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The Multifaceted Roles of PP2A-B56 in Tumor Progression

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Abstract Protein phosphatase 2A (PP2A) regulatory B56 subunits play multifaceted and context- dependent roles in cancer progression by modulating key signaling pathways that govern cell growth, survival, migration, and apoptosis. Dysregulation of PP2A-B56 complexes is commonly observed across diverse malignancies, contributing to oncogenic signaling, therapy resistance, and tumor development. Recent advances have uncovered complex mechanisms controlling PP2A-B56 function, including post-translational modifications such as nitration and phosphorylation, protein interactions, and viral exploitation, highlighting the nuanced role of these subunits in tumor biology. The development of isoform-specific modulators and innovative biosensors offers promising avenues for precise therapeutic targeting of PP2A-B56 dysfunction in cancer. Continued investigation into the regulatory networks and context-specific functions of PP2A-B56 is critical for unlocking new strategies to combat tumor progression and overcome treatment resistance.

Keywords PP2A, B56, Cancer, Cell Migration

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1. Introduction

Protein phosphatase 2A (PP2A) is a highly conserved serine/threonine phosphatase complex that plays a pivotal role in regulating numerous cellular processes, including cell growth, division, apoptosis, and signal transduction (Janssens & Goris, 2001; Sontag, 2001). The functional specificity of PP2A is largely determined by its regulatory B subunits, of which the B56 (PPP2R5) family is a critical subset (McCright, Butterfield, & Virshup, 1995; Janssens, Longin, & Goris, 2008). The B56 regulatory isoforms—B56α, B56β, B56γ, B56δ, and B56ε—exert diverse and context-dependent effects on cellular signaling pathways, influencing tumorigenesis in multiple cancer types (Sangodkar et al., 2017). In contrast, the social amoeba *Dictyostelium discoideum* possesses a single B56 ortholog, PsrA (*Lee et al.*, 2008; Rodríguez Pino et al., 2015), of which functions - regulating cell differentiation and migration - may represent core ancestral roles of the B56 family.

Dysregulation of PP2A-B56 subunits has emerged as a fundamental contributor to cancer progression, with aberrant activity frequently linked to oncogenic signaling, impaired apoptosis, enhanced migration, and therapy resistance (Westermarck & Hahn, 2008; Sangodkar et al., 2017). Among these, PP2A-B56α stands out as a well-characterized tumor suppressor whose loss or inactivation promotes stabilization of oncogenes such as c-MYC, facilitating malignant transformation and tumor maintenance in cancers ranging from melanoma to hematologic malignancies (Junttila et al., 2007). Similarly, B56β modulates oncogenic kinases like Pim-1 in lymphomas (Ma et al., 2007), whereas B56γ governs key processes including focal adhesion dynamics, p53-dependent apoptosis, and cell migration, with its role varying across tumor contexts (Ito et al., 2000; Shouse et al, 2008; Hsiao et al., 2023). B56δ and B56ε also contribute to tumorigenesis through regulation of apoptosis, oncogenic signaling, and the tumor immune microenvironment, highlighting the broad impact of B56 isoform dysfunction (Lambrecht et al., 2018; Wu et al., 2024).

Recent advances in molecular and cellular studies have begun to unravel the intricate regulatory networks controlled by PP2A-B56 complexes, revealing mechanisms such as phosphorylation- dependent modulation, protein–protein interactions, and viral exploitation (Barski et al., 2020). Furthermore, novel experimental tools—such as compartment-specific biosensors—and pharmacological activators of PP2A offer promising avenues to restore PP2A function therapeutically (Sangodkar et al., 2017; Lum et al., 2025).

This review synthesizes current knowledge on the distinct roles of PP2A-B56 isoforms in cancer biology, with particular emphasis on their mechanistic contributions to tumor suppression and oncogenic activation. Studies pertaining to non-cancer diseases were not considered. Relevant literature was systematically identified through Web of Science, covering the period from 1995 to 2025.

2. PP2A-B56α Inactivation and Its Impact on Cancer Progression

PP2A-B56α functions as a critical tumor suppressor, yet its activity is frequently compromised in diverse cancers through multiple mechanisms. In melanoma, B56α plays a central role in regulating c-MYC stability. Mannava et al. (2012) reported that metastatic melanoma cells express markedly lower levels of PP2A-B56α compared with normal melanocytes, leading to increased c-MYC stability. Clinically, higher B56α expression correlates with improved patient outcomes. Experimentally restoring B56α reduces c-MYC levels and triggers oncogene-induced senescence (OIS), while its depletion in normal melanocytes elevates c-MYC and suppresses senescence. These findings position B56α as a key regulator of both oncogene signaling and cellular aging in melanocytic cells. To further dissect PP2A regulation, novel bioluminescence resonance energy transfer (BRET) sensors targeting PPP2R5A (B56α) have been developed to monitor PP2A activity in distinct cellular compartments. The nuclear-targeted sensor successfully detected interactions with c-MYC, revealing compartment-specific PP2A functions and providing powerful tools for therapeutic development.

In hematologic malignancies, B56α-dependent PP2A activity modulates critical oncogenic pathways. In myeloproliferative neoplasms driven by the JAK2V617F mutation, metformin suppresses malignant growth through two mechanisms: (1) increasing reactive oxygen species to inhibit SHP-2 via AMPK activation, and (2) activating B56α-containing PP2A complexes that directly antagonize JAK2V617F. Notably, B56α-PP2A also inhibits AMPK, creating a regulatory feedback loop. Metformin synergizes with ruxolitinib, a JAK inhibitor, suggesting that combined therapy and PP2A-B56α activation could be a promising strategy (Kawashima & Kirito, 2016).

In acute myeloid leukemia (AML), PP2A inactivation contributes to poor therapeutic response. Peris et al. (2023) demonstrated that reactivating PP2A with small-molecule activators enhances venetoclax-induced apoptosis via

B56α-containing complexes. This reactivation suppresses BCL2 and ERK signaling, destabilizes Myeloid Cell Leukemia 1 (MCL1), and improves efficacy when combined with azacitidine—highlighting PP2A activation as a means to potentiate existing AML therapies.

Direct inhibition of B56α is another oncogenic mechanism. Pavic et al. (2023) revealed that the oncoprotein Cancerous Inhibitor of PP2A (CIP2A) binds B56α, displacing the PP2A scaffolding A subunit and forming a non-functional CIP2A–B56α–PP2Ac pseudotrimer. This prevents substrate access and impairs phosphatase activity. The N-terminal domain of CIP2A stabilizes the protein; mutations in this region reduce MYC expression, MEK phosphorylation, and tumor growth in breast cancer models. By blocking PP2A-B56α-mediated degradation of oncogenic proteins such as c-MYC, CIP2A sustains tumor-promoting signaling, enhancing proliferation, survival, and resistance. CIP2A overexpression—common in breast, lung, liver, and hematologic cancers—correlates with aggressive disease and poor prognosis.

Similar mechanisms operate in solid tumors driven by KRAS mutations. In pancreatic ductal adenocarcinoma (PDAC), where KRAS mutations occur in ~95% of cases, Tinsley et al. (2024) found that KRASG12D upregulates CIP2A, increasing c-MYC phosphorylation and sequestering B56α, which is essential for MYC degradation. Loss of B56α accelerates KRAS-driven tumorigenesis, while pharmacological PP2A activation reduces acinar-to-ductal metaplasia, underscoring the role of B56α inhibition in sustaining MYC-dependent oncogenesis.

Beyond transcriptional and signaling regulation, B56α also influences translational control. Dysregulated eIF4E-dependent translation promotes tumorigenesis and therapy resistance through inactivation of eIF4E-binding proteins (4E-BP1/2/3). Lum et al. (2025) demonstrated that small-molecule PP2A activators (SMAPs) restore 4E-BP1/2 activity via B56α -mediated hypo-phosphorylation, suppressing cap-dependent translation and inducing 4E-BP1-dependent apoptosis. These findings highlight PP2A activation as a promising therapeutic avenue to reinstate translational control and overcome drug resistance.

3. B56β and Lymphoma

Pim protein kinases are critical regulators of signaling pathways that promote the development and progression of c-Myc–driven lymphomas. These kinases enhance oncogenic signaling, contributing to uncontrolled cell growth and survival. Ma et al. (2007) revealed that the tumor suppressor phosphatase PP2A plays a significant role in regulating Pim-1. Their study showed that increasing the expression of PP2A's catalytic subunit leads to a reduction in Pim-1 kinase levels and activity. Conversely, inhibiting PP2A or disrupting its association with regulatory B subunits reverses this suppression.

Crucially, Pim-1 was found to bind specifically to the PP2A B56β regulatory subunit, which mediates its dephosphorylation and controls its stability. When B56β expression is reduced via knockdown approaches, Pim-1 becomes more stable due to decreased ubiquitination, suggesting that B56β directs Pim-1 toward proteasomal degradation. This mechanism underscores the importance of B56β-containing PP2A holoenzymes in restraining oncogenic signaling by targeting Pim-1 for degradation. Together, these findings highlight B56β as a key modulator of Pim-1 stability and activity in lymphoma cells, positioning it as a potential tumor suppressor component whose dysfunction may contribute to lymphoma progression through sustained Pim-1 signaling.

4. PP2A- B56γ and Its Impact on Cancer Progression

PP2A regulatory subunits, particularly B56γ, play critical and context-dependent roles in modulating cancer cell migration, invasion, and survival. Their influence spans focal adhesion dynamics, cytoskeletal reorganization, and p53-mediated apoptosis, with effects varying across cancer types and molecular contexts.

At the mechanistic level of migration, Ito et al. (2000) identified a truncated PP2A B56γ1 isoform in mouse melanoma cells that enhances cell motility by promoting phosphorylation of paxillin, a key focal adhesion protein. Subsequent studies by Tang et al. (2018) and Rajah et al. (2019) expanded on this, showing that PAK kinase–mediated phosphorylation of paxillin at Ser-273 increases its association with a regulatory complex governing focal adhesion turnover and directional migration.

The relationship between B56γ and migration is further shaped by its interaction with p53 signaling. While ATM kinase typically activates p53 following DNA damage, Liu et al. (2021) discovered that ATM depletion paradoxically upregulates B56γ2 in colon cancer cells, leading to Chk1 activation, p53 stabilization, and suppression of CD44

expression. Because CD44 drives PI3K/Akt signaling (Chen et al., 2024), this pathway ultimately suppresses proliferation and migration.

Loss or suppression of B56γ also disrupts migration control. Kawahara et al. (2013) reported that inactivating B56γ mutations sustain ERK activation, enhancing EGF-induced migration on collagen matrices. Supporting this, Qiu et al. (2014) found that miR-183–mediated suppression of both PP2A catalytic subunits and B56 in renal cancer cells increased proliferation, migration, and invasion. Similarly, Ripamonti et al. (2022) demonstrated that in breast cancer cells, liprin α1 recruits B56γ-containing PP2A complexes to leading-edge plasma membrane platforms, with loss of either liprin α1 or B56γ impairing cell spreading, lamellipodia dynamics, and invasion.

Importantly, B56γ's function can switch from tumor-suppressive to oncogenic depending on context. Traditionally recognized for stabilizing p53 and maintaining genomic integrity, B56γ3 was shown by Hsiao et al. (2023) to promote Akt activation in colorectal cancer by inhibiting p70S6K—a negative Akt regulator—thereby driving EMT, cytoskeletal changes, and invasiveness.

B56γ also directly impacts apoptosis regulation through p53 modulation. In melanoma, Koma et al. (2004) found that BL6 cells derived from F10 melanoma express a truncated B56γ variant, Deltagamma1, following irradiation. This variant reduces Mdm2 phosphorylation, preventing p53 stabilization and lowering apoptosis, ultimately enhancing radio resistance. Shouse et al. (2008, 2010) further clarified that ATM-mediated phosphorylation of p53 at Ser15 and Ser20 facilitates its association with B56γ-PP2A, which then dephosphorylates p53 at Thr55 to fully stabilize and activate its tumor-suppressor functions. Conversely, Nobumori et al. (2013) showed that B56γ loss destabilizes p53, favoring cancer cell survival.

Beyond p53, B56γ regulates other oncogenic pathways. In most adenocarcinomas, Immediate Early Response 3 (IER3) is overexpressed alongside elevated phospho-ERK. By inhibiting PP2A/B56γ-mediated ERK dephosphorylation, IER3 sustains ERK activation, especially in lung adenocarcinomas where B56γ deletion or EGFR mutations are frequent. In hepatocellular carcinoma (HCC), Che et al. (2022) found that B56γ dephosphorylates Drp1 at Ser616, promoting apoptosis by inhibiting mitophagy—a process counteracted in HBV-related HCC, where viral protein HBx inhibits B56γ to activate Akt-driven survival pathways.

Finally, B56γ is also targeted by viruses to enhance their replication. Human T-cell lymphotropic virus type 1 (HTLV-1) uses B56γ to integrate viral DNA into the host genome via its integrase (Barski et al., 2020). Similarly, Kämper et al. (2025) showed that Ebola virus relies on B56γ to dephosphorylate its transcriptional activator VP30, a process coordinated by the viral nucleoprotein.

Together, these findings illustrate that PP2A-B56γ subunits serve as pivotal regulators at the intersection of migration, apoptosis, and oncogenic signaling. Their roles are highly context-dependent—sometimes restraining malignancy through p53 stabilization, and at other times facilitating tumor progression or viral exploitation—making them compelling but complex targets for therapeutic intervention.

5. B56δ and Cancer Progression

Low et al. (2014) demonstrated that in human breast cancer and nasopharyngeal carcinoma (NPC) cells, exposure to pro-oxidant conditions causes selective nitration of tyrosine 289 on the PP2A regulatory subunit B56δ. This nitration event disrupts the assembly of the PP2A holoenzyme by preventing B56δ from properly binding to the catalytic and scaffolding subunits. As a consequence, the PP2A phosphatase activity toward certain substrates is impaired. One key substrate affected is the antiapoptotic protein Bcl-2, where persistent phosphorylation at Ser70 maintains its activity, thereby promoting cancer cell survival and resistance to apoptosis under oxidative stress conditions.

Lambrecht et al. (2018) investigated the effects of complete loss of the B56δ regulatory subunit using a genetic mouse model with targeted knockout of the gene encoding B56δ. These mice spontaneously developed multiple primary tumors, with hematologic malignancies (such as lymphomas and leukemias) and hepatocellular carcinomas (HCCs) being the most frequent.

Detailed RNA sequencing analyses of the HCC tumors revealed a consistent upregulation of oncogenic pathways, prominently involving activation of the c-Myc proto-oncogene. This was corroborated by increased phosphorylation of c-Myc at Ser62, a modification known to enhance its stability and transcriptional activity.

Further upstream, the study identified hyperphosphorylation of glycogen synthase kinase-3 beta (GSK-3β) at Ser9 in both the tumors and the otherwise normal liver tissue of B56δ-null mice.

Phosphorylation at Ser9 inhibits GSK-3β kinase activity, preventing it from phosphorylating c- Myc on sites that mark it for degradation. Therefore, inactivation of GSK-3β due to B56δ loss removes a critical negative regulatory checkpoint, leading to the accumulation and persistent activation of c-Myc. This mechanistic link between B56δ, GSK-3β, and c-Myc highlights a pathway through which PP2A dysfunction predisposes to tumorigenesis by dysregulating cell proliferation and survival signals.

Together, these studies underscore the tumor-suppressive role of PP2A-B56δ and demonstrate how its impairment—whether through post-translational modifications like nitration or genetic deletion—can lead to sustained oncogenic signaling, resistance to apoptosis, and ultimately cancer development. These insights also point to B56δ and its regulatory network as potential therapeutic targets for cancers characterized by aberrant PP2A activity.

6. B56ε and Associated Diseases

The study by Wu et al (2024) investigated the expression and functional role of the PP2A regulatory subunit B56ε across multiple cancer types, with a particular focus on hepatocellular carcinoma (HCC). By analyzing data from several large-scale cancer databases, the researchers found that B56ε is significantly upregulated in the majority of tumors examined. Elevated B56ε expression was identified as a risk factor in several cancers, including adrenocortical carcinoma, HCC, pancreatic adenocarcinoma, pheochromocytoma, and paraganglioma.

Furthermore, B56ε levels showed strong positive correlations with various immune cell populations such as T helper 17 cells, B cells, and macrophages. There was also a notable association between B56ε expression and immune checkpoint molecules as well as human leukocyte antigen (HLA)-related genes, suggesting a role in modulating the tumor immune microenvironment. Interestingly, B56ε expression generally correlated with decreased sensitivity to most chemotherapy agents, although a few drugs exhibited a positive correlation.

Gene set enrichment analysis linked high B56ε expression to key oncogenic pathways, including those related to cancer progression, p53 downstream signaling, and interleukin-mediated immune responses within HCC. To validate these findings experimentally, knockdown of B56ε in hepatocellular carcinoma cell lines was performed, which significantly impaired the cells' proliferative, migratory, and invasive capabilities. Although specific phosphorylation sites aren't detailed, these altered phosphorylation events may promote tumor progression and a tumor- promoting inflammatory microenvironment.

Together, these results highlight B56ε as a critical regulator of tumor biology, influencing both cancer cell behavior and the immune landscape. Its involvement in tumor progression and immune modulation positions B56ε as a promising prognostic biomarker and a potential therapeutic target, particularly in hepatocellular carcinoma.

7. Summary and Future Directions

PP2A/B56 isoforms (α, β, γ, δ, ε) play distinct roles in tumorigenesis by regulating oncogenic signaling, apoptosis, migration, and immune responses (Table 1 and Figure 1). B56α functions as a tumor suppressor but is often inhibited in cancers, with reactivation strategies showing therapeutic promise. B56β suppresses lymphoma by promoting Pim-1 degradation, while B56γ has context-dependent roles, stabilizing p53 in some settings but promoting tumor progression by activating Akt and sustaining ERK in others. B56δ regulates c-Myc and Bcl-2, with its loss driving proliferation, and B56ε is upregulated in hepatocellular carcinoma and other cancers, supporting tumor growth and therapy resistance. Together, these isoforms highlight the complex, context-dependent contributions of PP2A/B56 to cancer biology and therapeutic potential.

Emerging technologies such as single-cell transcriptomics, spatial omics, and isoform-specific biomarkers may refine anti-cancer strategies targeting PP2A/B56 by overcoming the limitations of bulk analysis. Single-cell approaches can reveal isoform-specific expression of PP2A subunits across tumor, immune, and stromal cells, while spatial omics can map their localization within the tumor microenvironment, offering insights into tumor progression and immune evasion.

Several PP2A/B56 isoforms show biomarker potential in cancer. B56α undergoes aberrant splicing in SF3B1-mutant breast cancers, driving AKT hyperactivation and inflammatory signaling (Liu et al., 2021), and its reduced expression correlates with poor response to PP2A-activating therapies in AML (Peris et al., 2023). B56γ is linked to poor AML survival (El Taweel et al., 2020), promotes melanoma motility through splicing variants (Ito et al., 2016), and regulates p53 dephosphorylation, with its loss impairing DNA damage responses (Li et al., 2007). B56ε shows context-dependent prognostic effects, acting as an unfavorable marker in liver and ovarian cancers but favorable in some renal cancers (Chen et al., 2024). These isoform-specific changes—especially in B56α, B56γ, and B56ε—

highlight their potential as biomarkers and therapeutic targets. Future studies clarifying the cancer relevance of B56β and B56δ could provide prognostic insights currently unavailable.

Despite promising preclinical data, the clinical translation of PP2A-targeting therapies may face substantial challenges. Specificity is a concern, as broad-acting activators can affect healthy cells given the diversity of PP2A/B56 functions; fingolimod, for example, is limited by cardiotoxicity (Enjeti et al., 2016). Tumor heterogeneity may further complicate treatment, with responses varying across cancer subpopulations. Resistance may also emerge through compensatory signaling or genetic and epigenetic changes reducing PP2A activity. Addressing these barriers will be critical for designing combination therapies and monitoring patient responses.

This table summarizes the roles, key mechanisms and effects, and therapeutic insights related to the five B56 isoforms discussed in the article.

Table 1. Summary of PP2A B56 Isoforms Roles in Cancer.

Isoform	Role in Cancer	Key Mechanisms / Effects	Therapeutic Insights	Types of Associated Cancer
B56α	Tumor suppressor	Regulates oncogenic proteins (e.g., c-MYC); suppressed by inhibitors like CIP2A; frequently inhibited in melanoma, hematologic malignancies, KRAS-driven pancreatic cancer	Reactivation by metformin/small molecules restores tumor suppression, enhances therapy response, counters progression and resistance	Melanoma, Acute Myeloid Leukemia (AML), Pancreatic Ductal Adenocarcinoma (PDAC)
B56β	Tumor suppressor	Promotes degradation of Pim-1 kinase; loss stabilizes Pim-1, sustaining lymphoma growth	Targeting Pim-1 degradation pathway could suppress lymphoma progression	c-Myc-driven Lymphoma
B56γ	Context-dependent (tumor suppressor or promoter)	Regulates cell migration, invasion, survival; stabilizes p53 for apoptosis; can activate oncogenic Akt/ERK pathways; exploited by viruses for replication	Complex target; modulation may require context-specific strategies; potential antiviral and anticancer target	Melanoma, Renal Cancer, Breast Cancer, Colorectal Cancer
B56δ	Tumor suppressor	Maintains holoenzyme function; regulates Bcl-2 and c-Myc; loss or nitration disrupts function, promotes survival and proliferation	Restoring B56δ function or preventing its loss/nitration may inhibit tumor growth	Breast Cancer, Nasopharyngeal Carcinoma (NPC), Lymphoma, Hepatocellular Carcinoma (HCC)
B56ε	Tumor promoter	Upregulated in many cancers, especially hepatocellular carcinoma; promotes tumor progression, immune infiltration, chemo-resistance.	Knockdown reduces proliferation and invasion; promising target for HCC therapies	Hepatocellular Carcinoma (HCC), Adrenocortical Carcinoma, Pancreatic Adenocarcinoma, Pheochromocytoma, Paraganglioma

Figure 1. Major Molecular Targets of PP2A/B56 in Cancer. This figure illustrates the major molecular targets of PP2A/B56, with inhibitory or destabilizing interactions indicated by T-bars and activating or stabilizing interactions shown with arrows. The dashed line denotes a putative interaction.

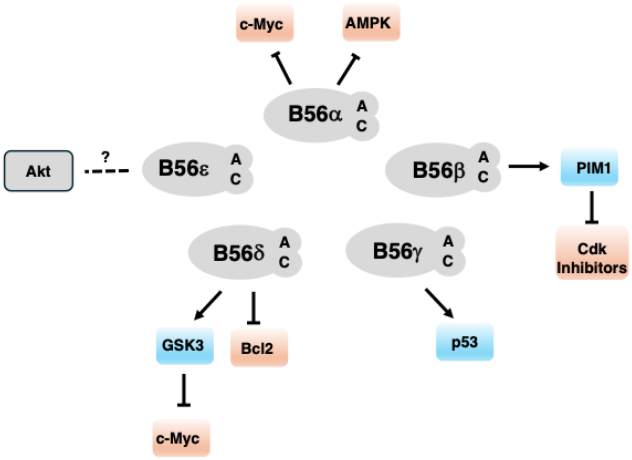

Figure 1. Major Molecular Targets of PP2A/B56 in Cancer

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