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REVISIÓN

Signal transduction in cancer: a cross-talk

Señales de transducción en cáncer: una comunicación cruzada

»Juan Esteban Garcia-Robledo [1]
»Andrés F. Cardona [2]

[1] Centro de Investigación Hemato Oncológico (CIHO), IDC Instituto de Cáncer Hemato Oncólogos, Cali, Colombia
[2] Direction of Research and Education, Luis Carlos Sarmiento Angulo Cancer Treatment and Research Center – CTIC, Bogotá, Colombia

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Abstract

Introduction: Aberrant signal transduction is a defining feature of cancer, governing proliferation, survival, stemness, immune evasion, and therapeutic resistance. The MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin pathways are frequently altered in solid tumors and function as key regulatory hubs within an interconnected signaling network.

Methods: We conducted a comprehensive literature review focused on the structure, activation mechanisms, oncogenic alterations, and interactions among MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin pathways. We analyzed preclinical and clinical data on therapeutic strategies targeting these pathways and examined specific implementation challenges in Latin America.

Results: MAPK signaling is frequently dysregulated through RAS and BRAF mutations, promoting uncontrolled proliferation. PI3K/AKT/mTOR alterations, including PIK3CA mutations and PTEN loss, drive growth and metabolic reprogramming. Wnt/β-catenin activation supports stemness and immune evasion, often via APC or CTNNB1 mutations. Crosstalk between these pathways amplifies oncogenic signaling and contributes to therapeutic resistance. Dual inhibition strategies show preclinical promise but are limited by toxicity and compensatory feedback. Functional biomarkers and combinatorial regimens are under investigation to overcome resistance. In Latin America, access to molecular diagnostics and targeted therapies remains limited, though efforts to expand

*** Autor para correspondencia:** Juan Esteban Garcia-Robledo, MD. Centro de Investigación Hemato Oncológico (CIHO), IDC Instituto de Cáncer Hemato Oncólogos, Cali, Colombia.
Dirección: Calle 5B5 #38-10, Cali, Colombia
Correo electrónico: juanegarcia@hematooncologos.com.co; resmedjegr@proton.me
https//doi.org/10.51643/22562915.836

precision oncology are underway.

Conclusions: Cancer signaling is shaped by a complex, adaptive network rather than isolated pathways. Therapeutic success will depend on integrated strategies that target signaling interactions. Regional implementation requires context-specific solutions, including minimal biomarker panels, expanded diagnostics, and collaborative infrastructure.

Keywords: tumor microenvironment; tumor escape; intercellular signaling peptides and proteins; signal transduction; epithelial-mesenchymal transition.

Resumen

Introducción: La transducción de señales aberrantes es una característica distintiva del cáncer, que regula la proliferación, la supervivencia, la pluripotencia, la evasión inmune y la resistencia terapéutica. Las vías MAPK, PI3K/AKT/mTOR y Wnt/β-catenina están frecuentemente alteradas en tumores sólidos y actúan como ejes regulatorios clave dentro de una red interconectada de señales.

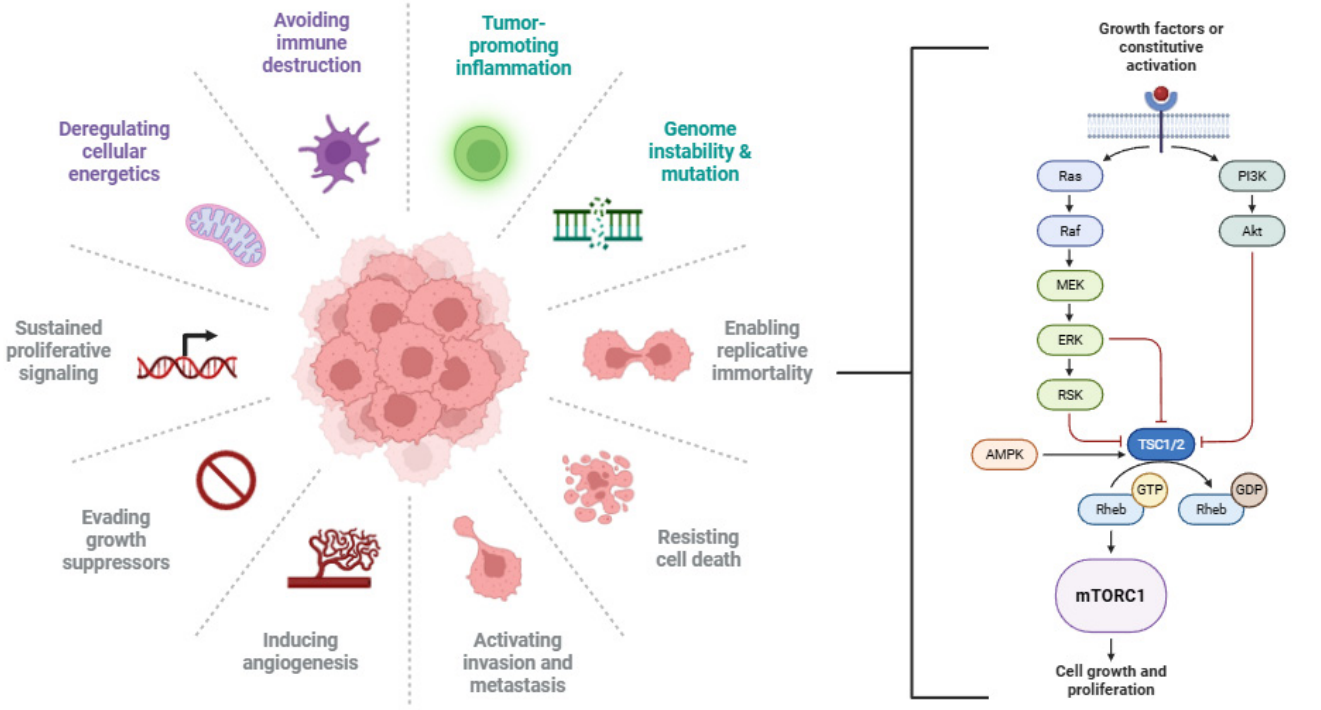
Métodos: Se realizó una revisión exhaustiva de la literatura centrada en la estructura, los mecanismos de activación, las alteraciones oncogénicas y las interacciones entre las vías MAPK, PI3K/AKT/mTOR y Wnt/β-catenina. Se analizaron datos preclínicos y clínicos sobre estrategias terapéuticas dirigidas y se examinaron los desafíos específicos para su implementación en América Latina.

Resultados: La vía MAPK se encuentra frecuentemente desregulada por mutaciones en RAS y BRAF, promoviendo una proliferación descontrolada. Las alteraciones en PI3K/AKT/mTOR, como mutaciones en PIK3CA y pérdida de PTEN, impulsan el crecimiento y la reprogramación metabólica. La activación de Wnt/β-catenina favorece la pluripotencia y la evasión inmune, frecuentemente a través de mutaciones en APC o CTNNB1. La comunicación cruzada entre estas vías amplifica la señalización oncogénica y contribuye a la resistencia terapéutica. Las estrategias de inhibición dual muestran resultados promisorios, pero están limitadas por toxicidad y retroalimentación compensatoria. Se investigan biomarcadores funcionales y combinaciones terapéuticas para superar estas limitaciones. En América Latina, el acceso a diagnóstico molecular y terapias dirigidas sigue siendo limitado, aunque hay avances en la expansión de la oncología de precisión.

Conclusiones: La señalización oncogénica en cáncer se define por redes adaptativas complejas, no por vías aisladas. El éxito terapéutico requiere estrategias integradas que aborden estas interacciones. Su implementación regional demanda soluciones contextuales, como paneles biomarcadores estratégicos, diagnóstico expandido e infraestructura colaborativa.

Palabras clave: microambiente tumoral; escape del tumor; péptidos y proteínas de señalización intercelular; transducción de señal; transición epitelial-mesenquimal.

Graphical abstract



This graphical abstract depicts the hallmarks of cancer and their underlying mechanisms, driven but multiple intracellular signal transductions that are parallel and that crosstalk.

Key points

- Cellular signal transduction is a fundamental process in the development and progression of cancer.
- The mitogen-activated protein kinase (MAPK)-dependent transduction pathway comprises several signaling components that play a crucial role in tumorigenesis.
- The phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR signaling pathway is essential for tumor cell growth and survival and often contributes to oncogenesis.
- Aberrant activation of Wnt/β-catenin signaling results in the accumulation of β-catenin in the nucleus, promotes the transcription of numerous oncogenes, and contributes to tumor progression.
- Targeted therapy against the MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin pathways offer promising therapeutic strategies.

Introduction

Cancer biology and cellular signaling are inseparable. At every stage of oncogenesis, from malignant transformation to metastatic dissemination, cells rely on a myriad of dynamic molecular networks in which growth factors, cytokines, the extracellular matrix (ECM), and intracellular stress interact. Oncogenesis is a continuous yet parallel process in which everything within and around a cell destined to become malignant interacts, and, as a result of stochastic events, cancer arises [1]. The conceptual framework of the "hallmarks of cancer" underscores this reality: nearly all hallmarks are mediated by aberrant signaling, whether through sustaining proliferative signaling, resisting cell death, deregulating cellular energetics, or avoiding immune destruction [1].

The linear view of signaling pathways, once represented as unidirectional cascades, has been replaced with a systems biology perspective. Oncogenic signaling is not a linear process from receptor to transcription factor, but rather a complex web of interactions characterized by impaired redundancy, feedback, and plasticity. In this web, specific signaling axes function as hubs of integration. Central cancer signaling pathways are, in fact, crucial mechanisms for cells under homeostatic conditions that undergo deviations or alterations in their expected behavior [2].

The mitogen-activated protein kinase (MAPK) pathway drives proliferation and cell-cycle initiation, while the PI3K/AKT/mTOR pathway integrates growth factor and metabolic inputs. The Wnt/β-catenin pathway governs cell fate and stemness. Their relevance is underscored by the frequency of mutations affecting their components across various cancers [3–5]Nevertheless, these pathways are rarely executed in isolation. Crosstalk between MAPK and PI3K signaling enables tumors to evade inhibitors of either pathway. PI3K/Wnt interactions stabilize β-catenin and promote the growth of cancer stem cells (CSCs). MAPK/Wnt convergence influences transcriptional reprogramming. Furthermore, additional modulators such as Notch, Hedgehog, TGF-β/SMAD, JAK/STAT, NF-κB, and Hippo/YAP-TAZ interplay with these principal axes to shape tumor behavior [6,7].

This manuscript aims to provide a comprehensive review of signal transduction in cancer, emphasizing not only the canonical pathways but also their intersections. We begin by dissecting each major axis, followed by a discussion of its points of intersection and modulation by the tumor microenvironment (TME). We then turn to the clinical implications, highlighting lessons from targeted therapies, mechanisms of resistance, and opportunities for combination approaches. Finally, we evaluate these general concepts in a Latin American context, where the challenges of access and infrastructure must keep pace with the rapid progress of precision oncology.

Methods

This work is a narrative review based on a comprehensive and selective analysis of the current scientific literature regarding intracellular signal transduction pathways in cancer. We focused on three major pathways with established relevance in tumor biology: MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin. The review also includes discussion of secondary signaling axes that modulate or intersect with these primary routes, such as Notch, Hedgehog, TGF-β/SMAD, JAK/STAT, NF-κB, and Hippo/YAP-TAZ.

We conducted a structured search of peer-reviewed articles published in PubMed, Scopus, and Web of Science using combinations of the following keywords: "MAPK", "RAS", "PI3K/

AKT/mTOR", "Wnt/β-catenin", "signal transduction", "oncogenic signaling", "crosstalk", "targeted therapy", and "therapeutic resistance". The selection was restricted to publications in English, with emphasis on original research articles and high-impact reviews from the last 15 years. Foundational papers and landmark studies published earlier were included when relevant.

To contextualize the clinical implications in Latin America, we reviewed regional studies, policy documents, and reports on healthcare access, molecular diagnostics, and implementation of precision oncology in countries such as Colombia. Therapeutic data and biomarker strategies were synthesized from clinical trial publications and updated guidelines.

The final manuscript was organized into thematic sections describing the core architecture, oncogenic alterations, feedback regulation, and therapeutic relevance of each pathway. Crosstalk and integration with other signaling networks were analyzed based on experimental and clinical evidence. No statistical analyses were performed, as this is not a meta-analysis or systematic review.

Results

The MAPK Pathway: a primary driver of proliferation and differentiation

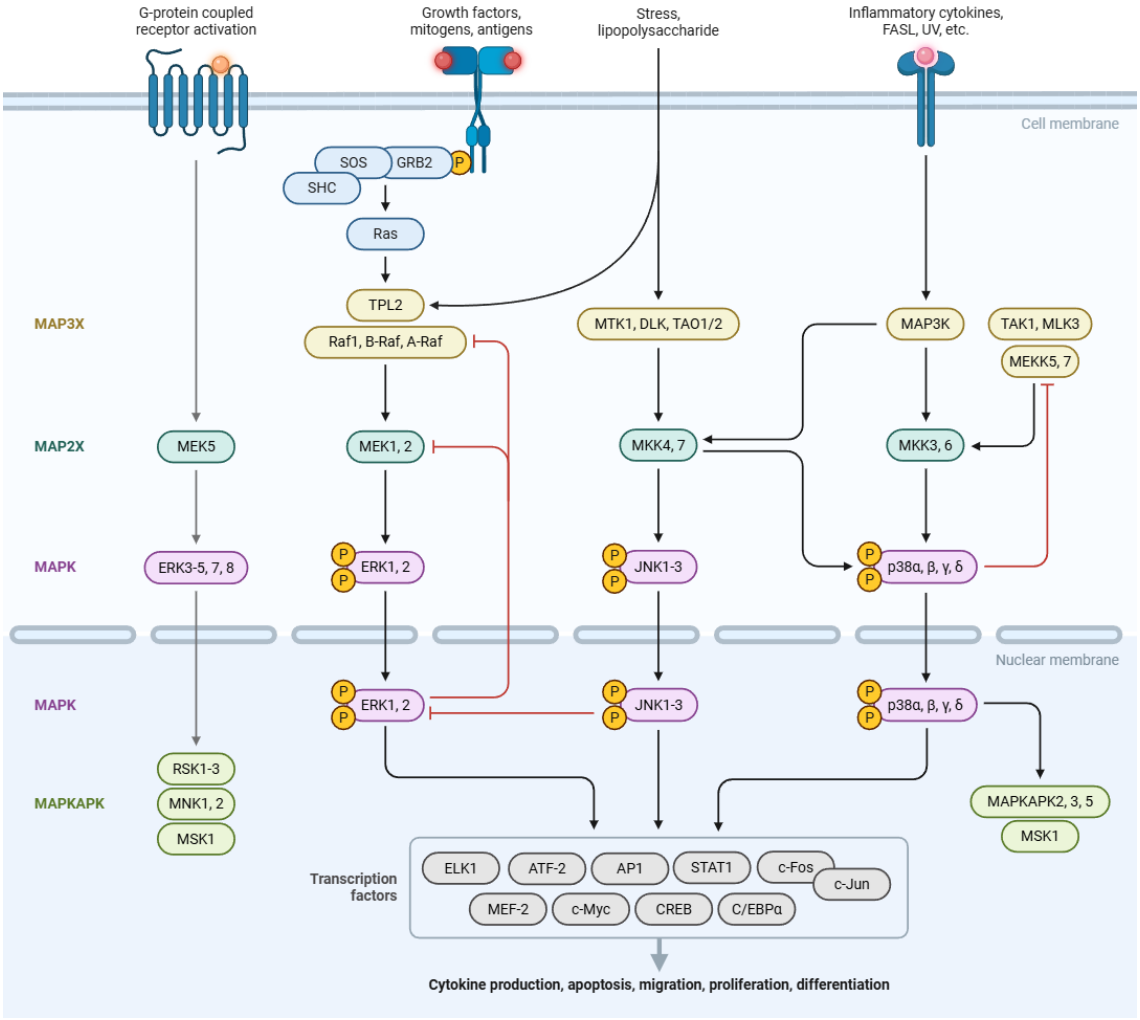
Core architecture: the MAPK pathway, also known as the RAS/RAF/MEK/ERK cascade, is one of the most conserved and central signaling pathways in eukaryotes. Activation typically begins at the plasma membrane when receptor tyrosine kinases (RTKs) such as EGFR, HER2, FGFR, or MET engage with their ligands and undergo autophosphorylation. Adapter proteins like GRB2 and SOS recruit and activate RAS, a small GTP-binding protein that cycles between inactive GDP-bound and active GTP-bound states [8]but mitogen-activated protein kinase (MAPK.

Activated RAS recruits RAF kinases (ARAF, BRAF, or CRAF), which dimerize and phosphorylate MEK1/2. MEK, a dual-specificity kinase, activates ERK1/2 through phosphorylation on threonine and tyrosine residues within the TEY motif [8]but mitogen-activated protein kinase (MAPK. Activated ERK translocates to the nucleus, where it phosphorylates transcription factors such as ELK1, c-FOS, and MYC, ultimately driving the expression of genes involved in proliferation, differentiation, and survival (Figure 1).

Oncogenic alterations: the oncogenic potential of MAPK signaling is highlighted by the prevalence of mutations in its main components. Mutations in RAS genes (KRAS, NRAS, and HRAS) are among the most common oncogenic drivers in human cancers, with KRAS mutations present in ~30% of lung adenocarcinomas, 40% of colorectal cancers, and 90% of pancreatic ductal adenocarcinoma cases [3,9]. BRAF mutations, particularly the V600E substitution, are highly prevalent in melanoma and thyroid cancer [10]. These mutations lock the pathway in a constitutively active state, bypassing upstream regulation and providing sustained proliferative signals. Furthermore, alterations in negative regulators such as DUSP phosphatases or SPROUTY proteins can further enhance MAPK output [11].

Figure 1.

The MAPK molecular pathway. This graph illustrates the various streams that comprise the MAPK pathway, including all the receptors and physiological processes associated with pathway activation, as well as the final transcription products that translate into distinct cellular processes.



Feedback and adaptive resistance: the MAPK cascade is characterized by multiple layers of negative feedback designed to limit signaling intensity and duration. Activated ERK induces expression of DUSPs, which dephosphorylate MAPKs, and SPRY proteins, which inhibit upstream RTK signaling. However, when inhibitors such as BRAF or MEK inhibitors are introduced, these feedback loops are relieved, leading to paradoxical reactivation of signaling [11]. For instance, in melanoma, treatment with BRAF inhibitors initially suppresses ERK activity but subsequently leads to upregulation of RTKs and NRAS activation, which reactivate MAPK signaling. This adaptive resistance underscores the pathway's plasticity and the challenge of achieving durable inhibition with single-agent therapy [12].

Crosstalk with other pathways: MAPK signaling overlaps extensively with other oncogenic axes:

- PI3K/AKT/mTOR: RAS directly interacts with and activates PI3K, linking cell division signaling to metabolic control [12]. Conversely, AKT can phosphorylate RAF, modulating its activity and providing a bypass route during MAPK inhibition.

- Wnt/β-catenin: ERK phosphorylates transcriptional regulators that cooperate with β-catenin, enhancing Wnt-driven transcription [5].

- FAK/SRC and integrins: Integrin-mediated adhesion activates FAK and SRC, which converge on ERK, providing growth factor–independent activation [13].

- mTOR signaling: ERK can activate mTORC1 through RSK-mediated phosphorylation of TSC2, linking mitogenic signaling to protein synthesis and growth [14]also known as protein kinase B (PKB.

Therapeutic targeting

The clinical translation of MAPK biology has been most prominent in melanoma, where BRAF inhibitors (vemurafenib, dabrafenib) combined with MEK inhibitors (trametinib, cobimetinib) have improved survival [15]. However, resistance typically arises through RAF dimerization, MEK mutations, or activation of parallel pathways. Next-generation ERK inhibitors are being explored, but their efficacy will likely also be constrained by compensatory signaling.

Combination strategies, such as MEK plus PI3K inhibitors or MAPK inhibition combined with immunotherapy, are being investigated to overcome these adaptive mechanisms. Importantly, biomarkers such as KRAS or BRAF mutations are essential for selecting patients most likely to benefit. Over the last decade, novel targeted therapies have demonstrated effectiveness in KRAS-mutated tumors, particularly in NSCLC, where adagrasib and sotorasib have been approved by the FDA, respectively [17].

The PI3K/AKT/mTOR Pathway: an integrator of growth, survival, and metabolism

Core architecture: the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway serves as a central integrator of growth factor signaling, metabolic cues, and survival pathways. Class I PI3Ks, heterodimers composed of a p110 catalytic subunit (α, β, γ, or δ) and a regulatory subunit (p85), phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 recruits pleckstrin homology domain–containing proteins, most notably AKT and PDK1, to the membrane. AKT is fully activated after phosphorylation at Thr308 (by PDK1) and Ser473 (by mTORC2) [16] (Figure 2).

Activated AKT phosphorylates a broad repertoire of substrates controlling cell cycle progression, apoptosis, metabolism, and growth. Key targets include:

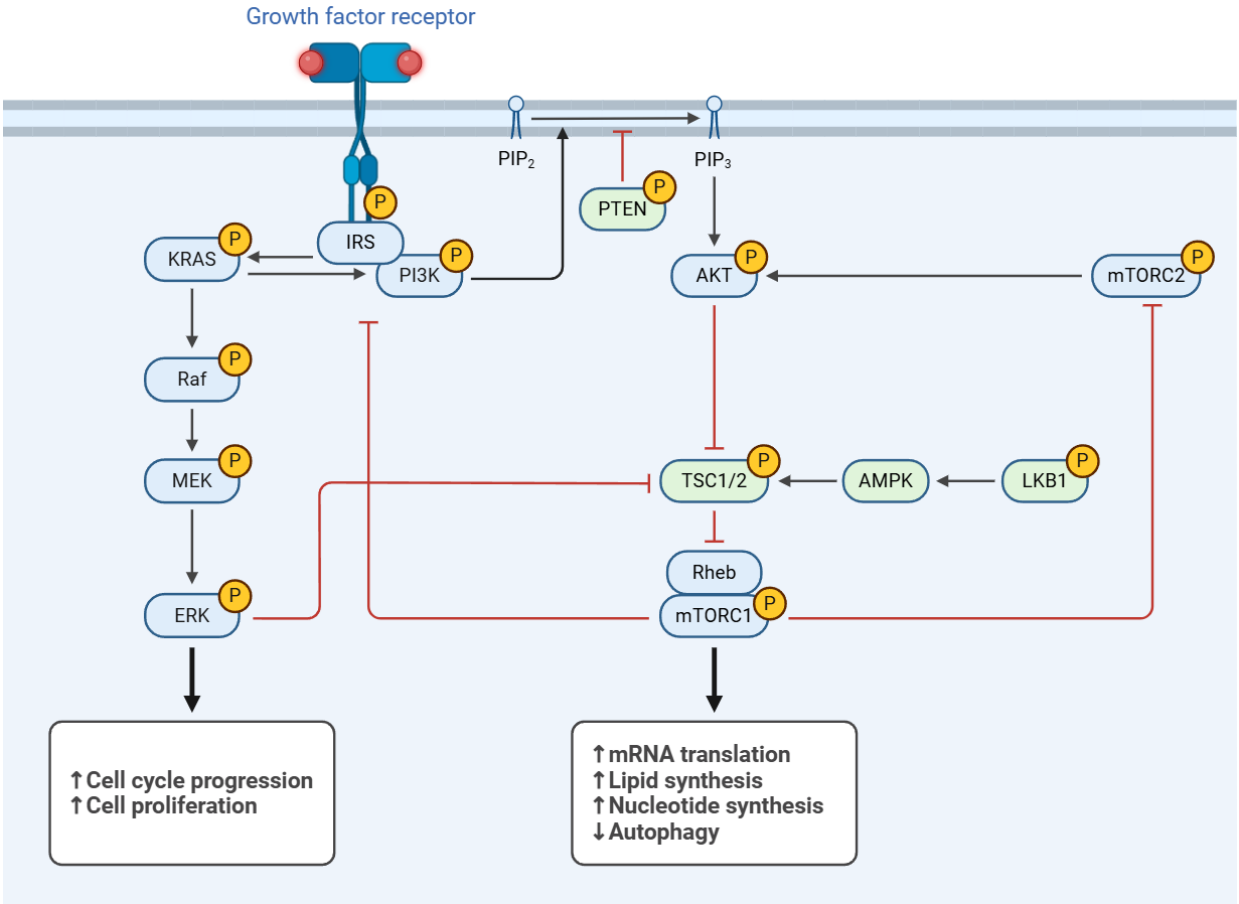
- TSC2: Phosphorylation inactivates the TSC1–TSC2 complex, relieving inhibition of mTORC1.

- FOXO transcription factors: Phosphorylation excludes them from the nucleus, suppressing transcription of pro-apoptotic genes.

- GSK3β: Inhibition stabilizes β-catenin, directly connecting PI3K/AKT to Wnt signaling.

- BAD: Phosphorylation prevents apoptosis by blocking pro-death BCL-2 family interactions.

Figure 2. The PI3K/Akt/mTOR pathway: a schematic representation of MAPK and PI3K/AKT/mTOR signaling cascades downstream of growth factor receptors, illustrating major nodes, feedback loops, and cellular outputs related to proliferation, metabolism, and survival.



The protein mTOR exists in two multiprotein complexes: mTORC1, containing Raptor, which regulates translation through 4EBP1 and S6K; and mTORC2, containing Rictor, which phosphorylates AKT, SGK, and regulates cytoskeletal dynamics [14]also known as protein kinase B (PKB.

Oncogenic alterations: aberrant activation of PI3K/AKT/mTOR is one of the most common features across solid tumors. Mechanisms include:

- PIK3CA mutations: Frequently seen in breast, colorectal, and endometrial cancers, often in helical (E542K, E545K) or kinase (H1047R) domains.
- PTEN loss: A tumor suppressor phosphatase that degrades PIP3; its deletion or mutation unleashes PI3K signaling.
- AKT amplification or mutation: e.g., AKT1 E17K in breast and bladder cancers.

- RTK amplification: HER2, EGFR, or MET can hyperactivate PI3K.

- mTOR mutations: Rare but contribute to constitutive activity.

These alterations drive uncontrolled growth and survival, often coexisting with mutations in MAPK pathway genes, underscoring the need for integrative analysis.

Feedback and resistance: mTORC1 activation triggers negative feedback through S6K-mediated phosphorylation of IRS1, attenuating upstream signaling. When mTORC1 is pharmacologically inhibited (e.g., with rapalogs), this brake is lifted, paradoxically enhancing PI3K/AKT activation [12]. Similarly, PI3K inhibition can relieve negative regulation of RTKs, leading to reactivation of MAPK signaling. These feedback loops complicate therapeutic targeting and contribute to the development of resistance.

Crosstalk with other networks: the PI3K/AKT/mTOR axis is deeply interconnected with other oncogenic pathways:

- MAPK: RAS directly activates PI3K; AKT modulates RAF activity.

- Wnt/β-catenin: AKT phosphorylation of GSK3β stabilizes β-catenin, enhancing stemness.

- Hippo/YAP–TAZ: AMPK and mTOR regulate YAP/TAZ activity, linking energy sensing to mechanotransduction.

- NF-κB: AKT phosphorylates IKK, promoting inflammatory transcriptional programs.

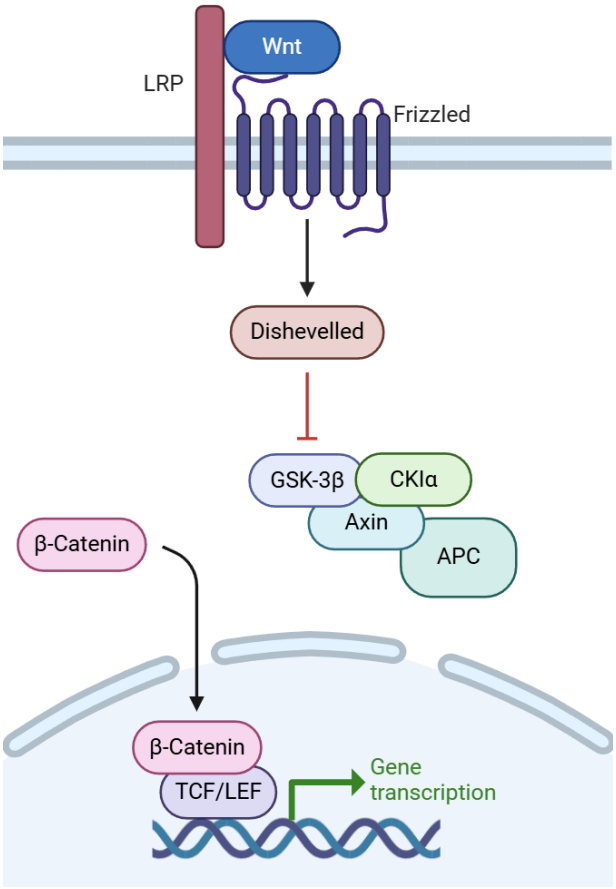
Therapeutic targeting: therapeutics include isoform-specific PI3K inhibitors (e.g., alpelisib for PIK3CA-mutant breast cancer), pan-PI3K inhibitors, AKT inhibitors (capivasertib, ipatasertib), and mTOR inhibitors (everolimus, temsirolimus). Clinical responses are heterogeneous: alpelisib improves progression-free survival in PIK3CA-mutant hormone receptor–positive breast cancer, but resistance often develops through RTK upregulation, MAPK reactivation, or metabolic rewiring [17].

Combination strategies such as PI3K plus CDK4/6 inhibitors in breast cancer, or PI3K plus MEK inhibitors in RAS-mutant tumors are under investigation [18]. Biomarker selection is crucial, but functional readouts (pAKT, pS6, metabolic flux) may be as important as static genomic markers.

The Wnt/β-catenin Pathway: the regulator of cell fate, plasticity, and immune evasion

Canonical Wnt signaling: in the absence of Wnt ligands, β-catenin is bound by a destruction complex composed of APC, AXIN, GSK3β, and CK1, which phosphorylates β-catenin, targeting it for ubiquitination and proteasomal degradation. Wnt ligand binding to Frizzled and LRP5/6 receptors recruits Dishevelled, disrupts the destruction complex, and stabilizes β-catenin. Nuclear β-catenin associates with TCF/LEF transcription factors to activate genes driving proliferation (e.g., MYC, CCND1) and stemness [19] (Figure 3).

Figure 3. Canonical Wnt/β-catenin pathway: after ligand binding, Frizzled/LRP receptors activate Dishevelled, inhibit the β-catenin destruction complex (APC, Axin, CK1α, GSK-3β), and enable β-catenin nuclear translocation to drive TCF/LEF-dependent transcription.



Non-canonical pathways:

- Planar cell polarity (PCP): Involving Rho, Rac, and JNK, regulating migration and polarity.
- Wnt–Ca^{2+} pathway: Activates CaMKII and NFAT, influencing cytoskeletal remodeling.

These pathways contribute to metastasis and invasion, often working in conjunction with EMT programs.

Oncogenic alterations: aberrant Wnt signaling is common in CRC, where truncating APC mutations occur in ~80% of cases, and CTNNB1 mutations stabilize β-catenin [5]. RNF43 mutations, which impair negative regulation of Wnt receptors, are seen in pancreatic and gastric cancers. Overproduction of Wnt ligands by stromal cells reinforces the signaling pathway.

Crosstalk with other pathways: Wnt signaling interfaces extensively with other oncogenic axes:

- PI3K/AKT: AKT-mediated inhibition of GSK3β enhances β-catenin stabilization.
- TGF-β/SMAD: Cooperates with Wnt in EMT and fibrosis-like tumor phenotypes.
- YAP/TAZ: Co-regulators that can synergize with or antagonize β-catenin transcription.
- MAPK: ERK phosphorylation of LEF/TCF enhances transcriptional output [8]but mitogen-activated protein kinase (MAPK.

Immune exclusion and resistance: tumor-intrinsic Wnt/β-catenin activation is associated with "cold" tumors characterized by T-cell exclusion. Mechanistically, β-catenin suppresses chemokine expression, such as CCL4, thereby impairing dendritic cell recruitment and T-cell priming [20]. This explains the resistance of Wnt-active tumors to checkpoint inhibitors.

Therapeutic targeting: therapies include PORCN inhibitors (e.g., WNT974), which block Wnt ligand secretion, Frizzled receptor antibodies, and β-catenin destabilizers [21]. Toxicities, particularly gastrointestinal, remain a challenge due to Wnt's role in intestinal homeostasis. Combinations with immunotherapy are under study to overcome immune evasion.

The Crosstalk among Major Pathways: the oncogenic potential of MAPK, PI3K/AKT/mTOR, and Wnt signaling lies not only in their individual functions but also in their capacity to reinforce one another. This crosstalk is the cornerstone of therapeutic resistance.

MAPK–PI3K interplay: RAS serves as a direct upstream activator of both RAF and PI3K, allowing simultaneous activation of MAPK and PI3K/AKT. Inhibiting one pathway often induces compensatory activation of the other. For instance, MEK inhibition relieves negative feedback on insulin receptor signaling, thereby hyperactivating the PI3K/AKT pathway [12]. Conversely, PI3K inhibition can activate ERK by upregulating RTKs.

PI3K–Wnt convergence: through inhibition of GSK3β, AKT stabilizes β-catenin, amplifying Wnt transcriptional programs. This convergence is particularly relevant in cancers with both PIK3CA and APC/CTNNB1 alterations, which display aggressive phenotypes and stem-like properties.

MAPK–Wnt interaction: ERK enhances β-catenin transcriptional activity by phosphorylating TCF/LEF factors, facilitating oncogenic transcriptional reprogramming. MAPK also influences Wnt ligand expression, creating a feedforward loop [7].

Integration with other pathways:

- Notch signaling intersects with Wnt in the regulation of stemness and differentiation.
- Hedgehog signaling cooperates with PI3K and TGF-β to sustain EMT.
- Hippo/YAP–TAZ acts as a mechanosensory hub connecting integrins, FAK, and cytoskeletal inputs to MAPK and Wnt.
- JAK/STAT and NF-κB further integrate inflammatory and cytokine signals with these core oncogenic nodes.

Clinical implications of crosstalk: Crosstalk mechanisms explain why single-pathway inhibitors often fail. Dual inhibition strategies such as MEK plus PI3K inhibitors show preclinical promise but are limited by toxicity [18]. Rationally designed regimens may be more effective. Understanding the context-dependent hierarchy of pathways in each tumor type is crucial for overcoming resistance [24].

Therapeutic Implications and Clinical Translation

Lessons learned from targeted therapies: The MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin pathways are central therapeutic targets. Successes include BRAF plus MEK inhibitors in melanoma[15] and PI3Kα inhibitors in PIK3CA-mutant breast cancer [17]. Yet in most cases, initial responses give way to resistance due to reactivation of the pathway or compensatory signaling. Wnt inhibitors remain largely investigational but are promising, particularly in tumors resistant to immunotherapy [22].

Mechanisms of therapeutic resistance: resistance mechanisms are diverse:

- MAPK reactivation: secondary NRAS mutations, BRAF splice variants, or MEK mutations.
- PI3K rebound: RTK upregulation or PTEN loss underlies resistance to PI3K inhibitors.
- Wnt plasticity: stromal Wnt ligand secretion circumvents tumor cell–intrinsic inhibition.
- TME-driven resistance: TAMs secrete HGF, activating MET and downstream PI3K/

MAPK; CAFs remodel ECM stiffness, activating FAK/YAP.

Combinatorial and adaptive strategies: rational approaches include:

- Vertical inhibition: blocking multiple nodes in the same pathway (e.g., BRAF + MEK + ERK).
- Horizontal inhibition: simultaneously targeting parallel pathways (e.g., MEK + PI3K).
- Integration with immunotherapy: MAPK and PI3K signaling modulate PD-L1 expression and antigen presentation, while Wnt/β-catenin contributes to T-cell exclusion. Trials are testing MEK plus PD-1 blockade or PI3Kγ inhibition plus checkpoint therapy [20,23].
- Adaptive dosing: intermittent schedules may mitigate toxicities and prevent feedback-driven resistance.

Biomarkers for patient stratification: precision targeting requires biomarkers. Genomic alterations (KRAS, BRAF, PIK3CA, PTEN, APC, CTNNB1) guide patient selection, but dynamic biomarkers such as phospho-ERK, phospho-AKT, or nuclear β-catenin may better reflect pathway activity. Liquid biopsies capturing circulating tumor DNA (ctDNA) and exosomal signatures offer minimally invasive tools for real-time monitoring [24].

Perspectives in Latin America and Colombia: implementation of pathway-targeted therapies in Latin America faces barriers, including limited access to molecular diagnostics, variable drug availability, and fragmented healthcare systems[25]. Yet progress is being made as next-generation sequencing panels are increasingly available in referral centers in Colombia, and molecular testing for KRAS/NRAS/BRAF in colorectal cancer is now standard practice.

Opportunities include:

- Minimal but strategic biomarker panels: focusing on high-yield mutations (KRAS/NRAS, BRAF, PIK3CA, PTEN, APC, CTNNB1, HER2).
- Expanded immunohistochemistry: assessing phospho-proteins (ERK, AKT, S6) and nuclear β-catenin as surrogates of activity.
- Collaborative biobanks and organoid platforms: to test pathway inhibitors ex vivo.
- Clinical trials inclusion: international collaborations to increase patient access to novel inhibitors and immunotherapy combinations.

By strengthening molecular oncology infrastructure, Colombia and neighboring countries can integrate pathway-based therapies into clinical care, reducing disparities in cancer outcomes.

Conclusions

Oncogenic signaling in cancer is not the product of isolated pathways but an emergent property of a dense, adaptive network. The MAPK, PI3K/AKT/mTOR, and Wnt/β-catenin pathways exemplify this principle, functioning as hubs of proliferation, metabolism, and cell fate while extensively communicating with one another and with auxiliary networks. Their integration

with tumor microenvironmental cues further enhances tumor plasticity and resilience.

Therapeutic progress has been achieved through pathway-specific inhibitors, but adaptive resistance remains the rule. Recognizing the centrality of crosstalk invites a paradigm shift: therapies must target signaling networks rather than linear cascades. Rational combinations, functional biomarkers, and integration with immunotherapy will be essential to translate molecular insights into durable clinical benefit.

In Latin America and Colombia, where healthcare resources are variable, implementing precision oncology requires innovative strategies that balance cost-effectiveness with scientific rigor. Building diagnostic capacity, fostering regional research collaborations, and securing access to clinical trials are necessary steps toward equitable delivery of cutting-edge cancer care.

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Authorship contribution The authors declare that the study is original. Both authors contributed equally to the design, execution, and revision of the final text.

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