenvironment-mediated survival signals may promote treatment resistance by allowing resistant cell states to persist or emerge under therapeutic pressure. These observations underscore that cancer signaling networks function as integrated systems rather than isolated pathways.

Accordingly, a network-based therapeutic framework has emerged, guiding strategies by pathway interactions and dynamic network behavior. Key approaches include targeting dominant oncogenic drivers such as EGFR, PI3K or BRAF; co-inhibition of parallel pathways to prevent compensatory signaling, notably combined targeting of PI3K and MAPK; vertical inhibition within signaling cascades to ensure sustained pathway suppression; and integration of targeted therapy with immunotherapy or conventional treatments to modulate both tumor-intrinsic and microenvironmental signaling (151). From a translational and pharmacological perspective, these strategies aim not only to suppress primary oncogenic drivers, but to preempt or overcome the pathway reactivation, bypass signaling and adaptive reprogramming that frequently emerge during treatment.

Despite these advances, major challenges remain, including intratumoral heterogeneity, acquired resistance and adaptive network responses (152). Addressing these challenges will require therapeutic strategies accounting for the dynamic and context-dependent signaling networks. A deeper understanding of network-level regulation and its interaction with the tumor microenvironment is warranted for advancing precision oncology with improved long-term clinical outcomes. Mechanistically, resistance to targeted therapies often arises from feedback reactivation of inhibited pathways or compensatory activation of parallel signaling networks, underscoring the need for rational combination therapies based on network-level interactions (153).

6. Current challenges and future perspectives

Despite substantial progress in targeting cancer signaling networks, certain challenges remain. Tumor heterogeneity is a primary challenge, as pathway activity vary across patients, tumor regions and microenvironments, complicating both network analysis and therapeutic targeting (154,155). In addition, integrating multi-omics data and monitoring dynamic signaling changes in real time remain technically crucial (156), limiting a comprehensive understanding of tumor adaptability and resistance mechanisms. These limitations also hinder the identification of clinically actionable vulnerabilities and the rational design of durable combination therapies.

Emerging technologies are beginning to address these limitations. Advances in single-cell omics, spatial transcriptomics and computational modeling have greatly improved the signaling network resolutions (157-159). These approaches enable more precise characterization of dynamic network rewiring and intercellular interactions, and support targeted discovery and development of more personalized therapeutic strategies.

Furthermore, artificial intelligence (AI) seems promising in this field (160). Machine learning and network-based algorithms can integrate multi-omics and spatial data to reconstruct signaling interactions, identify key regulatory hubs and predict context-specific responses (161). In drug development, AI-assisted approaches may prioritize therapeutic targets, predict synergistic drug combinations and identify resistance-associated adaptations at an earlier stage (162). In addition, AI-driven patient stratification based on signaling signatures may improve biomarker-guided treatment selection (163). However, important challenges remain, including data heterogeneity, limited interpretability and insufficient clinical generalizability.

Looking forward, network-level intervention and multi-target combination strategies are likely to become increasingly important for overcoming therapeutic resistance and improving patient outcomes. A deeper understanding of dynamic signaling networks, with continued integration of multi-omics profiling, real-time monitoring and computational modeling, will be essential for advancing precision oncology.

7. Conclusion

Research on cancer signaling networks has substantially advanced the current understanding of tumor biology and facilitated the development of precision therapeutic strategies. Rather than functioning as isolated pathways, these networks operate as highly interconnected and dynamic systems that shape tumor behavior, therapeutic response and drug resistance. In this review, it was emphasized that the biological and clinical significance of cancer signaling lies not only in individual oncogenic pathways, but also in the network-level interactions that link signaling architecture with adaptive reprogramming, phenotypic plasticity and therapeutic adaptation. A key challenge moving forward is to elucidate how crosstalk, compensatory activation and adaptive reprogramming collectively drive tumor phenotypes across diverse biological and clinical contexts. Addressing this challenge will require integrated approaches that combine multi-omics analysis, systems biology and real-time monitoring of signaling dynamics. Ultimately, deciphering context-dependent network behavior is essential to improve treatment outcomes and advance precision oncology.

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HL and SS wrote the original draft. LW and QL contributed to conceptualization, literature search and selection, interpretation of the literature, and critical revision of the manuscript. LW provided project administration. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

AI-assisted tools were used only for minor language polishing. Specifically, ChatGPT (OpenAI, GPT-5; https://chatgpt.com/) was used to improve the readability and language of the manuscript. The authors reviewed and edited the final manuscript and take full responsibility for its content. All contents of this review were conceptualized, analyzed and critically reviewed by the authors.

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