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Targeting Oncogenic Pathways In Cancer: Therapeutic Advances, Challenges, And Future Directions

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Cancer represents a multifaceted global health burden shaped by diverse genetic, epigenetic, and environmental factors. The GLOBOCAN 2022 data emphasize the growing incidence and regional variation of cancers such as breast, lung, colorectal, and oral malignancies. Underlying this burden are complex oncogenic signaling pathways—including Wnt/ß-catenin, Notch, Hedgehog, PI3K/AKT/mTOR, and JAK/STAT—that regulate cell proliferation, apoptosis, and metastasis. While therapeutic interventions targeting these pathways have shown promise, durable clinical outcomes remain limited due to pathway redundancy, crosstalk, and tumor heterogeneity. This review systematically explores these signaling networks, detailing current and investigational therapeutic targets and the clinical progress of pathway-specific inhibitors. We identify critical gaps in translating molecular insights into personalized therapies and emphasize the need for integrated, multi-targeted approaches. By synthesizing recent advances in molecular oncology and emerging therapeutic strategies, this work offers a forward-looking perspective on overcoming current challenges and optimizing cancer treatment paradigms.

Keywords: Cancer types; Global Burden; Malignancies; Molecular Pathways; Signaling.

Cancer is a biologically complex and multifactorial disease characterized by the uncontrolled proliferation and spread of abnormal cells. It arises from a combination of genetic mutations, environmental exposures, lifestyle factors, and infectious agents.[1] Despite the diverse triggers, a common hallmark across all cancer types is the disruption of regulatory mechanisms governing cell growth, division, and apoptosis—resulting in malignant tumor formation and potential metastasis.[2,3]

Globally, cancer poses a major public health burden, transcending geographic and socioeconomic boundaries. According to recent estimates, its growing incidence and mortality exert significant pressure on healthcare systems, economies, and the quality of life worldwide.[4,5] This challenge necessitates an integrated, multidisciplinary response that combines scientific research, clinical practice, and public health policy.[4]

Over the past decades, advancements in genomics, molecular biology, and epidemiology have enhanced our understanding of cancer etiology and risk. Modifiable factors such as tobacco use, poor diet, physical inactivity, and exposure to

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carcinogens, along with non-modifiable factors like age and genetic predisposition, collectively influence cancer risk.[6] Prevention strategies—including lifestyle interventions, environmental regulations, and vaccination programs against oncogenic infections—have become key tools in reducing incidence.[7]

Meanwhile, the emergence of targeted therapies, immunotherapies, and precision medicine has transformed cancer treatment paradigms. Yet, tumor heterogeneity and the complexity of molecular alterations continue to challenge therapeutic effectiveness.[7,8] To address this, a deeper exploration of the cellular and molecular pathways that drive cancer is essential.

This review provides a focused overview of the global cancer burden and delves into the core biological mechanisms of tumor progression. It highlights five major oncogenic pathways—Wnt/â-catenin, Notch, Hedgehog, PI3K/AKT/mTOR, and JAK/STAT—and evaluates their relevance as therapeutic targets. By synthesizing current knowledge and clinical advances, this review aims to inform future strategies for cancer treatment and contribute to the evolving landscape of precision oncology.

Literature Search Methodology

To ensure comprehensive coverage of the subject matter, a detailed literature search was conducted using multiple scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy was designed to identify peer-reviewed publications relevant to cancer signaling pathways and therapeutic interventions, with a particular focus on five major pathways: Wnt/â-catenin, Notch, Hedgehog, PI3K/AKT/mTOR, and JAK/STAT. The search included studies published between January 2010 and April 2024, using combinations of keywords such as "cancer signaling pathways," "targeted therapy," "Wnt inhibitors," "Notch signaling in cancer," "Hedgehog pathway antagonists," "PI3K/AKT/mTOR inhibitors," and "JAK/STAT pathway blockade." Only articles published in English were considered. Studies were selected based on their relevance to therapeutic targeting in cancer, with a preference for original research, systematic reviews, and clinical trial reports. Editorials, non-peer-reviewed articles, and studies not directly related to the scope of cancer signaling or therapeutic application were excluded. The final selection of sources emphasized scientific rigor, therapeutic relevance, and recency, prioritizing high-impact journals and landmark clinical data to ensure the review provides a robust and up-to-date synthesis.

Global cancer burden

Cancer is a major threat to the health of people everywhere. Cancer poses a significant global health challenge, with approximately 19.7 million new cases and nearly 10 million deaths reported worldwide in 2022 (Fig.1).[9-11] The GCO's 2022 data reveals the global cancer burden and emphasizes the intricate interactions between hereditary, environmental, and lifestyle factors.[11] The patterns of cancer incidence and mortality vary significantly across regions, underscoring the need for region-specific strategies to address this disease effectively.[10,11]

Globally, cancers of the trachea, bronchus, and lung are among the most common and are leading contributors to cancer mortality, particularly among males.[10] In contrast, breast cancer remains the most prevalent cancer among females and a significant cause of cancer-related deaths (Fig.2).[11] Asia, home to a substantial portion of the global population, bears the highest cancer burden (Fig.1). It accounts for a significant share of global cancer cases and deaths, with lung cancer leading as the primary cause of mortality in males and breast cancer ranking highest in incidence among females (Fig.3).[10,11]

In India, the trends align with these broader patterns, with breast cancer being the most common and fatal cancer among females. For males, lip and oral cavity cancers contribute significantly to the national cancer burden (Fig.4).[10,11] These variations emphasize the importance of tailored public health strategies to address specific cancer types within distinct demographic and geographic contexts.

Hallmarks of Cancer

Cancer cells exhibit a range of distinctive capabilities that enable tumor initiation, progression, and metastasis. These hallmark traits, first described by Hanahan and Weinberg, include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming energy metabolism, and avoiding immune

destruction. Additional emerging traits include genome instability, tumor-promoting inflammation, phenotypic plasticity, and non-mutational epigenetic reprogramming.[12-15]

• Sustaining Proliferative Signaling

Cancer cells acquire the ability to sustain chronic proliferation through mutations or overexpression of growth factor receptors (e.g., EGFR) and downstream signaling molecules (e.g., Ras, PI3K/AKT, MAPK).[12,13,15] These alterations decouple growth from external cues, supporting genomic instability and unchecked division.[14,16-18] Activating mutations in proto-oncogenes such as Ras and EGFR are among the most common drivers of this hallmark and are found in a significant proportion of lung, colon, and pancreatic cancers.[19-26] Targeted therapies such as Trastuzumab for HER2/neu and MEK inhibitors for Ras-driven tumors exemplify approaches that exploit this hallmark.[27-29]

• Evading Growth Suppressors

Mutations in tumor suppressor genes such as TP53 and RB1 disrupt cellular checkpoints that prevent proliferation under stress or DNA damage. Their loss facilitates unchecked growth and genomic instability.[12,13,15,29] Other tumor suppressors frequently inactivated in cancer include DPC4, which regulates TGF-â signaling, and NF1, which normally inhibits Ras signaling. Loss of these regulators is associated with tumor progression in several cancers, including colon and neurofibromatosis-associated malignancies.[30-33]

• Resisting Cell Death

Cancer cells often bypass apoptotic mechanisms by upregulating anti-apoptotic proteins (e.g., BCL-2) or downregulating pro-apoptotic factors, contributing to treatment resistance and tumor survival.[14,15] Restoration of tumor suppressor function, particularly p53, remains a therapeutic goal. Experimental compounds like PRIMA-1 and MIRA-1 aim to reactivate p53 function in mutated tumors, although clinical application remains challenging.[28,34]

• Enabling Replicative Immortality

Tumors achieve limitless replicative potential through telomerase reactivation, enabling cancer cells to bypass senescence and divide indefinitely.[12,14]

• Inducing Angiogenesis

To meet high metabolic demands, tumors secrete pro-angiogenic factors like VEGF, stimulating the formation of new blood vessels. However, this neo vasculature is often abnormal, contributing to hypoxia and therapeutic barriers.[12,14]

• Activating Invasion and Metastasis

Cancer cells undergo epithelial-mesenchymal transition (EMT), gaining motility and the ability to degrade extracellular matrices, facilitating metastasis to distant sites.[12-15,]

• Deregulating Cellular Energetics

Tumor cells favor aerobic glycolysis (the Warburg effect) over oxidative phosphorylation even in oxygen-rich conditions, enabling them to thrive in hypoxic, nutrient-poor environments.[12-14,16]

• Avoiding Immune Destruction

Cancer cells evade immune surveillance by expressing immune checkpoint molecules (e.g., PD-L1) or recruiting immunosuppressive cells, creating an immune-privileged tumor microenvironment.[12-15]

• Genome Instability and Mutation

Defects in DNA repair pathways (e.g., BRCA1/2 mutations) result in elevated mutation rates, increasing the likelihood of oncogenic alterations.[12,13,15] Genomic instability is also exacerbated by DNA replication errors, chromatin remodeling defects, and epigenetic dysregulation.[17]

• Tumor-Promoting Inflammation

Chronic inflammation releases cytokines and reactive oxygen species that promote DNA damage, proliferation, and metastasis.[12-15]

• Unlocking Phenotypic Plasticity

Cancer cells can transition between phenotypes, enabling adaptation to environmental changes and contributing to therapeutic resistance.[12-14]

• Non-Mutational Epigenetic Reprogramming

Altered DNA methylation and histone modifications can silence tumor suppressor genes or activate oncogenes without changing DNA sequences, driving malignancy.[12-14]

• Disruption of Cell Cycle Regulation

Dysregulation of cyclins (e.g., cyclin D, cyclin E) and cyclin-dependent kinases (CDK4/6) enables unchecked progression through the cell cycle.[35-39] Loss of checkpoint proteins such as p21 and p27, along with inactivation of p53 and RB1, disables critical cell cycle arrest mechanisms that typically respond to DNA damage and genomic instability.[36,37] These defects allow cancer cells

to bypass the G1/S checkpoint, resulting in uncontrolled proliferation. In some cancers, such as breast cancer, overexpression of cyclin E leads to premature S-phase entry and replication stress. Targeted therapies like CDK4/6 inhibitors (e.g., Palbociclib) aim to restore control over these deregulated checkpoints and have shown clinical efficacy, particularly in hormone receptor-positive breast cancer.[38,39]

Collectively, these hallmark traits represent the biological foundation of cancer and are sustained by complex networks of dysregulated signaling pathways. Rather than operating in isolation, these traits are often interconnected and reinforced by aberrant molecular cascades that regulate cell proliferation, survival, angiogenesis, immune evasion, and metastasis. Central among these are the Wnt/â-catenin, Notch, Hedgehog, PI3K/AKT/mTOR, and JAK/STAT pathways, which act as key molecular drivers behind many of these malignant capabilities. Understanding how these pathways intersect with specific hallmarks is essential for developing more effective and precise therapeutic strategies.

Pathways responsible for cancer development and their therapeutic targets

Genetic and epigenetic alterations that impair regular cellular processes, permitting unchecked cell proliferation and evasion of the body's natural survival and migratory restrictions, are the cause of cancer's formation and spread. These alterations affect the pathways that regulate cell division, growth, fate, and movement. Additionally, they support wider networks that influence the course of cancer development.[40-42] This includes angiogenesis, inflammation, changes in the tumor microenvironment, and resistance to radiation and chemotherapy. The alteration in pathways including NOTCH, WNT, Hedgehog, PI3K/AKT/mTOR, or JAK-STAT can give cancer cells multiple functions such drug efflux, activation of stem cell genes, and resilient to senescence and programmed cell death.[42,43] However, these pathways are complex, interrelated, and regulated by feedforward and feedback and hence it will be difficult to create treatments that target one pathway while ignoring others.[44,45]

Wnt/â-Catenin Signaling Pathway

The Wnt/â-catenin signaling pathway is a highly conserved cascade essential for embryonic development, tissue homeostasis, and stem cell renewal.[44,46,47] In the canonical pathway, Wnt ligands bind to Frizzled (FZD) receptors and LRP5/6 co-receptors, inhibiting the â-catenin destruction complex composed of Axin, APC, and GSK-3â. This inhibition stabilizes â-catenin, allowing it to accumulate in the cytoplasm and translocate to the nucleus, where it activates transcription of target genes involved in proliferation and survival.[44,48-50]

Aberrant activation of the Wnt/â-catenin pathway contributes to the initiation and progression of various cancers, including colorectal, breast, liver, and melanoma. Mutations in APC, CTNNB1 (encoding â-catenin), or other components result in constitutive activation, leading to unchecked cellular proliferation, invasion, and resistance to apoptosis.[51,52,53] Multiple therapeutic strategies are being explored to inhibit the Wnt/â-catenin pathway (Table 1):

• PORCN inhibitors, such as LGK974, WNT974, ETC-1922159, RXC004, and CGX1321 (with pembrolizumab) prevent the palmitoylation and secretion of Wnt ligands, limiting pathway activation in tumors such as melanoma, breast, pancreatic, and gastrointestinal cancers.[44,55]

• Frizzled receptor antagonists, including OMP-18R5 and OTSA101-DTPA-90Y, block Wnt ligand binding and receptor activation.[44]

• FZD8 decoy receptors, such as OMP-54F28, act as soluble traps for Wnt ligands, showing early promise in liver, pancreatic, and ovarian cancers.[44]

• CBP/â-catenin antagonists like PRI-724 and â-catenin gene expression inhibitors like SM08502 inhibit downstream transcriptional activity, targeting cancers such as pancreatic and solid tumors.[44]

• Wnt5a mimetic agents like Foxy-5 modulate non-canonical Wnt signaling and are under investigation in colon cancer.[54]

• Wnt ligand inhibitors, such as Plumbagin, have shown preclinical efficacy in endocrine-resistant breast cancer models.[44]

Several of these agents are in various phases of clinical trials, from preclinical to phase II.[44,48-54] While these approaches have demonstrated potential, challenges remain, particularly due to the essential role of Wnt signaling in normal tissue regeneration, leading to toxicity concerns. Resistance mechanisms and biomarker identification for patient stratification are

ongoing hurdles.[44,53-55] Selective and combinational targeting of the Wnt/â-catenin pathway—guided by predictive biomarkers—offers a promising direction for precision oncology. Further research is needed to enhance target specificity and mitigate off-target effects in non-tumor tissues.

Notch Signaling Pathway

The Notch signaling pathway is a critical mediator of cell fate decisions, differentiation, proliferation, and apoptosis.[44,56] It operates through direct cell-to-cell communication: when Notch ligands (e.g., Jagged or Delta-like) from one cell bind to Notch receptors on an adjacent cell, the receptor undergoes proteolytic cleavage by ã-secretase, releasing the Notch intracellular domain (NICD). The NICD translocates to the nucleus and activates gene transcription by interacting with CSL transcription factors. Dysregulated Notch signaling has been implicated in both oncogenic and tumor-suppressive roles, depending on cellular context and cancer type. Constitutive Notch activation promotes tumor progression in T-cell acute lymphoblastic leukemia (T-ALL), breast cancer, colorectal cancer, and pancreatic cancer. Conversely, Notch can suppress tumors in certain squamous cell carcinomas.[44,56,57] Efforts to therapeutically modulate Notch signaling have yielded several investigational approaches (Table 1):

• ã-Secretase inhibitors (GSIs), such as PF-03084014, BMS-906024, MK-0752, and RO4929097, prevent NICD release and inhibit downstream transcription. These agents are under investigation across a variety of cancers, including T-ALL, breast, renal, pancreatic, and non-small cell lung cancer (NSCLC).[57,58,59]

• Monoclonal antibodies, including Enoticumab, Demcizumab, Tarextumab, and Brontictuzumab, target Notch receptors or ligands to disrupt pathway activation. They are being evaluated in solid and hematological malignancies, such as ovarian, pancreatic, lung, and breast cancers.[33,57]

• DLL3-targeting agents, notably rovalpituzumab tesirine, have shown activity in neuroendocrine carcinomas like small cell lung cancer.[58,59]

• CB-103, a newer investigational agent, disrupts Notch transcriptional activation and is being studied in both solid and hematological cancers.[58,59]

Several GSIs and monoclonal antibodies have progressed to early-phase clinical trials. Although some show activity in hematologic and solid tumors, dose-limiting gastrointestinal toxicities (due to inhibition of Notch in intestinal epithelium) have limited clinical utility. Moreover, dual roles of Notch in tumorigenesis necessitate precise context-specific targeting. Future strategies must prioritize targeted delivery systems, biomarker-based patient stratification, and combination therapies to harness the pathway's therapeutic potential while mitigating adverse effects. The continued development of agents such as CB-103 and antibody-drug conjugates may expand the clinical applicability of Notch-targeted therapies.[44,56-59]

Hedgehog (Hh) Signaling Pathway

The Hedgehog (Hh) signaling pathway plays a vital role in embryonic development, tissue regeneration, and stem cell maintenance.[48,60,61] The pathway is initiated when Hh ligands (Sonic, Indian, or Desert Hedgehog) bind to the Patched (PTCH) receptor, relieving its inhibition of Smoothened (SMO), a G-protein-coupled receptor-like protein. Activated SMO triggers intracellular signaling cascades that activate GLI transcription factors, which regulate target gene expression. Aberrant Hh signaling is implicated in the pathogenesis of various cancers, particularly basal cell carcinoma (BCC), medulloblastoma, pancreatic, and prostate cancers. Mutations in PTCH or activating mutations in SMO can lead to ligand-independent constitutive pathway activation, driving proliferation and tumorigenesis.[60-63]

Several inhibitors have been developed to target key components of the Hh pathway (Table 1):

• SMO inhibitors, including vismodegib, sonidegib, and glasdegib, block the activation of downstream signaling and are approved or under evaluation for BCC, medulloblastoma, and pancreatic cancer.[48,60-63]

• GLI inhibitors, such as GANT61, arsenic trioxide, and itch inhibitors, target the final effectors of the pathway and are under preclinical or early-stage investigation for medulloblastoma, pancreatic, and other cancers. [48,60-63]

• PTCH inhibitors and antibody-based therapies, like 5E1 (anti-Shh antibody) and GDC-0449 (anti-SMO antibody), provide additional mechanisms for blocking upstream components of the pathway. [48,60-63]

• Downstream pathway modulators, such as BMS-

833923 and other GLI antagonists, are being explored for various solid tumors, including breast, lung, and pancreatic cancers. [48,60-63]

SMO inhibitors like vismodegib and sonidegib have received FDA approval for advanced BCC and have shown efficacy in clinical trials for other cancers. However, resistance—often via downstream mutations or GLI amplification—limits their long-term effectiveness. Toxicity, including muscle spasms and dysgeusia, also poses barriers to chronic use.

To overcome resistance and expand therapeutic applicability, next-generation Hh inhibitors targeting GLI and combination therapies with PI3K or immune checkpoint inhibitors are being explored. Precision medicine approaches based on genetic profiling may enhance patient selection and therapeutic efficacy. The development of antibody-based inhibitors and pathway-modulating agents like BMS-833923 represents promising avenues for future clinical impact.[48,60-63]

PI3K/AKT/mTOR Signaling Pathway

The PI3K/AKT/mTOR pathway is one of the most frequently altered signaling cascades in human cancers.[64] It plays a central role in regulating cell growth, survival, metabolism, and angiogenesis. Activation typically begins with receptor tyrosine kinases (RTKs), which stimulate phosphoinositide 3-kinase (PI3K) to convert PIP2 to PIP3, leading to the recruitment and activation of

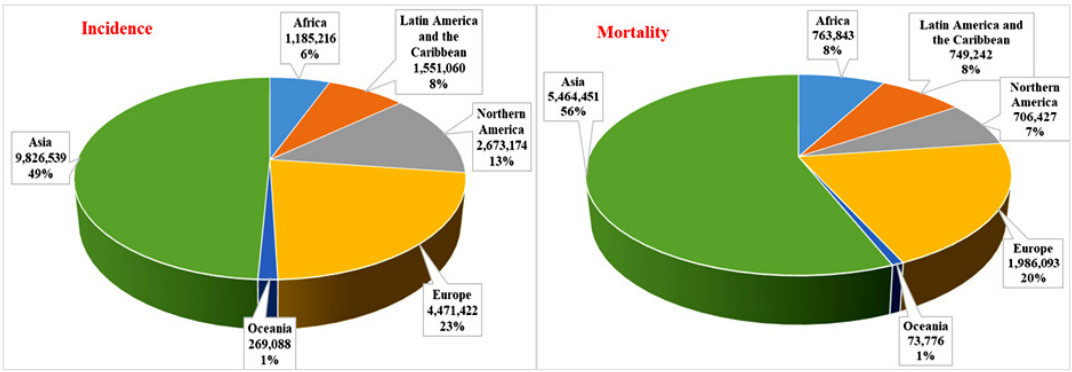

Fig. 1. Global Distribution of Cancer Mortality and Incidence by Region, Sourced from CANCER TODAY (https://gco.iarc.fr/today/), providing comprehensive data on the global cancer burden in 2022 from GLOBOCAN estimates for year 2022 across 185 countries, covering 36 cancer types by sex and age group.

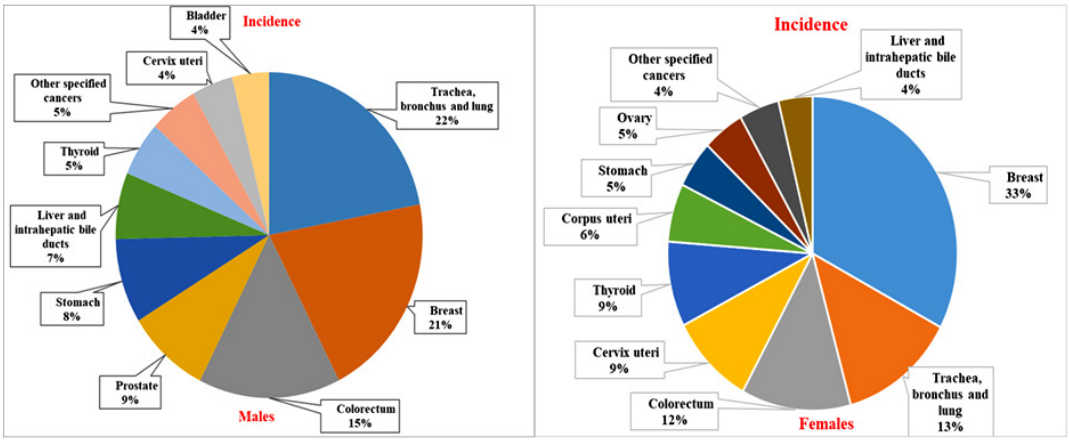

Fig. 2. Global Cancer Incidence Top 10 in male and female, Sourced from CANCER TODAY (https://gco.iarc.fr/today/), providing comprehensive data on the global cancer burden in 2022 from GLOBOCAN estimates for year 2022 across 185 countries, covering 36 cancer types by sex and age group.

AKT. AKT subsequently activates mTOR, a master regulator of protein synthesis and cell growth.[65,66]

Dysregulation of this pathway is observed in a wide range of malignancies, including breast, prostate, endometrial, colorectal, and glioblastoma. Oncogenic mutations in PIK3CA (encoding the catalytic subunit of PI3K), loss of PTEN (a tumor suppressor that inhibits PI3K activity), or amplification of AKT result in constitutive pathway activation, promoting proliferation, inhibiting apoptosis, and contributing to therapy resistance.[48,65-69] Several classes of inhibitors have been developed to target components of the PI3K/AKT/mTOR axis (Table 1):

• PI3K inhibitors (e.g., idelalisib, copanlisib, alpelisib) target specific isoforms or pan-PI3K activity.[65]
• AKT inhibitors (e.g., capivasertib, ipatasertib) block downstream signaling.[66]
• mTOR inhibitors (e.g., everolimus, temsirolimus) inhibit mTORC1 complex activity.[67,68]
• Dual PI3K/mTOR inhibitors (e.g., dactolisib) aim to overcome compensatory feedback loops.[68]

While mTOR inhibitors have received regulatory approval for certain cancers (e.g., renal cell carcinoma, breast cancer), responses are often modest and transient. Isoform-specific PI3K inhibitors (e.g., alpelisib in PIK3CA-mutant

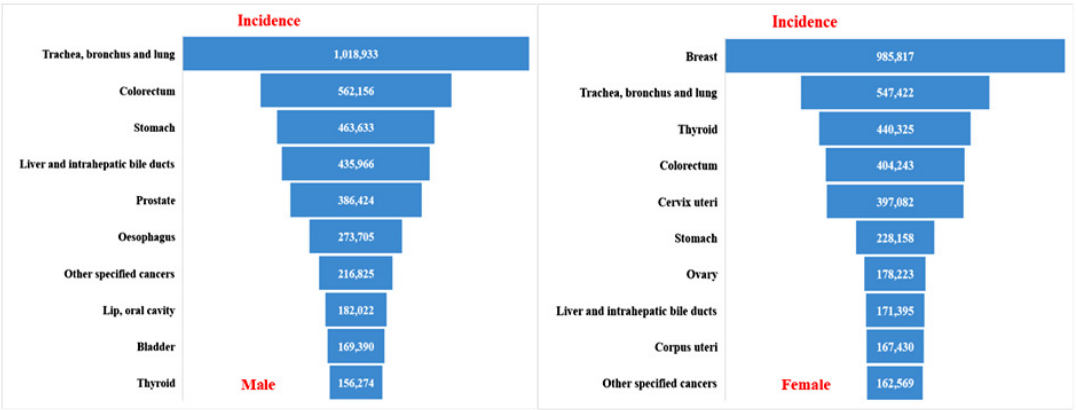

Fig. 3. Cancer Incidence Top 10 in male and female in Asia, Sourced from CANCER TODAY (https://gco.iarc.fr/today/), presenting detailed insights into cancer prevalence in 2022 based on GLOBOCAN estimates for year 2022 across 185 countries, covering 36 cancer types by sex and age group.

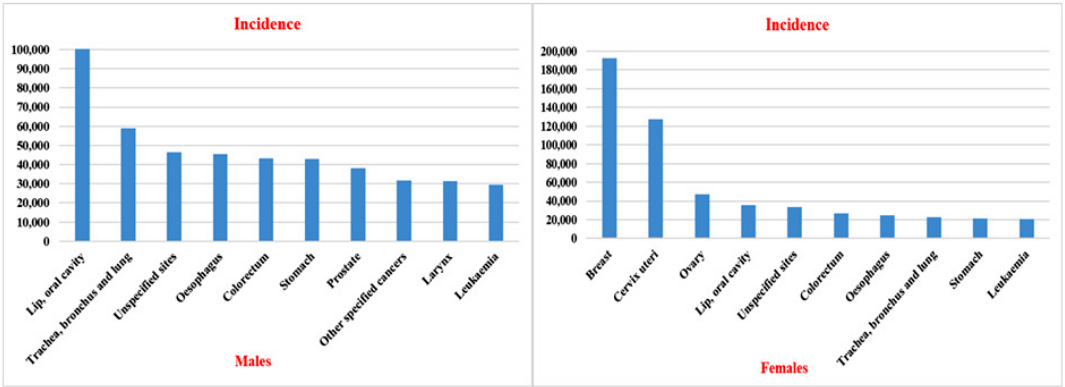

Fig. 4. Cancer Incidence Top 10 in male and female in India, Sourced from CANCER TODAY (https://gco.iarc.fr/today/), presenting detailed insights into cancer prevalence in 2022 based on GLOBOCAN estimates for year 2022 across 185 countries, covering 36 cancer types by sex and age group.

Table 1. Summary of Therapeutic Agents Targeting Key Oncogenic Pathways in Cancer

Pathway	Therapeutic Target	Agent(s)	Cancer Type / Model	Trial Phase	References
Wnt	PORCN Inhibitor	LGK974, WNT974, ETC-1922159, RXC004, CGX1321	Melanoma, breast, colorectal, GI cancers	Phase I–II	[44, 51, 54, 55]
	Wnt Ligand Inhibitor	Plumbagin	Endocrine-resistant breast cancer	Preclinical	[44]
	Wnt5a Mimetic	Foxy-5	Colon cancer	Phase II	[54]
	FZD Receptor Antagonist	OMP-18R5, OTSA101-DTPA-90Y	Breast, pancreatic, synovial sarcoma	Phase I	[44]
	FZD8 Decoy Receptor	OMP-54F28	Hepatocellular, pancreatic, ovarian, solid tumors	Phase I	[44]
	â-catenin/CBP Antagonist	PRI-724	Pancreatic cancer, AML, CML, solid tumors	Phase I–II	[44, 50, 51]
Notch	ã-Secretase Inhibitors (GSIs)	PF-03084014, BMS-906024, MK-0752, RO4929097	T-ALL, breast, renal, pancreatic, NSCLC	Phase I–III	[57–59]
	Monoclonal Antibodies	Enoticumab, Demcizumab, Tarextumab, Brontictuzumab	Ovarian, pancreatic, breast, lung, hematologic cancers	Phase I–II	[33, 57–59]
	DLL3 Targeting Agents	Rovalpituzumab Tesirine	Small cell lung cancer	Phase II	[58, 59]
	CB-103	CB-103	Advanced solid and hematologic malignancies	Phase I–IIa	
Hedgehog	SMO Inhibitors	Vismodegib, Sonidegib, Glasdegib	BCC, medulloblastoma, pancreatic, lung	Phase II–III	[44, 48, 60–63]
	GLI Inhibitors	GANT61, Arsenic Trioxide	Medulloblastoma, pancreatic cancer	Preclinical	
	Antibody Therapies	5E1, GDC-0449	Various tumors	Preclinical	
PI3K/AKT/mTOR	PI3K Inhibitors	Idelalisib, Copanlisib, Buparlisib	Various cancers	Phase III	[65]
	AKT Inhibitors	MK-2206, Perifosine, Ipatasertib	Breast, prostate, head & neck cancers	Ongoing trials	[66]
	mTOR Inhibitors	Everolimus, Temsirolimus, Rapamycin	Breast, colorectal, hepatocellular carcinoma	Phase III	[67, 68]
	Dual PI3K/mTOR Inhibitors	Palbociclib, Ribociclib, Abemaciclib	Various cancers	Clinical trials	[68]
	Metabolic Regulators	Matcha tea, Folate supplementation	Breast, lung cancer	Preclinical	[48]
JAK/STAT	JAK Inhibitors	Ruxolitinib, Tofacitinib	Myeloproliferative neoplasms, other cancers	Phase III	[65]
	STAT Inhibitors	Stattic, Cucurbitacin I	Various cancers	Preclinical	[44]
	Cytokine Receptor Blockers	Tocilizumab, Oclacitinib	Breast, HCC, colorectal, head & neck cancers	Ongoing trials	[66]
	MicroRNA Regulators	miR-30, miR-93	Breast, glioma, lung	Preclinical	[67]
	Endogenous Inhibitors	Von Hippel-Lindau	Glioma and lung cancer stem cells	Preclinical	[48]

breast cancer) have demonstrated improved efficacy with manageable toxicity. However, acquired resistance, metabolic side effects (e.g., hyperglycemia), and feedback activation of alternate pathways limit broader application. Future directions include rational combination therapies (e.g., with endocrine therapy, PARP inhibitors, or immunotherapy), biomarker-driven patient selection, and deeper understanding of resistance mechanisms. Integration of this pathway into multi-omics and precision oncology frameworks may enhance its clinical utility and therapeutic impact.[64-69]

JAK/STAT Signaling Pathway

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway is a critical mediator of cytokine signaling involved in cell proliferation, differentiation, immune regulation, and apoptosis. Upon cytokine or growth factor binding to cell surface receptors, associated JAKs become activated through phosphorylation. Activated JAKs then phosphorylate STAT transcription factors, which dimerize and translocate to the nucleus to regulate gene expression.[65,69] Constitutive activation of the JAK/STAT pathway contributes to oncogenesis in hematological malignancies and various solid tumors, including breast, colorectal, liver, and head and neck cancers. Common mechanisms include mutations in JAK2 (e.g., V617F in myeloproliferative neoplasms) and persistent activation of STAT3 or STAT5, which promote tumor growth, angiogenesis, immune evasion, and resistance to apoptosis.[44,48,66,70]

Targeting the JAK/STAT pathway has emerged as a promising therapeutic strategy, particularly in hematologic cancers (Table 1):

• JAK inhibitors (e.g., ruxolitinib, fedratinib) are approved for treating myelofibrosis and polycythemia vera.[65]

• STAT inhibitors (e.g., stattic, napabucasin) aim to disrupt STAT3 activation and transcriptional activity.[44]

• Cytokine receptor antagonists (e.g., tocilizumab targeting IL-6R) reduce upstream activation.[66]

• MicroRNA modulators and epigenetic agents are being investigated for their roles in modulating STAT-driven gene expression.[67]

JAK inhibitors have demonstrated clinical efficacy in specific hematologic contexts but are less established in solid tumors due to toxicity and limited target selectivity.[48] Resistance mechanisms, such as secondary mutations or compensatory activation of parallel pathways, remain significant hurdles. Moreover, directly targeting STAT proteins is technically challenging due to their structure and intracellular location. Future strategies will benefit from improved STAT-specific inhibitors, novel delivery mechanisms, and combination regimens that enhance anti-tumor immune responses. The JAK/STAT axis is also a key node in cancer stem cell regulation and immunosuppression, making it a valuable target for synergistic therapies involving checkpoint inhibitors or cancer vaccines.[48,66-67]

CONCLUSION

Targeted cancer therapy has emerged as a transformative approach in oncology, built upon our growing understanding of dysregulated signaling networks that sustain tumor development and progression. This review has explored five critical oncogenic pathways—Wnt/â-catenin, Notch, Hedgehog, PI3K/AKT/mTOR, and JAK/STAT—and their relevance to the hallmarks of cancer. While substantial progress has been made in identifying actionable targets within these pathways, translating this knowledge into lasting therapeutic outcomes remains a formidable challenge.

Each of these pathways plays a multifaceted role in tumor biology, from driving proliferation and evading apoptosis to fostering immune escape and therapeutic resistance. Although targeted agents—such as SMO inhibitors for Hedgehog, mTOR inhibitors for PI3K/AKT/mTOR, and JAK inhibitors in hematological malignancies—have achieved regulatory approval, their efficacy in solid tumors is often limited by pathway redundancy, compensatory signaling, and intratumoral heterogeneity. Additionally, many inhibitors suffer from off-target toxicity or lose effectiveness due to the emergence of resistance mechanisms.[44,48,54,64]

Importantly, crosstalk between these signaling cascades exacerbates the complexity of targeting a single pathway in isolation. For example, inhibition of PI3K may inadvertently activate MAPK or JAK/STAT signaling, diminishing the overall therapeutic benefit. Therefore, future

strategies must focus on rational combination therapies that can simultaneously target multiple oncogenic drivers or circumvent adaptive resistance. These may include combinations with immunotherapies, epigenetic modulators, or cell cycle checkpoint inhibitors.[48,54,64]

Another key challenge lies in patient stratification. The success of targeted therapy hinges on identifying individuals most likely to respond to specific interventions. The development and integration of predictive biomarkers, genomic profiling, and transcriptomic data are critical to implementing personalized medicine. Technologies such as single-cell sequencing, CRISPR-based functional genomics is accelerating this process and can help uncover novel vulnerabilities within these pathways.[50]

Furthermore, the tumor microenvironment (TME) presents both obstacles and opportunities. Many of the pathways discussed are influenced by or contribute to an immunosuppressive TME. Therapeutic interventions that modulate the TME—either by reprogramming stromal cells or enhancing immune infiltration—could synergize with pathway inhibitors to improve clinical responses.[44,65]

In conclusion, while our understanding of cancer biology has advanced considerably, the path toward durable, pathway-targeted cancer therapies requires continued innovation and refinement. A systems-level approach, integrating multi-omics data, machine learning, and patient-specific modeling, holds promise in navigating the complexity of cancer signaling. This review underscores the importance of pathway-centric therapeutic design and advocates for a future where cancer treatment is more precise, dynamic, and adaptive to the evolving nature of the disease.

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Conflict of interest

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

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Author contributions

Ritika Gera: Conceptualization, Writing – original draft, Data collection; Rajesh Kumar: Writing – review & editing, Supervision; Kamaljit Panchal: Reviewing; Vikas Sharma: Reviewing; Ramika Garg: Reviewing.

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