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Review

Contribution of Different Cell Signaling Pathways in Tumorigenesis

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Abstract

Cancer is a leading cause of death globally, and poses a major challenge to public health systems everyplace. The tumorigenesis is essentially initiated by the deregulation of fundamental intracellular signaling pathways which control important cell processes such as proliferation, survival and differentiation. Aberrations in these pathways have been shown for decades to underlie many of the hallmark capabilities of cancer cells such as unlimited replicative potential. Targeting oncogenic signaling has therefore become a major therapeutic strategy. We provide a review of five signaling networks that are often deregulated in cancer: PI3K/AKT/mTOR, NF-kappaB, Wnt/beta-catenin, Notch and Hippo/YAP-TAZ signaling and provide a unified analysis of this group of networks. We review here current knowledge of their individual and cooperative roles in tumor pathogenesis, and discuss implications for developing specific anticancer therapies.

1. INTRODUCTION

Cancer is a major public health problem worldwide, and has a complex and multifactorial etiology. The reasons are complex from the elusive causative factors to often ineffective treatments, and that is why cancer remains a leading cause of mortality worldwide. Globally, an estimated 20.0 million new cases and 9.7 million cancer deaths occurred in 2022. Cancer occurs in about 1 in 5 people during their lifetime and about 1 in 9 men and 1 in 12 women die from cancer (1). At its core, tumorigenesis is driven by the dysregulation of fundamental cellular signaling pathways. For a normal cell to undergo malignant transformation, it must acquire alterations in the intricate networks that govern processes such as proliferation, survival, and differentiation. Consequently, a primary objective in oncology has been the development of therapeutic agents designed to correct these specific pathway dysregulations (2, 3). The efficacy and reduced side effects of such targeted therapies hinge on a deep and integrated understanding of the underlying signaling mechanisms.

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Cancer development is driven by alterations in interconnected signaling networks, including RTK–RAS, PI3K/AKT/mTOR, cell-cycle, p53, Wnt, Notch, and Hippo pathways (2, 4) (**Figure 1**). Despite this knowledge, a significant gap persists in the literature. Many existing studies examine individual signaling pathways in isolation, often focusing on a specific therapeutic modality rather than providing a synthesized explanation of the pathway's fundamental role in oncogenesis. This fragmented approach overlooks the critical crosstalk and interplay between these pathways, which creates the complex molecular landscape underlying aggressive tumor behavior. Therefore, a unified and comprehensive examination is necessary to elucidate both the individual and interconnected roles of these dysregulated pathways.

To address this need, this narrative review provides a concise overview of the major signaling pathways implicated in cancer pathogenesis. We aim to delineate their core mechanisms, functional roles in tumorigenesis, and the therapeutic implications of their dysregulation, thereby offering an integrated framework for understanding this critical aspect of cancer biology. The principal upstream regulators, core molecular components, oncogenic consequences, representative tumor contexts, and therapeutic relevance of the five signaling pathways discussed in this review are summarized in **Table 1**.

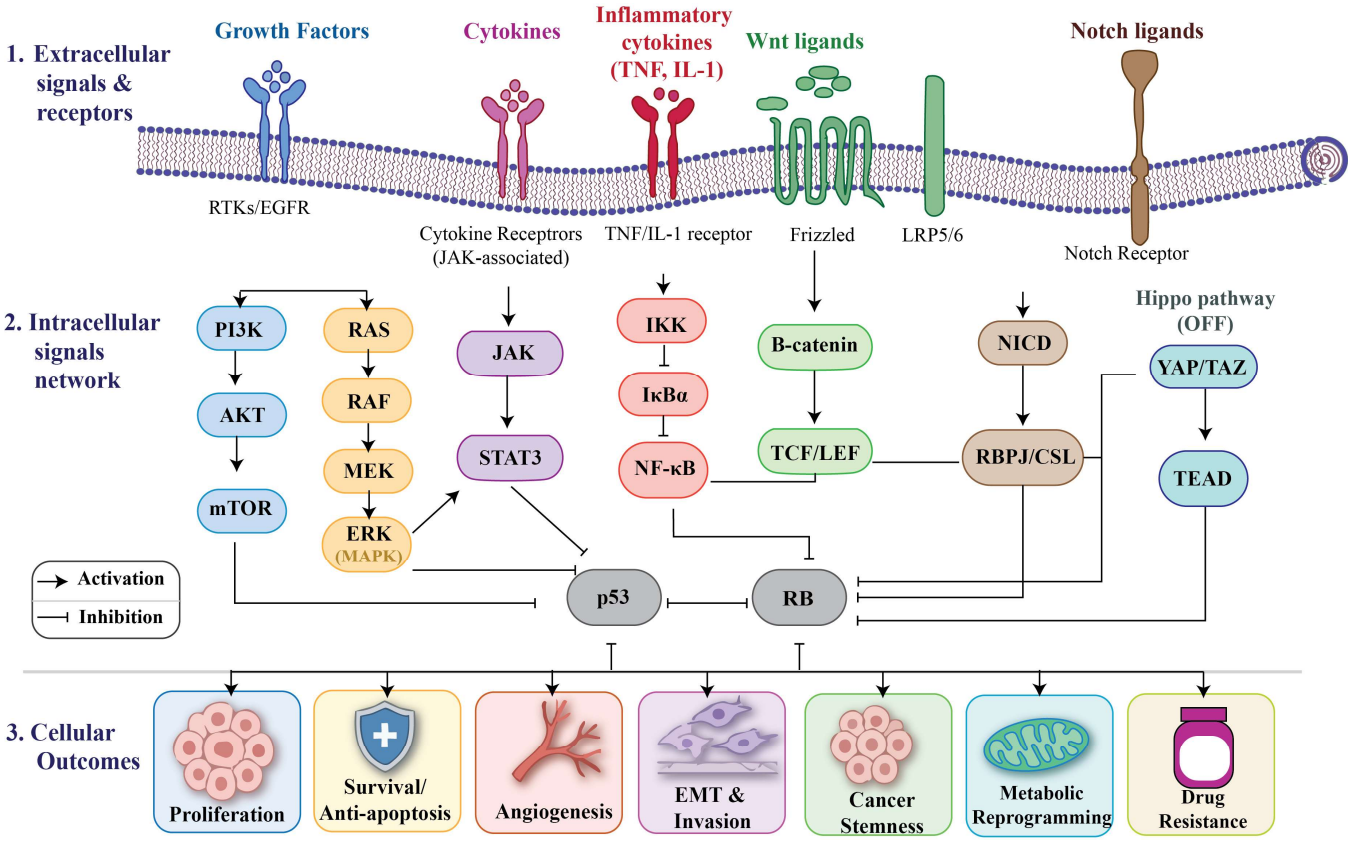


Figure 1. Integrated crosstalk among major oncogenic signaling pathways involved in tumorigenesis. Extracellular growth factors, cytokines, inflammatory mediators, and Wnt and Notch ligands activate interconnected PI3K/AKT/mTOR, RAS/RAF/MEK/ERK, JAK/STAT, NF-κB, Wnt/β-catenin, Notch, and Hippo/YAP–TAZ signaling networks. The schematic also illustrates selected interactions with the tumor-suppressor proteins p53 and RB and the major downstream cellular consequences, including proliferation, survival and resistance to apoptosis, angiogenesis, epithelial–mesenchymal transition and invasion, cancer stemness, metabolic reprogramming, and drug resistance. The figure was drawn by the authors using Adobe Illustrator 2022.

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2. SIGNALING PATHWAYS

2.1. The PI3K/AKT/mTOR Signaling Axis

The mechanistic target of rapamycin (mTOR) is a serine/threonine kinase encoded by the MTOR gene in humans. Its activity is regulated by upstream signals, including those from the phosphoinositide 3-kinase (PI3K) pathway, whose significance in oncogenesis was first identified in 1985 through its association with the polyoma middle-T antigen (5). mTOR integrates nutrient and growth-factor signals to coordinate cellular growth and metabolism and regulates fundamental processes ranging from protein synthesis to autophagy (6, 7). mTOR functions through two distinct multiprotein complexes, mTORC1 and mTORC2. mTORC1 is sensitive to acute rapamycin and integrates amino-acid, growth-factor, and energy signals to regulate anabolic and catabolic processes. In contrast, mTORC2 is relatively insensitive to acute rapamycin and regulates AKT and PKC signaling, cell survival, migration, and cytoskeletal remodeling (8, 9).

The PI3K/AKT/mTOR pathway is frequently hyperactivated in cancer. Activation begins when PI3K, a family of intracellular lipid kinases, phosphorylates phosphatidylinositol lipids at the plasma membrane. PIP3 recruits AKT to the plasma membrane, where phosphorylation at Thr308 by PDK1 and at Ser473 by mTORC2 leads to its complete activation (10). The PI3K–AKT axis regulates growth, proliferation, and survival, and its dysregulation is implicated in a wide array of malignancies, including colorectal, breast, lung, and cervical cancers (10, 11). Several mechanisms drive the hyperactivity of this pathway in tumors. A common event is the loss-of-function mutation in the PTEN tumor suppressor gene, which encodes a phosphatase that antagonizes PI3K signaling (12). PTEN loss leads to constitutive PI3K/AKT activation. Furthermore, mTOR activity is often deregulated by upstream activation of PI3K or AKT. Oncogenic signaling through mTOR promotes malignancy by several mechanisms: downstream overexpression of effectors like S6K1 and eIF4E enhances protein synthesis and cell proliferation (13); pathway activation increases the translation of hypoxia-inducible factor 1-alpha (HIF1A), stimulating angiogenesis to supply tumors with oxygen and nutrients (14); and mTOR signaling can contribute to the Warburg effect (aerobic glycolysis) by regulating glycolytic enzymes, including PKM2, thereby altering cellular metabolism (15).

Given its central role, the mTOR pathway is a prime target for therapeutic intervention. Several classes of mTOR-targeting agents have been developed, including rapamycin derivatives, ATP-competitive mTOR kinase inhibitors, and dual-target inhibitors (16).

2.2. The Wnt/β-Catenin Signaling Pathway

The first mammalian Wnt gene, initially termed int-1 and subsequently designated WNT1, was identified by Nusse and Varmus in 1982. Wnt signaling is now recognized as a highly conserved regulator of embryonic development and tissue homeostasis (17-19). Dysregulation of this pathway is a common driver of carcinogenesis. In the absence of a Wnt signal, cytoplasmic β-catenin is constitutively phosphorylated by a destruction complex comprising casein kinase 1α (CK1α) and glycogen synthase kinase 3β (GSK3β), leading to its proteasomal degradation. Upon Wnt activation, this complex is disrupted, allowing β-catenin to accumulate and translocate to the nucleus. There, it associates with T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors to activate target genes such as CCND1 (cyclin D1) and MYC (c-Myc), which promote cell cycle progression and proliferation. Aberrant Wnt/β-catenin signaling contributes to tumorigenesis through multiple mechanisms. Aberrant Wnt/β-catenin signaling can promote tumor-cell proliferation, survival, and treatment resistance, although its biological effects vary across tumor types and molecular contexts (19, 20). In head and neck squamous cell carcinoma models, Wnt/β-catenin signaling maintained the self-renewal, chemoresistance, and tumorigenicity of stem-like cells through OCT4 activation (21) . In blast-crisis CML, missplicing of GSK3β impairs β-catenin phosphorylation and promotes β-catenin stabilization and the self-renewal of granulocyte–macrophage progenitor-derived leukemia stem cells (22). Wnt ligand activation and secretion are tightly regulated processes that depend on post-translational palmitoylation, a lipid modification catalyzed by Porcupine (PORCN), a member of the membrane-associated O-acyltransferase (MBOAT) family. This modification is essential for Wnt activity, facilitating both Wnt–Frizzled (Fz) interactions and association with Wntless (WLS), a transmembrane protein required for Wnt secretion. The release of Wnt from WLS-containing secretory vesicles at the cell surface is further regulated through pH-dependent mechanisms. Due to the critical role of PORCN in Wnt secretion and signaling, inhibitors targeting this enzyme have emerged as promising therapeutic strategies for Wnt-driven malignancies. In addition, extracellular regulation of Wnt signaling is highly complex and involves multiple secreted agonists and antagonists. Key endogenous antagonists include Dickkopf (DKK) proteins, secreted frizzled-related proteins (SFRPs),

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and Wnt inhibitory factor 1 (WIF-1), which function to suppress pathway activation (23-25). Among these, the DKK family, particularly Dickkopf-3 (DKK3), has emerged as a promising area of therapeutic investigation. DKK3 is frequently epigenetically silenced via promoter hypermethylation in various solid and hematologic tumors. Functioning as a putative tumor suppressor, the loss of DKK3 expression correlates with tumor progression and increased nuclear β-catenin accumulation. Re-expression of DKK3 in cancer cells has been shown to induce apoptosis and suppress TCF/LEF-mediated transcription, positioning DKK3 restoration as a potential therapeutic strategy (26, 27).

2.3. The NF-κB Signaling Pathway

Nuclear factor kappa B (NF-kB) is a family of transcription factors that are first responders to many cellular stimuli including cytokines, pathogens, reactive oxygen species and DNA damage. The family is characterized by a conserved Rel homology domain mediating DNA binding and dimerization. Some members such as RelA (p65), RelB and c-Rel also contain a C-terminal transactivation domain which enhances their ability to control gene expression. NF-κB is a rapidly activated characteristic; NF-κB is bound to inhibitory proteins of the IκB family in the cytoplasm in an inactive state. This preformed status allows for activation without de novo protein synthesis and makes NF-κB an important mediator of acute stress and immune responses (28, 29). The canonical activation pathway is mediated by a p50-RelA heterodimer . The IκB kinase (IKK) complex is activated upon stimulation with activators such as tumor necrosis factor-alpha (TNFα) or interleukin-1 beta (IL-1β) . IKK then phosphorylates IκBα, which is ubiquitinated and degraded by the proteasome (30). This process frees the NF-κB dimer to translocate into the nucleus where it binds to specific κB DNA response elements and induces transcription of target genes (31, 32). Persistent NF-κB activation favors tumor-cell proliferation and survival, angiogenesis, epithelial–mesenchymal transition, metastasis, therapy resistance and can contribute to the formation of an immunosuppressive tumor microenvironment (33).

2.4. The Notch Signaling Pathway

The Notch signaling pathway is an evolutionarily conserved pathway mediating direct cell-to-cell communication, and is playing an essential role in cell fate determination, differentiation and stem cell maintenance (34, 35). The pathway consists of four receptors (Notch1-4) and five ligands (Jagged1, Jagged2, Delta-like 1, 3 and 4) in mammals . All the receptors and ligands are single-pass transmembrane proteins with extracellular epidermal growth factor (EGF)-like repeats . Notch activation begins with the interaction of the ligand and receptor between neighboring cells. This interaction induces a series of proteolytic cleavages of the receptor . ADAM family metalloproteases catalyze the first cleavage extracellularly. Second, intramembrane cleavage is catalyzed by the γ-secretase complex, releasing the Notch intracellular domain (NICD) (36, 37). The released NICD translocates to the nucleus where it binds to the DNA-binding transcription factor RBPJ/CSL, displacing corepressors and recruiting Mastermind-like coactivators to activate transcription of Notch target genes (38). Notch signaling outputs are highly context-dependent, regulating the expression of a broad set of target genes, including the HES and HEY families, CCND1 (cyclin D1), MYC, and CDKN1A (p21). Through these targets, Notch signaling exerts profound effects on cellular proliferation, apoptosis, and differentiation. Because its biological effects depend on cell type and molecular context, dysregulated Notch signaling may function as either an oncogenic driver or a tumor suppressor in different malignancies (39, 40).

2.5. The Hippo Signaling Pathway

The Hippo pathway is a key conserved regulator of organ size, tissue homeostasis, and stem cell biology by controlling cell proliferation and apoptosis. The core kinase cascade involves MST1/2 (homologs of Hippo in Drosophila) kinases phosphorylating and activating LATS1/2 kinases. LATS1/2, in turn, phosphorylate the key downstream effectors, Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) (41). Phosphorylation of YAP/TAZ promotes their cytoplasmic retention and proteasomal degradation, thereby inhibiting their transcriptional activity. In cancer, the Hippo pathway is frequently inactivated, leading to the de-repression of YAP and TAZ. These transcriptional co-activators lack DNA-binding domains and instead partner with transcription factors, primarily the TEAD family (TEAD1-4), to drive the expression of pro-proliferative and pro-survival genes (42, 43). Consequently, hyperactivation of YAP/TAZ is a common feature in many malignancies, promoting enhanced cell migration, invasion, and cancer stem cell traits. The structural regulation of YAP is complex. Its N-terminal region contains the TEAD-binding domain, while a central region includes the 14-3-3 binding motif that facilitates cytoplasmic sequestration upon phosphorylation by LATS1/2. Unique features of YAP, such as its N-terminal proline-rich region (which interacts with hnRNPU in

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mRNA processing) and an SH3-binding motif (facilitating interactions with SRC kinases), distinguish it from its paralog TAZ and contribute to its diverse functions (44, 45).

The tumor-suppressive function of the Hippo pathway is primarily executed through the MST-LATS kinase axis. Loss-of-function mutations or epigenetic silencing of MST1/2 or LATS1/2 genes are observed in various cancers, leading to uncontrolled YAP/TAZ activity and accelerated tumor growth (46). The biological consequences of LATS1/2 loss are cell-context dependent. In MC38 murine colon cancer cells, LATS1/2 deletion induced YAP/TAZ-dependent WISP2 and CCDC80 expression and a growth-inhibitory phenotype, whereas deletion of WISP2 and CCDC80 prevented this effect. In ER-positive breast cancer cells, LATS1/2 can support ERα expression and tumor-cell growth through inhibition of YAP/TAZ activity (47, 48).

Table 1. Major oncogenic signaling pathways: molecular components, dysregulated functions, representative tumor contexts, and therapeutic relevance.

Signaling pathway	Principal upstream regulators	Core molecular components	Major consequences of dysregulation in cancer	Representative tumor contexts*	Therapeutic relevance	Ref.
PI3K/AKT/mTOR	Receptor tyrosine kinases; PI3K activation; PIK3CA alterations; AKT activation; PTEN loss	PI3K, PIP3, PDK1, AKT, mTORC1, mTORC2, S6K1, 4E-BP1	Increased cell growth, proliferation, survival, protein synthesis, metabolic adaptation, and treatment resistance	Breast, colorectal, lung, and cervical cancers	PI3Kα, AKT, and mTOR inhibitors; clinical benefit is greatest in molecularly selected populations	(8, 9, 50-52)
Wnt/β-catenin	Wnt ligands; PORCN-dependent Wnt acylation; WLS-mediated secretion; loss or dysfunction of APC, AXIN, or extracellular Wnt antagonists	Frizzled/LRP5/6, Dishevelled, APC–AXIN–GSK3β–CK1α destruction complex, β-catenin, TCF/LEF	β-catenin stabilization, increased proliferation, cancer stem-cell maintenance, invasion, metastasis, and resistance to therapy	Colorectal, hepatocellular, breast, and hematologic malignancies	PORCN inhibitors and agents targeting β-catenin-dependent transcription remain predominantly investigational	(53)
NF-κB	TNF-α, IL-1β, pattern-recognition receptors, inflammatory mediators, cellular stress, and DNA damage	IKK complex, IκB proteins, p50, RelA/p65, RelB, and c-Rel	Sustained inflammatory signaling, increased tumor-cell proliferation and survival, altered metabolism, angiogenesis, metastasis, and therapy resistance	Solid tumors and hematologic malignancies	Direct pathway inhibition remains challenging; proteasome inhibition can indirectly modulate NF-κB signaling	(33)
Notch	JAG1, JAG2, DLL1, DLL3, and DLL4 expressed on adjacent cells	NOTCH1–4 receptors, ADAM-family proteases, γ-secretase, NICD, RBPJ/CSL, and MAML coactivators	Context-dependent regulation of cell fate, differentiation, proliferation, stemness, and treatment response; oncogenic or tumor-suppressive activity may occur according to tumor context	T-cell acute lymphoblastic leukemia, breast, pancreatic, lung, and other solid tumors	γ-secretase inhibitors and antibodies targeting Notch receptors or ligands have entered clinical evaluation	(40)
Hippo/YAP–TAZ	Cell density, cell polarity, extracellular-matrix stiffness, mechanical stress, and growth-factor signaling	MST1/2, SAV1, LATS1/2, MOB1, YAP, TAZ, and TEAD1–4	Nuclear YAP/TAZ activation, increased proliferation, survival, invasion, cancer stem-cell properties, microenvironmental remodeling, and treatment resistance	Mesothelioma, liver, breast, lung, and colorectal cancers	TEAD palmitoylation inhibitors represent the most clinically advanced strategy for disrupting YAP/TAZ–TEAD transcription	(54, 55)

Abbreviations: 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; APC, adenomatous polyposis coli; CK1α, casein kinase 1α; DLL, Delta-like ligand; IKK, IκB kinase; MAML, Mastermind-like; NICD, Notch intracellular domain; PDK1, phosphoinositide-dependent kinase 1; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PORCN, Porcupine; S6K1, ribosomal protein S6 kinase 1; TCF/LEF, T-cell factor/lymphoid enhancer factor; TEAD, TEA domain transcription factor; WLS, Wntless. The tumor types listed are representative examples and do not constitute an exhaustive list.

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MST1 and MST2, serine-threonine kinases with 76% amino acid identity, function as pro-apoptotic tumor suppressors. For instance, in non-small cell lung cancer (NSCLC), overexpression of MST1 suppresses proliferation, induces apoptosis, and promotes the inhibitory phosphorylation of YAP. MST1 overexpression inhibited A549-cell proliferation, induced apoptosis, increased the inhibitory phosphorylation of YAP at Ser127, and suppressed NSCLC growth in vivo (49).

2.6. Pathway Crosstalk

Emerging evidence highlights extensive crosstalk among PI3K/AKT/mTOR, Wnt/β-catenin, NF-κB, Notch, and Hippo pathways. For example, AKT can activate NF-κB through the IKK complex (56). Crosstalk between PI3K/AKT/mTORC1 and Wnt/β-catenin signaling is context-dependent; in colorectal cancer models, inhibition of PI3K/AKT/mTORC1 can increase MNK-dependent eIF4E phosphorylation, which is associated with β-catenin nuclear translocation (57). Conversely, YAP/TAZ (Hippo effectors) interact with both NF-κB and Wnt: nuclear YAP can co-activate NF-κB (p65)–dependent transcription (e.g. upregulating IL-11) , but in some contexts YAP competes with p65 and inhibits NF-κB activity (54). YAP/TAZ also forms complexes with β-catenin to drive or suppress Wnt target genes, creating feedback loops between Hippo and Wnt pathways . Similarly, the Wnt and Notch pathways are tightly interwoven: β-catenin can modulate Notch target genes (e.g. via Hes1 regulation) and NICD/CSL complexes can bind β-catenin to influence Wnt signaling (53). These signaling networks are also regulated by non-coding RNAs; in bone tumors, specific microRNAs have been reported to modulate PI3K/AKT, Wnt/β-catenin, MEK/ERK, STAT3, and YAP-related signaling, thereby influencing tumor-cell proliferation, invasion, metastasis, and treatment response (58). These intersecting circuits mean that perturbing one pathway (for instance, EGFR/PI3K signaling) often reshapes others, forming a robust oncogenic network.

2.7. Translational and Clinical Update

Several pathway-targeted drugs have reached the clinic, though resistance remains a challenge. In the PI3K/AKT/mTOR axis, clinically established combinations include alpelisib plus fulvestrant for PIK3CA-mutated, HR-positive/HER2-negative advanced or metastatic breast cancer after progression on endocrine-based therapy (50), everolimus plus exemestane for postmenopausal patients with HR-positive advanced breast cancer recurring or progressing during previous nonsteroidal aromatase-inhibitor therapy (51), and capivasertib plus fulvestrant for HR-positive/HER2-negative locally advanced or metastatic breast cancer with PIK3CA, AKT1, or PTEN alterations after progression on endocrine-based therapy (52). By contrast, Wnt-pathway agents remain investigational; the PORCN inhibitor WNT974 has undergone phase 1 evaluation in patients with advanced solid tumors (59). The NF-κB pathway has no direct inhibitor in routine clinical use. Bortezomib, an approved 26S proteasome inhibitor for multiple myeloma and mantle-cell lymphoma, can indirectly modulate NF-κB signaling by limiting the proteasomal degradation of IκB proteins(60).

Notch-directed therapeutic strategies include γ-secretase inhibitors and monoclonal antibodies targeting Notch receptors or ligands (40). In the phase 3 DeFi trial, nirogacestat significantly improved progression-free survival and objective response in adults with progressing desmoid tumors (61). In a phase Ib trial, demcizumab combined with pemetrexed and carboplatin produced objective responses in 20 of 40 evaluable patients with metastatic non-squamous NSCLC (62). However, the development of safe, effective, and tumor-specific Notch-targeted therapies remains challenging because the biological effects of Notch signaling are highly context-dependent . Representative clinically established and investigational agents targeting the signaling pathways discussed in this review are summarized in **Table 2.**

2.8. Limitations and future directions

Despite these insights, limitations remain. Pathway interactions are highly context-dependent: the effect of a given mutation or signal can differ by tumor type or microenvironment. For instance, YAP may activate NF-κB in one tissue but inhibit it in another, reflecting differences in co-factors or cellular state. Intratumoral heterogeneity and the influence of stromal and immune cells can further modulate signaling outputs. To address this complexity, emerging technologies are essential. Single-cell and spatial ‘omics can map pathway activation states across individual tumor cells and microenvironment niches (54). Coupling single-cell transcriptomics or proteomics with chromatin/epigenetic profiling will clarify how signals like NF-κB or Wnt are deployed in different cell subsets. Moreover, integrative computational models and CRISPR screens could predict how network rewiring under therapy leads to resistance. Evidence from leukemia further illustrates how the integration of genetic and transcriptomic profiling, single-cell analysis, and artificial intelligence may support therapeutic-target identification, risk stratification, and treatment optimization (64). Incorporating these approaches will be critical for translating pathway biology into precise biomarkers and tailored combination therapies.

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Table 2. Representative clinically established and investigational agents targeting major oncogenic signaling pathways.

Agent or regimen	Principal molecular target	Pathway	Evidence-supported disease setting	Regulatory or clinical-development status**	Key published evidence	Ref.
Alpelisib plus fulvestrant	PI3Kα	PI3K/AKT/mTOR	PIK3CA-mutated, HR-positive/HER2-negative advanced or metastatic breast cancer after progression on endocrine therapy	FDA-approved combination	Regulatory approval was supported by clinical benefit in the biomarker-selected population evaluated in SOLAR-1	(50)
Everolimus plus exemestane	mTORC1	PI3K/AKT/mTOR	Postmenopausal patients with HR-positive advanced breast cancer recurring or progressing during prior nonsteroidal aromatase-inhibitor therapy	Clinically established combination	BOLERO-2 showed significantly prolonged progression-free survival compared with exemestane plus placebo	(51)
Capivasertib plus fulvestrant	AKT1, AKT2, and AKT3	PI3K/AKT/mTOR	HR-positive/HER2-negative locally advanced or metastatic breast cancer with PIK3CA, AKT1, or PTEN alterations after progression on endocrine-based therapy	FDA-approved combination	CAPItello-291 demonstrated improved progression-free survival with capivasertib plus fulvestrant	(52)
WNT974	PORCN	Wnt/β-catenin	Advanced solid tumors	Investigational; phase 1 evaluation	First-in-human evaluation demonstrated pathway modulation and defined the safety and pharmacodynamic profile of single-agent WNT974	(59)
Bortezomib	26S proteasome	Indirect modulation of NF-κB signaling	Multiple myeloma and mantle-cell lymphoma	FDA-approved	Bortezomib is approved as a proteasome inhibitor for adult patients with multiple myeloma and mantle-cell lymphoma; it should not be described as a direct NF-κB inhibitor	(60)
Nirogacestat	γ-secretase	Notch	Adults with progressing desmoid tumors requiring systemic treatment	FDA-approved in 2023	The phase 3 DeFi trial demonstrated significant improvements in progression-free survival and objective response	(61, 63)
Demcizumab plus pemetrexed and carboplatin	DLL4	Notch	First-line treatment of metastatic non-squamous NSCLC	Investigational; phase Ib	Objective responses were reported in 20 of 40 evaluable patients; the result relates to the combination regimen, not demcizumab monotherapy	(62)
VT3989	TEAD palmitoylation	Hippo/YAP–TAZ	Refractory solid tumors, with a major focus on mesothelioma	Investigational; phase 1/2	The first-in-human phase 1/2 study evaluated inhibition of YAP–TEAD transcription by the oral TEAD palmitoylation inhibitor VT3989	(55)

Abbreviations: DLL4, Delta-like ligand 4; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSCLC, non-small cell lung cancer; PORCN, Porcupine; TEAD, TEA domain transcription factor. Regulatory status refers to the US Food and Drug Administration where FDA approval is stated. Investigational agents are not approved for routine oncologic use.

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3. CONCLUSION

Unraveling the dysregulated signaling networks in cancer has direct implications for therapy. The PI3K/AKT/mTOR axis, for example, is highly druggable with multiple approved inhibitors (and newly approved AKT inhibitors), making it one of the most tractable targets. In contrast, targeting Wnt and Hippo remains challenging; these pathways have few clinical agents and are active areas of drug discovery. The Notch pathway occupies an intermediate position: recent approvals (e.g. nirogacestat) and trial results highlight its potential, but systemic toxicities require careful management. Overall, a combinatorial approach is emerging as a priority – for instance, pairing pathway inhibitors to prevent compensatory activation, or combining with immunotherapy to exploit tumor inflammation. Research should focus on identifying predictive biomarkers of pathway addiction and on designing sophisticated drugs (such as protein degraders or allosteric inhibitors) that overcome the limitations of current agents. A deep mechanistic understanding of pathway crosstalk (as outlined above) will inform these strategies. Ultimately, continued integration of molecular insights with clinical trials will be essential to move from bench to bedside, improving outcomes by precisely targeting the core signaling abnormalities driving each patient's cancer.

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Conflict of interest

The authors declare there is no conflict of interest.

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Ethical statement

This is a review article. Therefore, ethical approval is not required for the study. Declaration of Generative AI and AI-Assisted Technologies: During the preparation of this manuscript, the authors used ChatGPT solely for preliminary organization of manuscript sections, language refinement, and conceptual brainstorming regarding the visual layout of Figure 1. The final figure was independently designed and drawn by the authors using Adobe Illustrator 2022. All scientific content, interpretations, and references were critically reviewed and approved by the authors, who take full responsibility for the accuracy and integrity of the work.

Abbreviations

AKT, protein kinase B; EGFR, epidermal growth factor receptor; eIF4E, eukaryotic translation initiation factor 4E; ERK, extracellular signal-regulated kinase; GSK3β, glycogen synthase kinase 3 beta; JAK, Janus kinase; LATS1/2, large tumor suppressor kinase 1/2; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MST1/2, mammalian sterile 20-like kinase 1/2; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; mTORC2, mechanistic target of rapamycin complex 2; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma; RB, retinoblastoma protein; RTK, receptor tyrosine kinase; STAT, signal transducer and activator of transcription; TAZ, transcriptional coactivator with PDZ-binding motif; YAP, Yes-associated protein.

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