Protein Cell, 2025, **16**, 840–857
https://doi.org/10.1093/procel/pwaf043
Advance access publication 26 May 2025
Review

Protein & Cell

Review

The nuclear phosphoinositide-p53 signalosome in the regulation of cell motility

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Abstract

Dysregulation of p53 and phosphoinositide (PIP_n) signaling are both key drivers of oncogenesis and metastasis. Our recent findings reveal a previously unrecognized interaction between these pathways, converging in the nucleus to form a PIP_n-p53 signalosome that modulates nuclear AKT activation and downstream signaling, thereby influencing cancer cell survival and motility. This review examines recent insights into nuclear PIP_n signaling in the context of established roles for p53 in cell dynamics and migration while also deliberating current research on how nuclear PIP_ns interact with p53 to form signalosomes that affect cell motility. We emphasize the critical role of PIP_ns in stabilizing p53 and activating *de novo* nuclear AKT signaling, which subsequently modulates key motility-related pathways. Understanding the unique operation and function of the PIP_n-p53 signalosome in nuclear phosphatidylinositol 3-kinase (PI3K)-AKT activation offers novel therapeutic strategies for controlling cancer metastasis by targeting pertinent interactions and events.

Keywords phosphoinositide, p53, signalosome, nucleus, cell motility

Introduction

Cell motility is a fundamental process that, when aberrantly regulated, can lead to the invasive and metastatic characteristics of cancer (Merino-Casallo et al., 2022; Stuelten et al., 2018). The phosphoinositide (PIP_n) signaling pathways and the tumor suppressor protein p53 are central to the control of this process (Balla, 2013; Hou et al., 2025a; Muller et al., 2011). Independent dysregulation of these pathways is often a key driver in the transition from benign to malignant cell growth and the subsequent spread of cancer (Kandoth et al., 2013; Sinkala, 2023). The p53 protein, revered as the "guardian of the genome," is a multifaceted regulator of cellular responses to stress, including cell cycle arrest, apoptosis, and DNA repair (Oren and Prives, 2024). Similarly, PIP_ns, a family of phosphorylated lipids, play pivotal roles in cellular signaling, particularly in the modulation of membrane-associated events and cellular dynamics (Balla, 2013; Thapa et al., 2020, 2024).

Recent discoveries that reveal an intricate interplay between p53 and PIP_ns within the nucleus of cancer cells have significantly advanced our understanding of

Received 14 February 2025; **accepted** 29 April 2025.

these pathways (Chen et al., 2020, 2022; Choi et al., 2019; Ren et al., 2024). This emerging body of work suggests that these two pathways converge to form a nuclear PIP_n-p53 signalosome. This functional complex regulates nuclear AKT activity and influences cancer cell survival and motility (Carrillo et al., 2023; Chen et al., 2022; Choi et al., 2019). The formation of this signalosome represents a novel mechanism through which p53 and PIP_ns can jointly orchestrate the cellular behavior of cancers, offering overlapping targets for oncogenic phenotypes.

This review presents the latest insights into nuclear PIP_n signaling and examines p53's established roles in regulating cytoskeletal dynamics, cell adhesion, and migration. We integrate recent findings on how nuclear PIP_ns interact with p53 to form signalosomes that directly influence cancer cell motility. Special attention is given to the role of PIP_ns in stabilizing p53 and activating nuclear AKT signaling, which modulates key pathways essential for cell motility. By highlighting the unique functions of the PIP_n-p53 signalosome in nuclear phosphatidylinositol 3-kinase (PI3K)-AKT activation, we aim to identify novel therapeutic strategies to control cancer progression and metastasis.

Recent advances in nuclear PIP_n signaling

PIP_ns are phosphorylated derivatives of phosphatidylinositol (PI/PtdIns), a lipid that plays a critical role in cellular signaling. PI comprises a glycerol backbone, two fatty acid acyl chains, and an inositol ring (Fig. 1). The inositol ring can undergo phosphorylation and dephosphorylation at positions 3, 4, and 5 by specific kinases and phosphatases, leading to the generation of seven distinct PIP_n isomers. These isomers are PtdIns3P, PtdIns4P, PtdIns5P, PtdIns(3,4)P_2, PtdIns(3,5)P_2, PtdIns(4,5)P_2, and PtdIns(3,4,5)P_3. These phosphorylated derivatives are central to numerous intracellular signaling pathways regulating cellular functions, such as proliferation, survival, and motility.

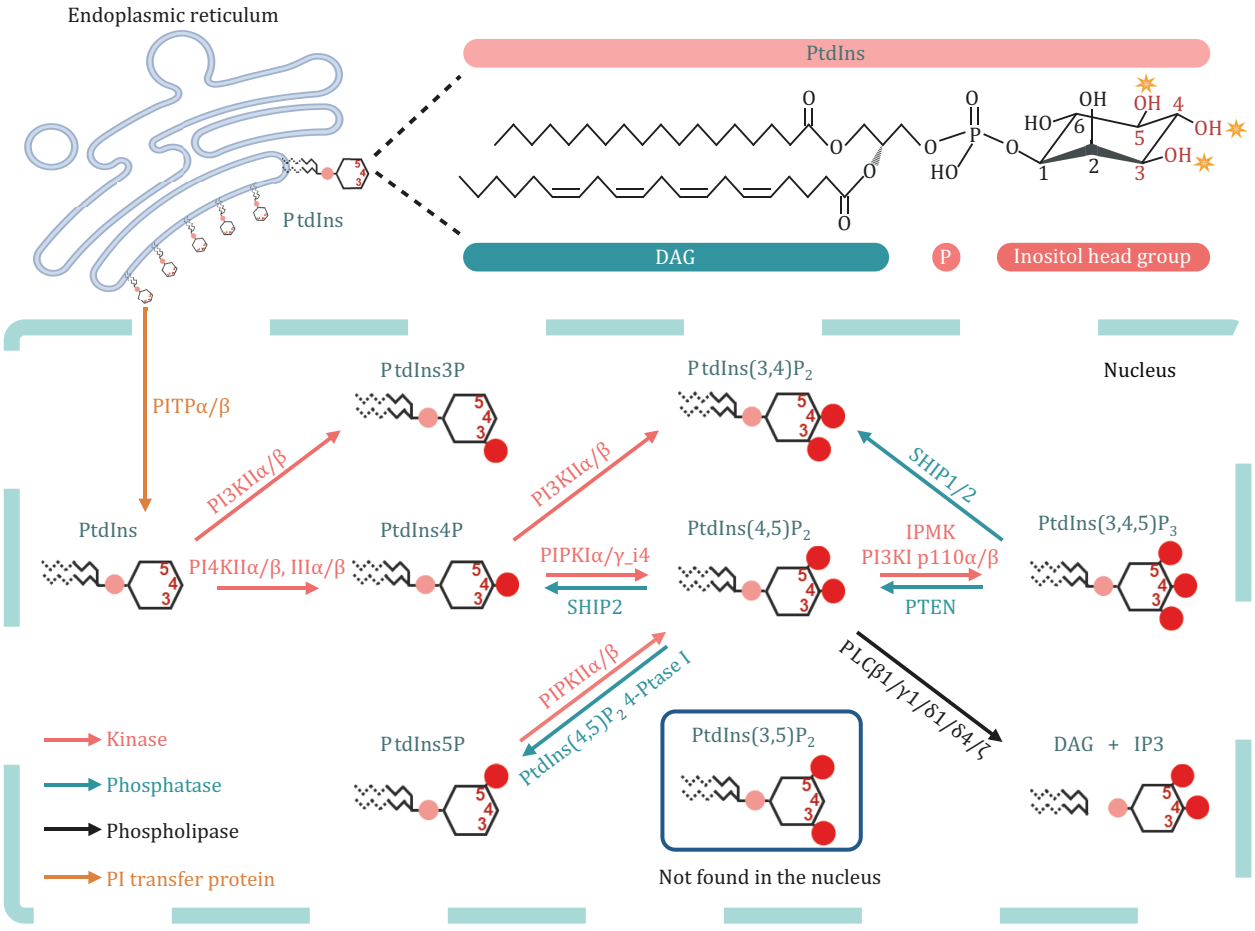

Figure 1. Nuclear PIP_n Metabolism. Schematic representation of PI/PtdIns structure and the nuclear PIP_n cycle. Phosphorylation sites on the hydroxyl groups of the inositol ring are marked by yellow stars, with carbon atom numbers labeled in red. Key components of the nuclear PIP_n metabolism, including PI transfer proteins (PITPs), kinases, phosphatases, and phospholipases, are depicted. Abbreviations: IP_3 ($Ins(1,4,5)P_3$), DAG (diacylglycerol), PtdIns(4,5)P_2 4-Ptase I (Type I PtdIns(4,5)P_2 4-phosphatase). The figure was created using BioRender.

PI synthesis occurs in the endoplasmic reticulum (ER) membrane, facilitated by multiple vital enzymes. The process starts with the acylation of glycerol-3-phosphate (G3P) by acyltransferases, producing phosphatidic acid (PA)—the first step in phospholipid biosynthesis across prokaryotes and eukaryotes (Blunsom and Cockcroft, 2020a). PA is then converted into CDP-diacylglycerol (CDP-DAG), a vital liponucleotide intermediate. In eukaryotes, PA serves as a precursor for both CDP-DAG and diacylglycerol (DAG) (Yang et al., 2018). CDP-DAG is crucial for the synthesis of PI, phosphatidylglycerol (PG), and cardiolipin (CL), while DAG is necessary for phosphatidylcholine (PC), phosphatidylethanolamine (PE), and triacylglycerol (TAG) production (Blunsom and Cockcroft, 2020a; Yang et al., 2018). The CDP-diacylglycerol synthase (CDS), also known as CTP:phosphatidate cytidylyltransferase, catalyzes CDP-DAG formation from CTP and PA. In mammals, two CDS enzymes, CDS1 and CDS2, operate in the ER (Blunsom and Cockcroft, 2020b). Following their action, CDP-DAG is utilized by PI synthase (PIS) to generate PI. Both CDS1/2 and PIS are integral ER membrane proteins, confining PI synthesis to the ER (Blunsom and Cockcroft, 2020b).

Due to their hydrophobic nature, lipids are generally restricted to cell membranes, preventing their free diffusion within the cell. Specific lipid transfer proteins (LTPs) are required to facilitate their transport (Wong et al., 2019). The subgroup of LTPs responsible for PI transport is known as PI transfer proteins (PITPs). Once PI is synthesized in the ER, PITPs mediate its movement to various cellular compartments (Hsuan and Cockcroft, 2001). In humans, five PITP family members have been identified and classified into two groups: class I, which includes PITPα and PITPβ, and class II, which comprises phosphatidylinositol transfer protein cytoplasmic 1 (PITPNC1), membrane-associated phosphatidylinositol transfer protein 1 (PITPNM1), and PITPNM2 (Hsuan and Cockcroft, 2001). Historically, PIs were thought to be restricted to the plasma membrane and endomembrane compartments for cytoplasmic signaling (Posor et al., 2022). According to the canonical model, PITPs shuttle PI between membranes in a countercurrent manner, often transporting an additional lipid cargo (Wong et al., 2019). Class I PITPs exchange PI and PC between membranes, while class II PITPs transfer PI and PA between membrane structures (Hsuan and Cockcroft, 2001) (Fig. 2).

Since the initial discovery of nuclear PIs in 1965, it has become evident that PIs are present in the nucleus and play crucial roles in regulating key cellular processes (Chen et al., 2020; Rose and Frenster, 1965; Tribble et al., 2016). Our recent findings reveal that class I PITPs, PITPα and PITPβ, localize to the nucleus in response to cellular stress, where they play a dominant role in establishing the nuclear PIP_n pool (Carrillo et al., 2023; Wen et al., 2024). This suggests lipid transfer proteins translocate PI from the ER to the nucleus. PITP executes lipid vectorial transport by establishing a stereochemically constrained microenvironment: its hydrophobic substrate-binding domain encapsulates fatty acyl chains while precisely positioning the inositol moiety at the solvent interface (Wong et al., 2019). This dual spatial organization enables concurrent fulfillment of metabolic imperatives, stabilizing the labile phospholipid during transmembrane transit while presenting an orientation-locked phosphorylation platform for nuclear kinase recognition. Prior to these studies, PITPs were rarely considered in the context of the nucleus, particularly concerning non-membrane regions within the nucleoplasm. In the canonical model, lipid transfer proteins, including PITPs, are proposed to transfer lipids from membrane to membrane (Fig. 2). The discovery that PITPs mediate lipid transfer from membrane-bound structures to the nucleoplasm challenges the traditional view of lipid transfer, which was thought to be confined to membrane structures. In the updated non-canonical model, PITPs could transfer lipids from the membrane to non-membrane structures, including their protein targets. Consistent with the nuclear presence of PITPs, various PIP_n species—including PtdIns3P, PtdIns4P, PtdIns5P, PtdIns(3,4)P_2, PtdIns(4,5)P_2, and PtdIns(3,4,5)P_3—have been identified in the nucleus, with PtdIns(3,5)P_2 being the only exception (Chen et al., 2020). This expands the understanding of lipid signaling within nuclear domains, underscoring its significance in nuclear functions and cellular stress responses.

In 1983, PI kinase and PIP_n kinase activity were first detected in the nucleus, supporting the presence of PI-modifying enzymes that convert specific PIP_ns into their phosphorylated forms (Barlow et al., 2010; Boronenkov et al., 1998; Chen et al., 2020; Cocco et al., 1987; Manzoli et al., 1977; Rose and Frenster, 1965; Smith and Wells, 1983). Subsequent studies have established the nuclear localization and activity of PI/PIP_n kinases, phosphatases, phospholipases, and downstream PIP_n effectors, indicating the existence of a dynamic pool of nuclear PIP_ns independent of cytoplasmic stores (Chen et al., 2020; Cocco et al., 1987; Faenza et al., 2013). These nuclear PIP_ns are synthesized from nuclear PI and metabolized in the nucleus, pointing to a membrane-independent PIP_n signaling network in the nucleoplasm. Nuclear PIP_ns play essential roles in DNA repair, chromatin remodeling, and gene expression, and they are critical for genome stability and cell fate determination (Barlow et al., 2010; Gozani et al., 2003; Sztacho et al., 2019). As shown in Table 1, the nuclear-localized PITPs and PI-metabolizing enzymes, including PIP_n kinases, phosphatases, and phospholipases, are all integral to regulating cell motility. Their nuclear localization is likely a critical factor in their ability to modulate cell motility, underscoring the importance of further investigation into this regulatory mechanism.

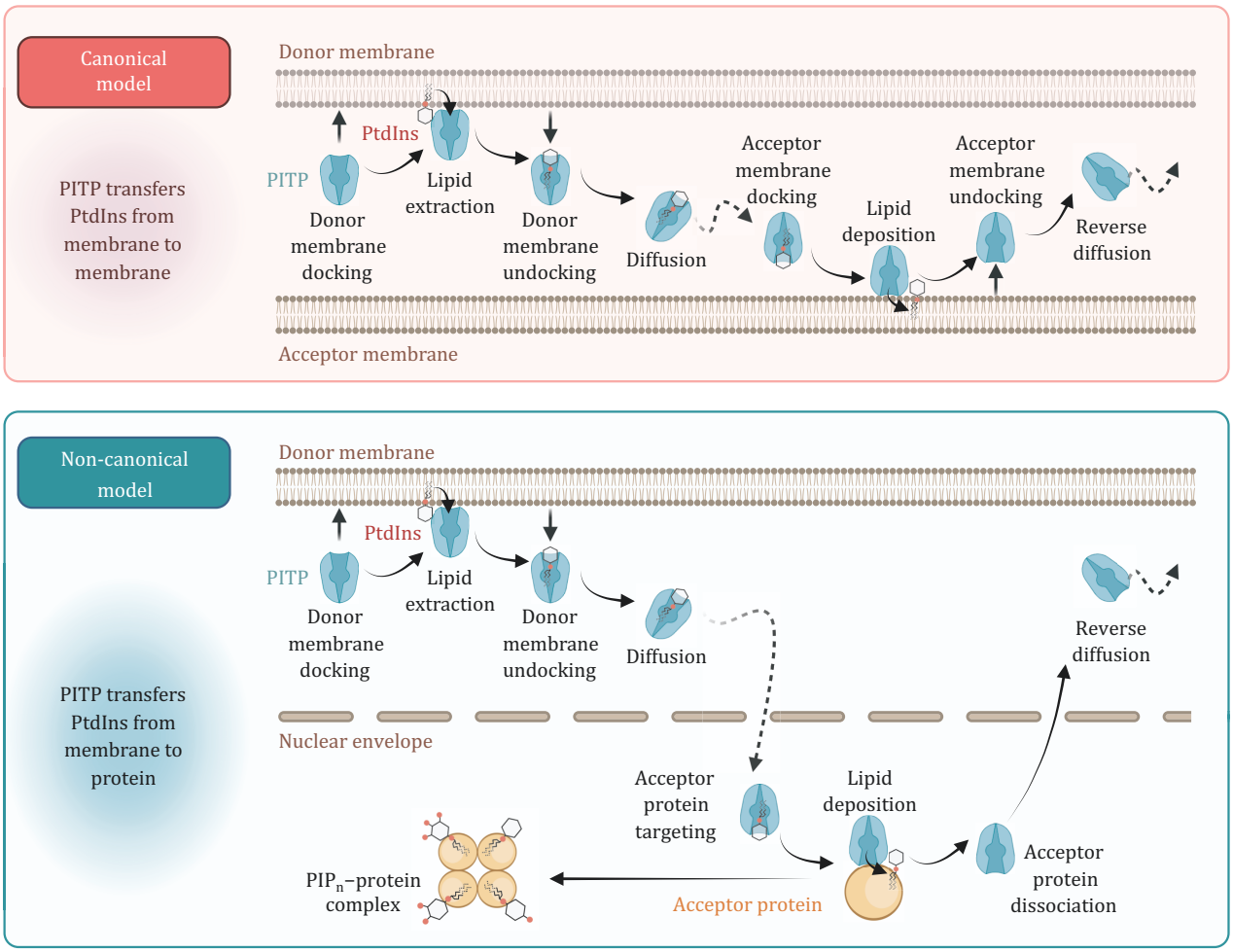

Figure 2. Canonical and non-canonical models of PITP-mediated lipid transfer. In the canonical model (top panel), PITP facilitates the transport of PtdIns between membranes. Upon docking at the donor membrane, PITP extracts PtdIns, then undocks and diffuses through the cytosol. It subsequently docks at the acceptor membrane to deliver the lipid. After undocking, PITP diffuses back to repeat the cycle. In the non-canonical model (bottom panel), PITP transfers PtdIns from the membrane to a protein acceptor instead of a membrane. This process follows similar steps—lipid extraction, membrane undocking, and diffusion—but instead of docking onto an acceptor membrane, PITP interacts with a protein acceptor. This interaction results in lipid deposition and the formation of a PIP$_n$-protein complex. The cycle completes as PITP dissociates and diffuses back to the donor site. The figure was created using BioRender.

The role of p53 in cell dynamics

The tumor suppressor protein p53, encoded by the *TP53* gene, is the most well-known protein for maintaining cellular integrity (Agarwal et al., 1998; Hollstein et al., 1991; May and May, 1999). It regulates a wide range of cellular processes, including cell cycle arrest, apoptosis, senescence, DNA repair, and metabolism (Agarwal et al., 1998; Hassin and Oren, 2023). By orchestrating these functions, p53 serves as a critical defense mechanism against oncogenesis, preventing the proliferation of cells with damaged DNA (Hassin and Oren, 2023; Hollstein et al., 1991; May and May, 1999).

Under normal physiological conditions, p53 levels are kept low through interaction with mouse double minute 2/4 (MDM2/4), an E3 ubiquitin ligase that ubiquitinates p53, leading to its degradation via the proteasome (Hassin and Oren, 2023; Kruse and Gu, 2009; Kubbutat et al., 1997). This interaction serves as a critical regulatory mechanism preventing inappropriate activation of p53 under basal conditions. However, in response to various stress signals, such as DNA damage, oxidative stress, and oncogene activation, p53 undergoes a series of post-translational modifications that result in its stabilization and activation (Hollstein et al., 1991; Kruse and Gu, 2009; Kubbutat et al., 1997; Mantovani et al., 2019). These modifications include phosphorylation, acetylation, and SUMOylation, which disrupt the p53-MDM2 interaction and enhance p53's transcriptional activity. Upon activation, p53 operates as a transcription factor by binding to specific DNA response elements, thereby inducing the expression of target genes encoding p21,

Table 1. The role of nuclear PI transfer proteins and metabolizing enzymes in cell motility.

Nuclear PI transfer proteins				
Gene name	**Courier**	**Cargo**	**Nuclear location**	**Role in cell motility**
PITPNA	PITPα	PtdIns (Ashlin et al., 2021), PC (Ashlin et al., 2021)	Nucleoplasm (Carrillo et al., 2023; Wen et al., 2024), nuclear speckles (Carrillo et al., 2023; Wen et al., 2024)	Collaborate with PITPβ to establish the nuclear PI pool, promoting cancer cell proliferation, migration, and invasion (Carrillo et al., 2023)
PITPNB	PITPβ	PtdIns (Ashlin et al., 2021), PC (Ashlin et al., 2021)	Nucleoplasm (Carrillo et al., 2023; Wen et al., 2024), nuclear speckles (Carrillo et al., 2023; Wen et al., 2024)	Collaborate with PITPα to establish the nuclear PI pool, promoting cancer cell proliferation, migration, and invasion (Carrillo et al., 2023)
Nuclear PIP_n kinases				
Gene name	**Enzyme**	**Substrate**	**Nuclear location**	**Role in cell motility**
PI4K2A	PI4KIIα	PtdIns(Balla and Balla, 2006)	Nucleus(Kakuk et al., 2006), nucleoplasmic Ca^{2+} store vesicles (Yoo et al., 2014), nucleoplasm (Carrillo et al., 2023; Wen et al., 2024), nuclear speckles (Carrillo et al., 2023; Chen et al., 2022; Wen et al., 2024)	Mediate cancer cell proliferation, migration, and invasion (Carrillo et al., 2023; Chen et al., 2022; Isaji et al., 2019; Li et al., 2017; Wen et al., 2024)
PI4K2B	PI4KIIβ	PtdIns (Balla and Balla, 2006)	Nucleoplasmic Ca^{2+} store vesicles (Yoo et al., 2014)	Facilitate cancer cell invasion (Alli-Balogun et al., 2016)
PI4KA	PI4KIIIα	PtdIns (Balla and Balla, 2006)	Nucleoplasm (Kakuk et al., 2006), nucleoli (Kakuk et al., 2006, 2008)	Facilitate cancer cell proliferation, migration, and invasion (Govindarajan et al., 2023; Sbrissa et al., 2019; Tran et al., 2024)
PI4KB	PI4KIIIβ	PtdIns (Balla and Balla, 2006)	Nuclear lamina-pore complexes (de Graaf et al., 2002), nuclear speckles (Szivak et al., 2006)	Facilitate cancer cell proliferation (Morrow et al., 2014; Tan et al., 2020)
PIP5K1A	PIPKIα	PtdIns4P (Choi et al., 2019)	Nuclear matrix (Barlow et al., 2010), nucleoplasm (Chen et al., 2022; Choi et al., 2019), nuclear speckles (Carrillo et al., 2023; Chen et al., 2022; Wen et al., 2024), nucleoli (Chakrabarti et al., 2015), chromatin (Choi et al., 2019)	Facilitate cancer cell proliferation, migration, and invasion (Carrillo et al., 2023; Chen et al., 2022; Choi et al., 2019; Wen et al., 2024)
PIP5K1C	PIPKIɣ_i4	PtdIns4P (Schill and Anderson, 2009)	Nuclear matrix (Barlow et al., 2010), nuclear speckles (Schill and Anderson, 2009)	Facilitate cancer cell migration, proliferation, and invasion (Sun et al., 2010)
PIP4K2A	PIPKIIα	PtdIns5P (Boronenkov et al., 1998)	Nuclear matrix (Barlow et al., 2010), nuclear speckles (Boronenkov et al., 1998)	Facilitate cancer cell proliferation (Choi et al., 2019)
PIP4K2B	PIPKIIβ	PtdIns5P (Kouchi et al., 2011)	Nuclear matrix (Barlow et al., 2010), nuclear speckles (Boronenkov et al., 1998; Bunce et al., 2008), chromatin (Kouchi et al., 2011; Stijf-Bultsma et al., 2015)	Inhibit cancer cell migration and invasion (Kouchi et al., 2011)

Table 1. Continued

Nuclear PIP_n kinases				
PIK3R1	Class I PI3K, p85α	-	Nucleus (Tanaka et al., 1999)	Complex with p110α to regulate cancer cell proliferation (Thapa et al., 2020, 2024; Vallejo-Díaz et al., 2019)
PIK3R2	Class I PI3K, p85β	-	Nucleus (Kumar et al., 2011)	Complex with p110α to regulate cancer cell proliferation (Hao et al., 2022; Thapa et al., 20202024)
PIK3CA	Class I PI3K, p110α	PtdIns(4,5)P_2 (Jean and Kiger, 2014)	Nucleus (Marques et al., 2009), chromatin (Marques et al., 2009)	Complex with p85α/p85β to control cancer cell proliferation (Thapa et al., 2020, 2024)
PIK3CB	Class I PI3K, p110β	PtdIns(4,5)P_2 (Jean and Kiger, 2014)	Nucleoli (Karlsson et al., 2016), chromatin (Marques et al., 2009)	Facilitate cancer cell proliferation (Mazloumi Gavgani et al., 2018)
PIK3C2A	Class IIα PI3K	PtdIns (Jean and Kiger, 2014), PtdIns4P (Jean and Kiger, 2014)	Nuclear speckles (Didichenko and Thelen, 2001)	Facilitate cancer cell proliferation and migration (Elis et al., 2008; Seok et al., 2010)
PIK3C2B	Class IIβ PI3K	PtdIns (Jean and Kiger, 2014), PtdIns4P (Jean and Kiger, 2014)	Nuclear envelope (Visnjic et al., 2002), nuclear matrix (Banfic et al., 2009; Sindić et al., 2001)	Facilitate cancer cell proliferation (Russo et al., 2015)
IPMK	IPMK	PtdIns(4,5)P_2 (Blind et al., 2012)	Chromatin (Blind et al., 2012; Xu et al., 2013), nucleoplasm (Carrillo et al., 2023; Chen et al., 2022; Wen et al., 2024), nuclear speckles (Carrillo et al., 2023; Chen et al., 2022; Wen et al., 2024)	Contribute to cancer cell proliferation, migration, and invasion (Carrillo et al., 2023; Chen et al., 2022; Wen et al., 2024)
Nuclear PIP_n phosphatases				
Gene name	**Enzyme**	**Substrate**	**Nuclear location**	**Role in cell motility**
PTEN	PTEN	PtdIns(3,4,5)P_3 (Deleris et al., 2003)	Nucleoli (Li et al., 2014), chromatin (Choi et al., 2013; Shen et al., 2007), nucleoplasm (Carrillo et al., 2023; Chen et al., 2022; Wen et al., 2024), nuclear speckle (Carrillo et al., 2023; Chen et al., 2022; Wen et al., 2024)	Inhibit cancer cell proliferation, migration, and invasion (Carrillo et al., 2023; Chen et al., 2022; Wen et al., 2024)
INPP5D	SHIP1	PtdIns(3,4,5)P_3 (Ehm et al., 2015)	Nucleoli (Ehm et al., 2015)	Inhibit cancer cell proliferation (Pedicone et al., 2021)
INPPL1	SHIP2	PtdIns(3,4,5)P_3 (Deleris et al., 2003), PtdIns(4,5)P_2 (Elong Edimo et al., 2011)	Nuclear speckles (Deleris et al., 2003; Elong Edimo et al., 2011)	Inhibit cancer cell proliferation (Pedicone et al., 2021)
PIP4P1	Type I PtdIns(4,5)P_2 4-phosphatase	PtdIns(4,5)P_2 (Zou et al., 2007)	Nucleus (Zou et al., 2007)	Unknown

Table 1. Continued

Nuclear phospholipases				
Gene name	**Enzyme**	**Substrate**	**Nuclear location**	**Role in cell motility**
PLCB1	PLCβ1	PtdIns(4,5)P_2 (Neri et al., 2002)	Nuclear matrix (Cocco et al., 1999), nuclear speckles (Tabellini et al., 2003)	Facilitate cancer cell migration (Owusu Obeng et al., 2020)
PLCG1	PLCγ1	PtdIns(4,5)P_2 (Lattanzio et al., 2019)	Nucleus (Lattanzio et al., 2019)	Facilitate cancer cell proliferation (Lattanzio et al., 2019; Owusu Obeng et al., 2020; Razmara et al., 2013)
PLCD1	PLCδ1	PtdIns(4,5)P_2 (Stallings et al., 2005)	Nuclear matrix (Stallings et al., 2005)	Inhibit cancer cell migration and invasion (Owusu Obeng et al., 2020)
PLCD4	PLCδ4	PtdIns(4,5)P_2 (Kunrath-Lima et al., 2018)	Nucleus (Kunrath-Lima et al., 2018)	Facilitate cancer cell proliferation and migration (Owusu Obeng et al., 2020)
PLCZ1	PLCζ	PtdIns(4,5)P_2 (Kunrath-Lima et al., 2018)	Nucleus (Faenza et al., 2013; Sone et al., 2005)	Facilitate cancer cell proliferation and migration (Li and Luan, 2018)

This table provides an overview of the types of couriers/enzymes, their respective cargo/substrates, and specific nuclear locations for PITPs and PI-metabolizing enzymes, including PIP_n kinases, phosphatases, and phospholipases. It also details the roles of these proteins in cell motility. Their nuclear localization likely contributes to their role in regulating cell motility, a function that warrants further investigation.

Ku86, miR-34a, Fas, Bax, and others (Li et al., 2002; Meza-Sosa et al., 2022; Okazaki, 2022; Sigalotti et al., 2010). These genes are crucial for cell cycle arrest, DNA repair, and apoptosis, thus positioning p53 as a central regulator in maintaining genomic integrity and preventing tumorigenesis.

Mutations in the *TP53* gene are the most common genetic alterations found in human cancers, occurring in nearly every type of cancer, such as lung, breast, colon, and ovarian cancers (Hollstein et al., 1991; Langerød et al., 2007; Olivier et al., 2010; Wang et al., 2004a, 2004b). These mutations can lead to various outcomes, primarily resulting in a loss of p53's transcriptional activity and tumor-suppressive functions (Hollstein et al., 1991; Olivier et al., 2010). In many cases, mutated p53 proteins acquire dominant-negative properties, where they fail to transcribe target genes and inhibit the activity of any remaining wild-type p53 (de Vries et al., 2002; Kennedy and Lowe, 2022). This interference allows cancer cells to bypass critical regulatory checkpoints, evading growth control mechanisms and apoptotic pathways that would generally curtail their proliferation (Butera and Amelio, 2024; de Vries et al., 2002; Kennedy and Lowe, 2022). The pervasive nature of *TP53* mutations underscores the importance of p53 as a guardian of the genome and highlights its central role in cancer biology (Fig. 3).

Beyond its role in regulating cell survival, p53 also prominently contributes to cancer cell motility, which is fundamental to the mechanisms of cancer metastasis (Walerych et al., 2012, 2015). Cell motility, the ability of cells to move, is tightly regulated in healthy cells; however, in cancer, this process becomes dysregulated, enabling cancerous cells to invade surrounding tissues and metastasize to distant sites (Stuelten et al., 2018).

p53 affects cell motility by influencing several vital mechanisms, including cytoskeleton regulation, epithelial-to-mesenchymal transition (EMT), and control of cell adhesion (Araki et al., 2015; Chang et al., 2011; Coutts et al., 2009; Muller et al., 2011; Yeudall et al., 2013). Through regulation of actin filament dynamics, p53 helps maintain cytoskeletal stability, preventing overactive rearrangements associated with increased cell motility. Specifically, p53 modulates cell motility by impacting the activity of key Rho GTPases, including RhoA, Rac1, and Cdc42, which are essential regulators of actin cytoskeletal dynamics (Araki et al., 2015; Gadea et al., 2007; Gadéa et al., 2002; Guo et al., 2003; Mizuarai et al., 2006; Muller et al., 2011). These GTPases control various aspects of actin polymerization and organization, contributing to forming cellular protrusions such as lamellipodia and filopodia, which are critical for cell movement (Charest and Firtel, 2007; Gadéa et al., 2002; Srinivasan et al., 2003). By inhibiting the activity of RhoA,

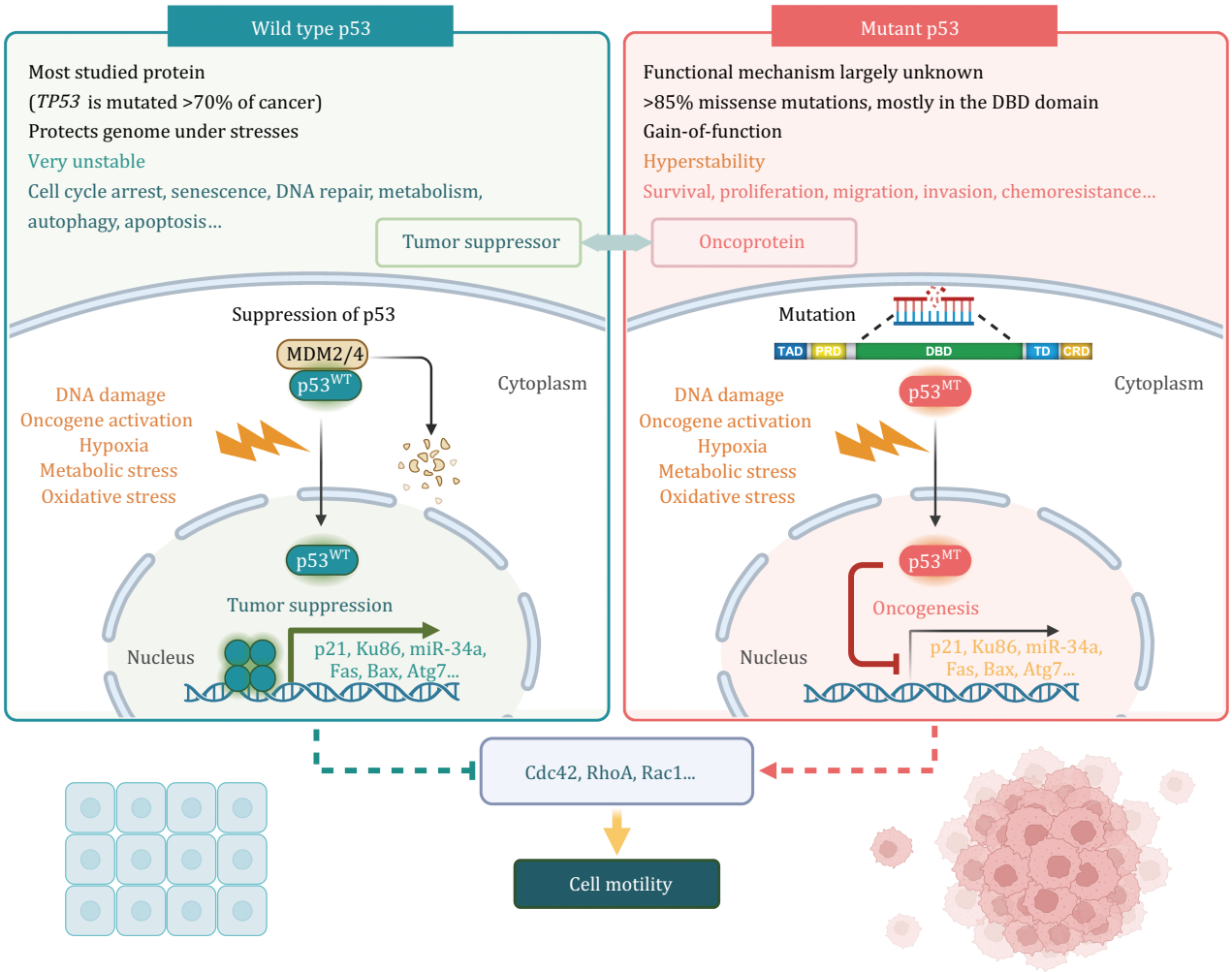

Figure 3. Functional comparison of wild type and mutant p53. Schematic representation compares wild type p53 (p53^{WT}) and mutant p53 (p53^{MT}) roles. Wild type p53, encoded by the *TP53* gene, is one of the most extensively studied proteins and is mutated in over 70% of cancers. Under normal conditions, p53^{WT} is highly unstable, as it binds to MDM2/4, leading to its ubiquitination and degradation. Upon cellular stress, p53^{WT} translocates to the nucleus, forms a tetramer, and functions as a transcription factor. It activates the expression of genes encoding p21, Ku86, miR-34a, Fas, Bax, and Atg7, which promote cell cycle arrest, senescence, DNA repair, metabolism, autophagy, and apoptosis. In contrast, p53^{MT} loses its transcriptional activity but exhibits gain-of-function properties. With over 85% of mutations being missense, mainly in the DNA-binding domain (DBD), p53^{MT} becomes hyperstable. It is constitutively expressed at basal levels and further upregulated under stress, functioning as an oncoprotein that promotes cancer cell survival, proliferation, migration, invasion, and chemoresistance. The proposed roles of both wild type and mutant p53 in tumor suppression and oncogenesis could affect critical regulators of cell dynamics, such as Cdc42, RhoA, and Rac1, thereby modulating cell motility. The figure was created using BioRender.

wild-type p53 reduces stress fiber formation, promoting a more rounded cellular morphology that is less conducive to invasive behavior (Gadea et al., 2007).

Conversely, mutant p53 can indirectly activate RhoA through the intermediary of guanine nucleotide exchange factor-H1 (GEF-H1), which enhances the directional migration of cells (Mizuarai et al., 2006). Furthermore, the wild-type p53 protein exerts an inhibitory effect on the activity of Cdc42, consequently impeding the formation of filopodia and suppressing cell motility (Gadéa et al., 2002). Many mutant p53 variants engage in a molecular interaction with Rac1, consequently impeding the association between Rac1 and the SENP1 (SUMO-specific protease 1). This interaction abrogates the SENP1-dependent de-SUMOylation of Rac1, a prerequisite for activating Rac1, thereby facilitating tumor progression (Yue et al., 2017). Moreover, p53's regulation of these GTPases is crucial for maintaining the balance between motility and adhesion, ensuring that cells do not become overly mobile, which could lead to local and distant metastasis. This dual role highlights p53's importance in tumor suppression and in regulating the delicate interplay between cell adhesion and motility, further demonstrating diverse therapeutic avenues to explore in the treatment of cancers with mutant p53.

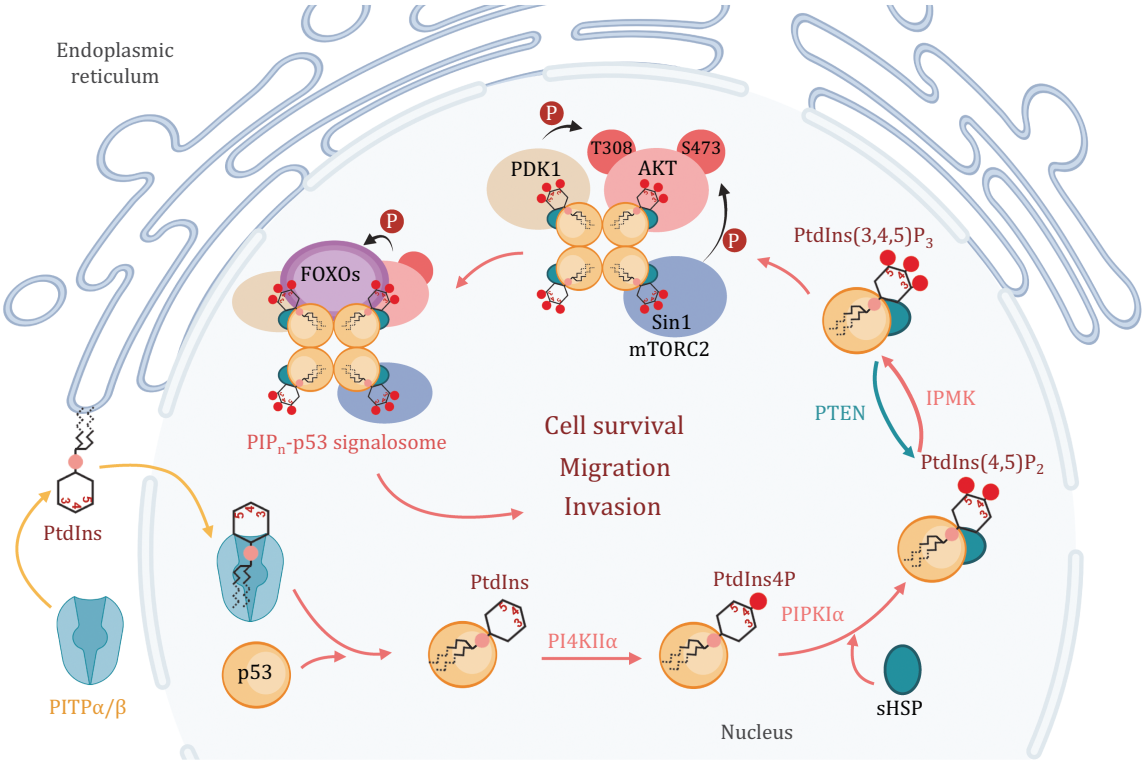

Figure 4. Nuclear PIP$_n$-p53 signalosome assembly and function in cell survival and motility. The nuclear PIP$_n$-p53 signalosome, a key regulator of cancer cell survival and motility, is assembled through interactions between PIP$_n$s, PITPs, kinases, phosphatases, p53, and downstream nuclear effectors. Critical steps in its formation include PI transport to the nucleus by class I PITPs, phosphorylation to PtdIns4P by PI4KIIα, and the generation of PtdIns(4,5)P$_2$ and PtdIns(3,4,5)P$_3$ by PIPKIα and IPMK, respectively. These lipids stabilize p53 and activate nuclear AKT, affecting cell survival and motility. Regulation by wild-type p53 ensures cellular homeostasis, while mutant p53 drives constitutive AKT activation and oncogenic processes. PTEN counteracts this by dephosphorylating PtdIns(3,4,5 P$_3$ to PtdIns(4,5)P$_2$, preventing further AKT activation. This model highlights the pivotal role of the nuclear PIP$_n$-p53 signalosome in modulating cancer cell behavior. The figure was created using BioRender.

In summary, p53 is critical in controlling cancer cell behavior, particularly in preventing cell motility and metastasis. However, when p53 is mutated or dysregulated, these protective mechanisms are lost, leading to increased cancer progression and metastasis and connecting p53 dysfunction to many hallmarks of aggressive cancers. Understanding the role of p53 in regulating cancer cell motility is vital for developing targeted therapies to restore its wild-type function and mitigate mutant oncogenic functions to prevent metastatic disease.

Assembly of the nuclear PIP$_n$-p53 signalosome

Within the nucleus, PIP$_n$s interact with various nuclear proteins, including p53, speckle-targeted PIPKIα-regulated poly(A) polymerase (Star-PAP), steroidogenic factor-1 (SF-1), nuclear factor erythroid 2-related factor 2 (NRF2), and Hippo pathway effectors such as yes-associated protein 1 (YAP), to form functional signalosomes that regulate essential cellular processes (Chen et al., 2024; Enomoto et al., 2005; Jung et al., 2024; Mellman et al., 2008; Wang and Sheetz, 2022). The nuclear PIP$_n$-p53 signalosome, in particular, plays a critical role in modulating cancer cell motility and invasion.

Our recent findings revealed that the PIP$_n$-p53 signalosome is central to regulating cancer cell motility, especially during cancer progression and metastasis, when cell movement and invasion into surrounding tissues are crucial (Chen et al., 2021, 2022; Choi et al., 2019). This signalosome is formed by interacting with various PIP$_n$ species, kinases, phosphatases, and lipid effectors, with both wild-type and mutant p53 in the nucleus (Ren et al., 2024) (Fig. 4).

The assembly of the nuclear PIP$_n$-p53 signalosome begins with the transport of PI from the ER to the nucleus by PITPs. Notably, class I PITPβ was identified as a significant component of the p53 interactome (Huang et al., 2012), and we later demonstrated that both class I PITPα and PITPβ interact with p53 inside the nucleus in a stress-responsive manner (Carrillo et al., 2023). The stress-induced nuclear accumulation of PIP$_n$s is primarily driven by class I PITPs, while class II PITPs, including PITPNC1, PITPNM1, and PITPNM2, play a minimal role in

maintaining or inducing nuclear PIP_n pools (Carrillo et al., 2023; Wen et al., 2024).

Once in the nucleus, PI complexed with p53 recruits PI kinase PI4KIIα to initiate signaling by phosphorylating PI into PtdIns4P (Carrillo et al., 2023). This newly generated PtdIns4P further recruits phosphatidylinositol phosphokinase type I alpha (PIPKIα) under conditions of cellular stress, which phosphorylates PtdIns4P to produce $PtdIns(4,5)P_2$ directly linked to p53 (Choi et al., 2019). $PtdIns(4,5)P_2$ generation stabilizes p53 by facilitating its interaction with molecular chaperones HSP27 (HSPB1) and αB-crystallin (HSPB5) (Choi et al., 2019). These interactions are crucial for maintaining the nuclear stability of p53 under stress as inhibition of PIPKIα activity or disruption of $PtdIns(4,5)P_2$ binding to p53 results in the destabilization of nuclear p53, highlighting the importance of this pathway in maintaining p53 functionality.

The triphosphate form of PI, $PtdIns(3,4,5)P_3$, generated at the signalosome complex on p53 in the nucleus, activates nuclear AKT in response to genotoxic stress via a unique p53-dependent mechanism (Chen et al., 2022). When exposed to genotoxic stress, nuclear inositol polyphosphate multikinase (IPMK) associates with p53 in non-membrane nucleoplasm, forming a complex that includes p53 and $PtdIns(3,4,5)P_3$ (Chen et al., 2022). This complex recruits key signaling molecules dependent on $PtdIns(3,4,5)P_3$ binding, such as phosphoinositide-dependent kinase 1 (PDK1), which phosphorylates AKT at threonine 308, and mammalian target of rapamycin complex 2 (mTORC2), which phosphorylates AKT at serine 473. This process fully activates AKT in the nucleus. Once activated, AKT phosphorylates forkhead box O (FOXO) proteins, leading to FOXO degradation and the subsequent suppression of DNA damage-induced apoptosis (Chen et al., 2022).

The activation of nuclear AKT is tightly regulated by wild-type p53, which modulates AKT activation in response to stress stimuli (Chen et al., 2022). In contrast, mutant p53 results in consistently elevated basal AKT activity, which is dose-dependent and contributes to oncogenic processes (Carrillo et al., 2023; Chen et al., 2022). The $PtdIns(3,4,5)P_3$-p53 complex is eventually dephosphorylated by phosphatase and tensin homolog deleted on chromosome ten (PTEN), converting it into a $PtdIns(4,5)P_2$-p53 complex that is insufficient for PDK1 and mTORC2 recruitment preventing further AKT activation (Chen et al., 2022).

Regulation of the nuclear PIP_n-p53 signalosome on cell motility

PI is transported into the nucleus by class I PITPs, contributing to forming a nuclear PIP_n pool (Carrillo et al., 2023; Wen et al., 2024). Within the nucleus, its downstream metabolites—PtdIns4P, $PtdIns(4,5)P_2$, and $PtdIns(3,4,5)P_3$—along with the enzymes responsible for their synthesis, are also present (Chen et al., 2021, 2022; Choi et al., 2019). In this context, p53 functions as a nuclear scaffolding protein, analogous to the cytosolic scaffold protein IQ motif-containing GTPase-activating protein 1 (IQGAP1) platform (Chen et al., 2019; Choi et al., 2016), assembling a signalosome with PIP_ns. This PIP_n-p53 signalosome regulates p53 stability and activates the AKT signaling pathway within the nucleus, thereby modulating various cellular processes (Fig. 4).

AKT signaling is a crucial pathway in various cellular processes, including cell growth, survival, proliferation, and metabolism (Cingolani and Goda, 2008; Ke et al., 2024; Vara et al., 2004). Human AKT comprises three isoforms (AKT1–3), each potentially serving distinct functions (Gonzalez and McGraw, 2009). Traditionally, AKT (also known as protein kinase B) has been studied in its roles at the plasma membrane, where it is activated by PIP_n signaling, particularly by $PtdIns(3,4,5)P_3$ generated by PI3K. However, further works have identified the existence of intranuclear AKT, which extends the functional repertoire of AKT beyond its classical cytoplasmic roles (Lee et al., 2008; Wainstein et al., 2022).

Since the 1990s, accumulating evidence has demonstrated that AKT is localized within the nucleus, with all three isoforms exhibiting a classic leucine-rich, leptomycin-sensitive nuclear export sequence (NES) (Ahmed et al., 1993; Meier et al., 1997; Saji et al., 2005). Notably, AKT is highly expressed in thyroid cancer, and its expression and localization correlate closely with cancer cell invasion and migration in this context (Vasko et al., 2004). Research by Ehud Wainstein et al. indicated that in breast cancer cells, AKT3 is constitutively phosphorylated at the nuclear membrane, facilitating the continuous phosphorylation of tuberous sclerosis complex 2 (TSC2) at this site (Wainstein et al., 2022). Moreover, the knockdown of AKT3 resulted in a moderate reduction in breast cancer cell proliferation. In non-small cell lung cancer (NSCLC), ionizing radiation (IR)-induced activation of nuclear AKT has been shown to depend significantly on human epidermal growth factor receptor 3 (HER3) expression (Toulany et al., 2022).

Furthermore, in PC12 cells, nuclear AKT interacts with nucleophosmin (NPM/B23), a protein that regulates cell growth and apoptosis, modulating its stability and activity (Lee et al., 2008). This interaction protects B23 from degradation, promotes cell survival, and influences cell cycle progression, with AKT2 specifically governing B23 SUMOylation. These findings underscore the multifaceted roles of intranuclear AKT in cancer biology, emphasizing its critical importance in regulating processes, such as cell survival, proliferation, and migration, which are essential for cancer progression and metastasis.

Nuclear AKT is instrumental in modulating cancer cell motility by influencing the dynamics of the actin

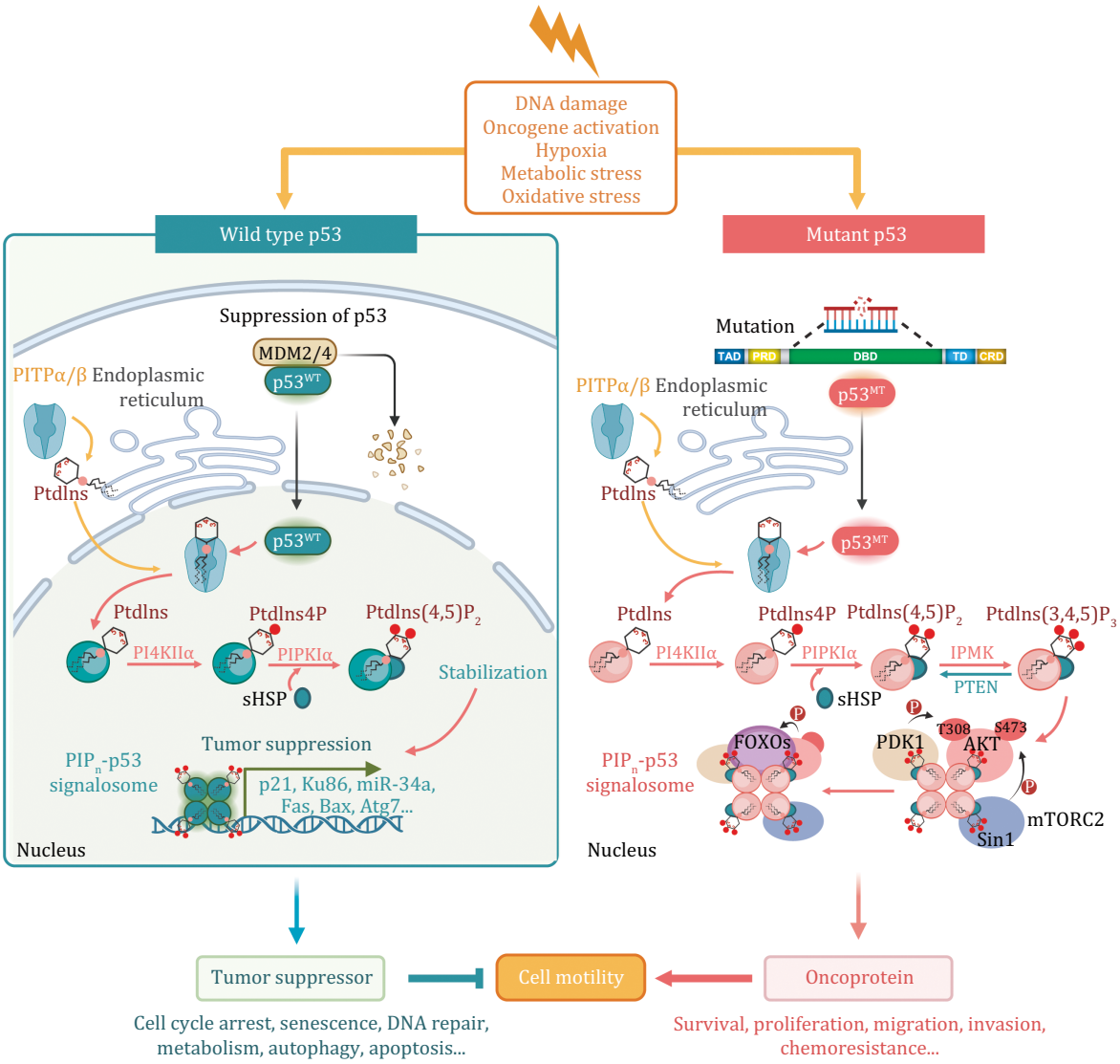

Figure 5. The nuclear PIP$_n$-p53 signalosome in regulating cell motility. This schematic illustrates the pivotal role of the nuclear PIP$_n$-p53 signalosome in regulating both p53^{WT} and p53^{MT} functions, with direct implications for cell motility. Under normal conditions, p53^{WT} is unstable due to its interaction with MDM2/4, leading to its ubiquitination and degradation. In response to stress, class I PITPα/β shuttles PI to the nucleus with p53^{WT}, forming the PIP$_n$-p53 signalosome. The binding of PtdIns(4,5)P$_2$ recruits sHSPs, stabilizing p53 and facilitating tetramer assembly. As a transcription factor, p53^{WT} activates genes that regulate cell cycle arrest, senescence, DNA repair, metabolism, autophagy, and apoptosis. In contrast, p53^{MT} forms a constitutive complex with PIP$_n$s, creating the PIP$_n$-p53 signalosome. Upon stress, nuclear targeting of class I PITPα/β enhances this signalosome formation, further stabilizing p53^{MT}. This also induces the generation of the PtdIns(3,4,5)P$_3$ pathway linked to p53^{MT}, leading to *de novo* activation of the nuclear AKT pathway, which drives oncogenesis, such as cancer cell survival, proliferation, migration, invasion, and chemoresistance. This graphical abstract underscores the central role of the nuclear PIP$_n$-p53 signalosome in modulating p53-mediated cellular functions, including cell motility. The figure was created using BioRender.

cytoskeleton, which is crucial for cell migration (Cheng et al., 2008; Manning and Toker, 2017; Martelli et al., 2012; Sale and Sale, 2008). Studies have demonstrated that AKT influences cell proliferation, division, and invasion by modulating downstream effectors such as mTORC2 and Rho GTPases (Enomoto et al., 2005; Xue and Hemmings, 2013; Yoeli-Lerner et al., 2005). While AKT has been identified as a nuclear protein with significant functional implications, the mechanisms underlying its activation within the nucleus have been controversial. Our research offers a novel perspective on the nuclear activation of AKT, emphasizing its relevance in this framework. The PIP$_n$-p53 signalosome activates the AKT signaling pathway independent of clinically targeted PI3Ks, impacting cellular activities through downstream signaling cascades.

Moreover, the stabilization of p53 within the nucleus, facilitated by PtdIns(4,5)P_2 and its associated small heat shock proteins, inhibits uncontrolled cell migration and invasion (Choi et al., 2019). When p53 is functional, it helps suppress EMT, a process by which cancer cells lose their epithelial characteristics and gain migratory properties (Chang et al., 2011; Coutts et al., 2009; Yeudall et al., 2013). However, when this signalosome is disrupted, either by mutations in p53 or alterations in nuclear PIP_n signaling, it can enhance cell motility and contribute to the invasive potential of metastatic cancer.

In summary, intranuclear PIP_ns play an essential role in maintaining the stability of p53 under stress. In this process, p53 acts as a scaffolding protein whereby PI-related enzymes and effectors form a complex with p53. PIP_ns affect the stability of p53 by creating an intricate complex in the nucleus involving multiple proteins, and PIP_ns thus directly affect cancer cell motility. The distinct nuclear PIP_n-p53 signaling pathway, independent of canonical membrane-bound AKT activation and unaffected by existing PI3K inhibitors, highlights the potential for innovative therapeutic interventions that target these specific interactions in cancer treatment.

Conclusion

The PIP_n-p53 signalosome has emerged as a crucial regulator of cancer cell motility by providing the missing link between the independent relationships of this cellular process with both p53 and PIP_n signaling, particularly in metastasis. This review has shown that nuclear PIP_ns, such as PtdIns4P, PtdIns(4,5)P_2, and PtdIns(3,4,5)P_3, interact with both wild type and mutant p53 to form signaling complexes that regulate cytoskeletal dynamics, cell adhesion, and nuclear AKT activation (Fig. 5). These interactions are essential in controlling the migration and invasion of cancer cells, with p53 acting as a critical scaffold in the nucleus to stabilize signaling pathways. Disruption of this signalosome through p53 mutations or altered PIP_n signaling promotes increased cell motility and metastasis, making this axis a promising target for therapeutic interventions.

The involvement of nuclear PIP_ns in both stabilizing p53 and activating AKT reflects a non-transcriptional function of p53 that is triggered under stress conditions (Chen et al., 2020, 2022; Choi et al., 2019). This mechanism operates in both wild type and mutant p53 contexts but is often amplified in cancer cells harboring mutant p53 due to the co-expression of nuclear PIP_n pathway components. Importantly, recent studies suggest that p53 is required for efficient nuclear PIP_n-mediated AKT activation under genotoxic stress, serving to organize the signaling complex and direct lipid channeling (Chen et al., 2022). However, the apparent contradiction between p53 stabilization and AKT activation can be reconciled by considering regulatory factors, including differential protein interactions, post-translational modifications, or the temporal dynamics of signalosome assembly, such as proximity to the PtdIns(3,4,5)P_3 phosphatase PTEN or nuclear AKT phosphatases (Chen et al., 2022; Chibaya et al., 2021; Huang et al., 2012; Ogawara et al., 2002; Zhang et al., 2011). These modulators likely dictate whether the net outcome favors tumor suppression or survival signaling.

To further elucidate the functional significance of this pathway, it is essential to consider the role of nuclear AKT activity in driving cancer cell motility. While AKT is traditionally associated with plasma membrane signaling, its nuclear functions have become increasingly recognized as key regulators of migration and invasion (Chen et al., 2022; Lee et al., 2008). Nuclear AKT phosphorylates transcription factors such as FOXO proteins, altering gene expression programs that influence cytoskeletal organization and cell adhesion (Hou et al., 2025b; Zhang et al., 2011). These transcriptional changes contribute to enhanced motility, particularly in metastatic cancer cells. Notably, aberrant nuclear AKT activation within the PIP_n-p53 signalosome has been linked to increased invasiveness, further underscoring its role as a central mediator of cell migration (Chen et al., 2022; Hou et al., 2025b). Understanding the interplay between nuclear PIP_ns, p53, and AKT in this context provides new insights into metastasis and highlights potential therapeutic strategies targeting this axis.

Combining PI3K/AKT inhibitors with agents that restore p53 function could produce a dual inhibitory effect on cancer cell migration (Abraham and O'Neill, 2014; Singh et al., 2002; Song et al., 2015; Turner et al., 2013). Cancer metastasis could be more effectively mitigated by blocking both the upstream activation of motility-related pathways (via PI3K inhibition) and restoring the ability of p53 to suppress cell motility. This combined approach may also enhance apoptosis in cancer cells, as p53 reactivation would regain its role in promoting cell death, while PI3K inhibition would reduce survival signaling. While most PI3K inhibitors, such as pan-PI3K inhibitors (e.g., BKM120 (buparlisib), GDC-0941), broadly suppress PI3K activity, recent studies have identified compounds with preferential nuclear activity (Sarker et al., 2015). For example, PI3Kα-specific inhibitors like BYL719 (alpelisib) have been shown to affect nuclear PtdIns(3,4,5)P_3 signaling, thereby modulating nuclear AKT activation in colorectal cancer (Palmieri et al., 2023). However, these effects may be cancer type-specific. In breast cancer cells, for instance, the nuclear PI3K isoform IPMK is responsible for generating nuclear PtdIns(3,4,5)P_3 and activating AKT (Chen et al., 2022). In this context, neither the pan-PI3K inhibitor BKM120 (buparlisib) nor the PI3Kα-specific inhibitor BYL719 (alpelisib) is effective, underscoring the need to develop more versatile PI3K inhibitors that also

target non-canonical isoforms such as IPMK (Chen et al., 2022).

Additionally, PI4KIIα is intricately linked to focal adhesion dynamics and plays a significant role in maintaining the stability of p53 (Carrillo et al., 2023; Sun et al., 2023). Targeting PI4KIIα to inhibit focal adhesion formation could be paired with therapies to reactivate wild-type p53 (Bura et al., 2023; Carrillo et al., 2023; Gozzelino et al., 2020). This combination strategy decreases the cancer cells' ability to establish stable attachments to the extracellular matrix, which is essential for migration and invasion, and it also suppresses pro-metastatic signals arising from mutant p53. By disrupting both the structural components of cell movement and the regulatory pathways influenced by p53, this integrated therapeutic approach holds promise for effectively reducing metastatic potential and improving treatment outcomes for patients with aggressive cancers. Further investigation into the structural dynamics of the PIP_n-p53 signalosome is needed to understand how these complexes regulate nuclear processes comprehensively. Detailed structural studies could reveal new therapeutic targets within this network.

Since nuclear PIP_n signaling is less understood than cytoplasmic signaling, more research is needed to develop specific inhibitors that target nuclear PIP_ns without affecting essential cytoplasmic functions. Future research will delve into the molecular mechanisms of these signalosomes, their role as biomarkers, and the development of targeted therapies.

A deeper understanding of how nuclear PIP_ns interact with p53 and other nuclear proteins is essential for unraveling the complex regulation of cancer cell motility. Studies should explore the structural and functional details of the nuclear PIP_n-p53 signalosome, particularly its role in mediating the nuclear localization and activity of essential signaling proteins.

Acknowledgments

We acknowledge the contributions of many significant studies that we cannot reference in this review due to space limitations. We sincerely thank all members of the 3rd Messenger Lab at UW–Madison and the PI Lab at the School of Medicine, Southern University of Science and Technology, for their valuable support.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

J.S. is supported by grants JCYJ20220818102611025 and RCYX20210706092040044 from the Science and Technology Foundation of Shenzhen, grant 82071193 from the National Natural Science Foundation of China, and grant 0920220233 from the Guangdong Zhujiang Program. M.C. is supported by grant JCYJ20240813094605008 from the Shenzhen Natural Science Foundation, grant D2301007 from the Shenzhen Medical Research Fund, grant 2023A1515110237 from the Guangdong Province Basic and Applied Basic Research Foundation, and grant 32400577 from the National Natural Science Foundation of China.

Consent for publication

All the authors listed have approved the manuscript.

Author contributions

X.H., Y.C., B.Z., J.S., and M.C. conceived and wrote the manuscript. X.H., Y.C., B.Z., and M.C. contributed to figure preparation. F.L., L.D., C.C., N.D.C., V.L.C., and R.A.A. provided critical insights and revisions to the manuscript. J.S. and M.C. supervised the study, provided funding support, and finalized the manuscript. All authors validated and approved the final manuscript.

References

Abraham AG, O'Neill E. PI3K/Akt-mediated regulation of p53 in cancer. *Biochem Soc Trans* 2014;**42**:798–803.

Agarwal ML, Taylor WR, Chernov MV *et al*. The p53 network. *J Biol Chem* 1998;**273**:1–4.

Ahmed NN, Franke TF, Bellacosa A *et al*. The proteins encoded by c-akt and v-akt differ in post-translational modification, subcellular localization and oncogenic potential. *Oncogene* 1993;**8**:1957–1963.

Alli-Balogun GO, Gewinner CA, Jacobs R *et al*. Phosphatidylinositol 4-kinase IIβ negatively regulates invadopodia formation and suppresses an invasive cellular phenotype. *Mol Biol Cell* 2016;**27**:4033–4042.

Araki K, Ebata T, Guo AK *et al*. p53 regulates cytoskeleton remodeling to suppress tumor progression. *Cell Mol Life Sci* 2015;**72**:4077–4094.

Ashlin TG, Blunsom NJ, Cockcroft S. Courier service for phosphatidylinositol: PITPs deliver on demand. *Biochim Biophys Acta Mol Cell Biol Lipids* 2021;**1866**:158985.

Balla T. Phosphoinositides: tiny lipids with giant impact on cell regulation. *Physiol Rev* 2013;**93**:1019–1137.

Balla A, Balla T. Phosphatidylinositol 4-kinases: old enzymes with emerging functions. *Trends Cell Biol* 2006;**16**:351–361.

Banfic H, Visnjic D, Mise N *et al*. Epidermal growth factor stimulates translocation of the class II phosphoinositide 3-kinase PI3K-C2β to the nucleus. *Biochem J* 2009;**422**:53–60.

Barlow CA, Laishram RS, Anderson RA. Nuclear phosphoinositides: a signaling enigma wrapped in a compartmental conundrum. *Trends Cell Biol* 2010;**20**:25–35.

Blind RD, Suzawa M, Ingraham HA. Direct modification and activation of a nuclear receptor-PIP_2 complex by the inositol lipid kinase IPMK. *Sci Signal* 2012;**5**:ra44.

Blunsom NJ, Cockcroft S. CDP-diacylglycerol synthases (CDS): gateway to phosphatidylinositol and cardiolipin synthesis. *Front Cell Dev Biol* 2020a;**8**:63.

Blunsom NJ, Cockcroft S. Phosphatidylinositol synthesis at the endoplasmic reticulum. *Biochim Biophys Acta Mol Cell Biol Lipids* 2020b;**1865**:158471.

Boronenkov IV, Loijens JC, Umeda M *et al*. Phosphoinositide signaling pathways in nuclei are associated with nuclear speckles containing pre-mRNA processing factors. *Mol Biol Cell* 1998;**9**:3547–3560.

Bunce MW, Boronenkov IV, Anderson RA. Coordinated activation of the nuclear ubiquitin ligase Cul3-SPOP by the generation of phosphatidylinositol 5-phosphate. *J Biol Chem* 2008;**283**:8678–8686.

Bura A, Čabrijan S, Đurić I *et al*. A plethora of functions condensed into tiny phospholipids: the story of PI4P and PI (4,5)P_2. *Cells* 2023;**12**:1411.

Butera A, Amelio I. Deciphering the significance of p53 mutant proteins. *Trends Cell Biol* 2025;**35**:258–268.

Carrillo ND, Chen M, Wen T *et al*. Lipid transfer proteins and a PI 4-kinase initiate nuclear phosphoinositide signaling. *BioRxiv* 2025:2023.05.08.539894.

Chakrabarti R, Sanyal S, Ghosh A *et al*. Phosphatidylinositol-4-phosphate 5-kinase 1α modulates ribosomal RNA gene silencing through its interaction with histone H3 Lysine 9 trimethylation and heterochromatin protein HP1-α. *J Biol Chem* 2015;**290**:20893–20903.

Chang CJ, Chao CH, Xia W *et al*. p53 regulates epithelial-mesenchymal transition and stem cell properties through modulating miRNAs. *Nat Cell Biol* 2011;**13**:317–323.

Charest PG, Firtel RA. Big roles for small GTPases in the control of directed cell movement. *Biochem J* 2007;**401**:377–390.

Chen M, Choi S, Jung O *et al*. The specificity of EGF-stimulated IQGAP1 scaffold towards the PI3K-Akt pathway is defined by the IQ3 motif. *Sci Rep* 2019;**9**:9126.

Chen M, Wen T, Horn HT *et al*. The nuclear phosphoinositide response to stress. *Cell Cycle* 2020;**19**:268–289.

Chen M, Horn HT, Wen T *et al*. Assessing *in situ* phosphoinositide-protein interactions through fluorescence proximity ligation assay in cultured cells. *Methods Mol Biol* 2021;**2251**:133–142.

Chen M, Choi S, Wen T *et al*. A p53–phosphoinositide signalosome regulates nuclear AKT activation. *Nat Cell Biol* 2022;**24**:1099–1113.

Chen C, Chen M, Wen T *et al*. Regulation of NRF2 by Phosphoinositides and small heat shock proteins. *bioRxiv* **2024**:2023.10.26.564194.

Cheng GZ, Zhang W, Wang L-H. Regulation of cancer cell survival, migration, and invasion by Twist: AKT2 comes to interplay. *Cancer Res* 2008;**68**:957–960.

Chibaya L, Karim B, Zhang H *et al*. Mdm2 phosphorylation by Akt regulates the p53 response to oxidative stress to promote cell proliferation and tumorigenesis. *Proc Natl Acad Sci USA* 2021;**118**:e2003193118.

Choi BH, Chen Y, Dai W. Chromatin PTEN is involved in DNA damage response partly through regulating Rad52 sumoylation. *Cell Cycle* 2013;**12**:3442–3447.

Choi S, Hedman AC, Sayedyahossein S *et al*. Agonist-stimulated phosphatidylinositol-3,4,5-trisphosphate generation by scaffolded phosphoinositide kinases. *Nat Cell Biol* 2016;**18**:1324–1335.

Choi S, Chen M, Cryns VL *et al*. A nuclear phosphoinositide kinase complex regulates p53. *Nat Cell Biol* 2019;**21**:462–475.

Cingolani LA, Goda Y. Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. *Nat Rev Neurosci* 2008;**9**:344–356.

Cocco L, Gilmour RS, Ognibene A *et al*. Synthesis of polyphosphoinositides in nuclei of Friend cells. Evidence for polyphosphoinositide metabolism inside the nucleus which changes with cell differentiation. *Biochem J* 1987;**248**:765–770.

Cocco L, Rubbini S, Manzoli L *et al*. Inositides in the nucleus: presence and characterisation of the isozymes of phospholipase β family in NIH 3T3 cells. *Biochim Biophys Acta* 1999;**1438**:295–299.

Coutts AS, Weston L, La Thangue NB. A transcription co-factor integrates cell adhesion and motility with the p53 response. *Proc Natl Acad Sci USA* 2009;**106**:19872–19877.

de Graaf P, Klapisz EE, Schulz TK *et al*. Nuclear localization of phosphatidylinositol 4-kinase β. *J Cell Sci* 2002;**115**:1769–1775.

Deleris P, Bacqueville D, Gayral S *et al*. SHIP-2 and PTEN are expressed and active in vascular smooth muscle cell nuclei, but only SHIP-2 is associated with nuclear speckles. *J Biol Chem* 2003;**278**:38884–38891.

de Vries A, Flores ER, Miranda B *et al*. Targeted point mutations of *p53* lead to dominant-negative inhibition of wild-type p53 function. *Proc Natl Acad Sci USA* 2002;**99**:2948–2953.

Didichenko SA, Thelen M. Phosphatidylinositol 3-kinase c2α contains a nuclear localization sequence and associates with nuclear speckles. *J Biol Chem* 2001;**276**:48135–48142.

Ehm P, Nalaskowski MM, Wundenberg T *et al*. The tumor suppressor SHIP1 colocalizes in nucleolar cavities with p53 and components of PML nuclear bodies. *Nucleus* 2015;**6**:154–164.

Elis W, Triantafellow E, Wolters NM *et al*. Down-regulation of class II phosphoinositide 3-kinase alpha expression below a critical threshold induces apoptotic cell death. *Mol Cancer Res* 2008;**6**:614–623.

Elong Edimo W, Derua R, Janssens V *et al*. Evidence of SHIP2 Ser132 phosphorylation, its nuclear localization and stability. *Biochem J* 2011;**439**:391–401.

Enomoto A, Murakami H, Asai N *et al*. Akt/PKB regulates actin organization and cell motility via Girdin/APE. *Dev Cell* 2005;**9**:389–402.

Faenza I, Fiume R, Piazzi M *et al*. Nuclear inositide specific phospholipase C signalling – interactions and activity. *FEBS J* 2013;**280**:6311–6321.

Gadéa G, Lapasset L, Gauthier-Rouvière C *et al*. Regulation of Cdc42-mediated morphological effects: a novel function for p53. *EMBO J* 2002;**21**:2373–2382.

Gadea G, de Toledo M, Anguille C *et al*. Loss of p53 promotes RhoA–ROCK-dependent cell migration and invasion in 3D matrices. *J Cell Biol* 2007;**178**:23–30.

Gonzalez E, McGraw TE. The Akt kinases: isoform specificity in metabolism and cancer. *Cell cycle* 2009;**8**:2502–2508.

Govindarajan B, Sbrissa D, Pressprich M *et al*. Adaptor proteins mediate CXCR4 and PI4KA crosstalk in prostate cancer cells and the significance of PI4KA in bone tumor growth. *Sci Rep* 2023;**13**:20634.

Gozani O, Karuman P, Jones DR *et al*. The PHD Finger of the chromatin-associated protein ING2 functions as a nuclear phosphoinositide receptor. *Cell* 2003;**114**:99–111.

Gozzelino L, De Santis MC, Gulluni F *et al*. PI(3,4)P2 signaling in cancer and metabolism. *Front Oncol* 2020;**10**:360.

Guo F, Gao Y, Wang L *et al*. p19Arf-p53 tumor suppressor pathway regulates cell motility by suppression of phosphoinositide 3-kinase and Rac1 GTPase activities. *J Biol Chem* 2003;**278**:14414–14419.

Hao Y, He B, Wu L *et al*. Nuclear translocation of p85β promotes tumorigenesis of PIK3CA helical domain mutant cancer. *Nat Commun* 2022;**13**:1974.

Hassin O, Oren M. Drugging p53 in cancer: one protein, many targets. *Nat Rev Drug Discovery* 2023;**22**:127–144.

Hollstein M, Sidransky D, Vogelstein B *et al*. p53 mutations in human cancers. *Science* 1991;**253**:49–53.

Hou X, Chen Y, Carrillo ND *et al*. Phosphoinositide signaling at the cytoskeleton in the regulation of cell dynamics. *Cell Death Dis* 2025a;**16**:296.

Hou X, Ren C, Jin J *et al*. Phosphoinositide signalling in cell motility and adhesion. *Nat Cell Biol* 2025b;**27**:736–748.

Hsuan J, Cockcroft S. The PITP family of phosphatidylinositol transfer proteins. *Genome Biol* 2001;**2**:REVIEWS3011.

Huang Y, Jeong JS, Okamura J *et al*. Global tumor protein p53/p63 interactome: making a case for cisplatin chemoresistance. *Cell Cycle* 2012;**11**:2367–2379.

Isaji T, Im S, Kameyama A *et al*. A complex between phosphatidylinositol 4-kinase IIα and integrin α3β1 is required for N-glycan sialylation in cancer cells. *J Biol Chem* 2019;**294**:4425–4436.

Jean S, Kiger AA. Classes of phosphoinositide 3-kinases at a glance. *J Cell Sci* 2014;**127**:923–928.

Jung O, Baek M-j, Wooldrik C *et al*. Nuclear phosphoinositide signaling promotes YAP/TAZ-TEAD transcriptional activity in breast cancer. *EMBO J* 2024;**43**:1740–1769.

Kakuk A, Friedlander E, Vereb G *et al*. Nucleolar localization of phosphatidylinositol 4-kinase PI4K230 in various mammalian cells. *Cytometry A* 2006;**69**:1174–1183.

Kakuk A, Friedlander E, Vereb G *et al*. Nuclear and nucleolar localization signals and their targeting function in phosphatidylinositol 4-kinase PI4K230. *Exp Cell Res* 2008;**314**:2376–2388.

Kandoth C, McLellan MD, Vandin F *et al*. Mutational landscape and significance across 12 major cancer types. *Nature* 2013;**502**:333–339.

Karlsson T, Altankhuyag A, Dobrovolska O *et al*. A polybasic motif in ErbB3-binding protein 1 (EBP1) has key functions in nucleolar localization and polyphosphoinositide interaction. *Biochem J* 2016;**473**:2033–2047.

Ke M, Zhu H, Lin Y *et al*. Actin-related protein 2/3 complex subunit 1B promotes ovarian cancer progression by regulating the AKT/PI3K/mTOR signaling pathway. *J Transl Int Med* 2024;**12**:406–423.

Kennedy MC, Lowe SW. Mutant p53: it's not all one and the same. *Cell Death Differ* 2022;**29**:983–987.

Kouchi Z, Fujiwara Y, Yamaguchi H *et al*. Phosphatidylinositol 5-phosphate 4-kinase type II beta is required for vitamin D receptor-dependent E-cadherin expression in SW480 cells. *Biochem Biophys Res Commun* 2011;**408**:523–529.

Kruse J-P, Gu W. Modes of p53 Regulation. *Cell* 2009;**137**:609–622.

Kubbutat MH, Jones SN, Vousden KH. Regulation of p53 stability by Mdm2. *Nature* 1997;**387**:299–303.

Kumar A, Redondo-Munoz J, Perez-Garcia V *et al*. Nuclear but not cytosolic phosphoinositide 3-kinase beta has an essential function in cell survival. *Mol Cell Biol* 2011;**31**:2122–2133.

Kunrath-Lima M, de Miranda MC, Ferreira ADF *et al*. Phospholipase C delta 4 (PLCδ4) is a nuclear protein involved in cell proliferation and senescence in mesenchymal stromal stem cells. *Cell Signal* 2018;**49**:59–67.

Langerød A, Zhao H, Borgan O *et al*. TP53 mutation status and gene expression profiles are powerful prognostic markers of breast cancer. *Breast Cancer Res* 2007;**9**:R30.

Lattanzio R, Iezzi M, Sala G *et al*. PLC-gamma-1 phosphorylation status is prognostic of metastatic risk in patients with early-stage Luminal-A and -B breast cancer subtypes. *BMC Cancer* 2019;**19**:747.

Lee SB, Xuan Nguyen TL, Choi JW *et al*. Nuclear Akt interacts with B23/NPM and protects it from proteolytic cleavage, enhancing cell survival. *Proc Natl Acad Sci USA* 2008;**105**:16584–16589.

Li Y, Luan C. PLCE1 promotes the invasion and migration of esophageal cancer cells by up-regulating the PKCα/NF-κB pathway. *Yonsei Med J* 2018;**59**:1159–1165.

Li G, Nelsen C, Hendrickson EA. Ku86 is essential in human somatic cells. *Proc Natl Acad Sci USA* 2002;**99**:832–837.

Li P, Wang D, Li H *et al*. Identification of nucleolus-localized PTEN and its function in regulating ribosome biogenesis. *Mol Biol Rep* 2014;**41**:6383–6390.

Li J, Gao Z, Zhao D *et al*. PI-273, a substrate-competitive, specific small-molecule inhibitor of PI4KIIα, inhibits the growth of breast cancer cells. *Cancer Res* 2017;**77**:6253–6266.

Manning BD, Toker A. AKT/PKB signaling: navigating the network. *Cell* 2017;**169**:381–405.

Mantovani F, Collavin L, Del Sal G. Mutant p53 as a guardian of the cancer cell. *Cell Death Differ* 2019;**26**:199–212.

Manzoli FA, Maraldi NM, Cocco L *et al*. Chromatin phospholipids in normal and chronic lymphocytic leukemia lymphocytes. *Cancer Res* 1977;**37**:843–849.

Marques M, Kumar A, Poveda AM *et al*. Specific function of phosphoinositide 3-kinase beta in the control of DNA replication. *Proc Natl Acad Sci USA* 2009;**106**:7525–7530.

Martelli AM, Tabellini G, Bressanin D *et al*. The emerging multiple roles of nuclear Akt. *Biochim Biophys Acta* 2012;**1823**:2168–2178.

May P, May E. Twenty years of p53 research: structural and functional aspects of the p53 protein. *Oncogene* 1999;**18**:7621–7636.

Mazloumi Gavgani F, Smith Arnesen V, Jacobsen RG *et al*. Class I Phosphoinositide 3-Kinase PIK3CA/p110α and PIK3CB/p110β Isoforms in Endometrial Cancer. *Int J Mol Sci* 2018;**19**:3931.

Meier R, Alessi DR, Cron P *et al*. Mitogenic activation, phosphorylation, and nuclear translocation of protein kinase Bbeta. *J Biol Chem* 1997;**272**:30491–30497.

Mellman DL, Gonzales ML, Song C *et al*. A PtdIns4, 5P2-regulated nuclear poly (A) polymerase controls expression of select mRNAs. *Nature* 2008;**451**:1013–1017.

Merino-Casallo F, Gomez-Benito MJ, Hervas-Raluy S *et al*. Unravelling cell migration: defining movement from the cell surface. *Cell Adh Migr* 2022;**16**:25–64.

Meza-Sosa KF, Miao R, Navarro F *et al*. SPARCLE, a p53-induced lncRNA, controls apoptosis after genotoxic stress by promoting PARP-1 cleavage. *Mol Cell* 2022;**82**:785–802.e10.

Mizuarai S, Yamanaka K, Kotani H. Mutant p53 induces the GEF-H1 oncogene, a guanine nucleotide exchange factor-H1 for RhoA, resulting in accelerated cell proliferation in tumor cells. *Cancer Res* 2006;**66**:6319–6326.

Morrow AA, Alipour MA, Bridges D *et al*. The lipid kinase PI4KIIIβ is highly expressed in breast tumors and activates Akt in cooperation with Rab11a. *Mol Cancer Res* 2014;**12**:1492–1508.

Muller PA, Vousden KH, Norman JC. p53 and its mutants in tumor cell migration and invasion. *J Cell Biol* 2011;**192**:209–218.

Neri LM, Bortul R, Borgatti P *et al*. Proliferating or differentiating stimuli act on different lipid-dependent signaling pathways in nuclei of human leukemia cells. *Mol Biol Cell* 2002;**13**:947–964.

Ogawara Y, Kishishita S, Obata T *et al*. Akt enhances Mdm2-mediated ubiquitination and degradation of p53. *J Biol Chem* 2002;**277**:21843–21850.

Okazaki R. Role of p53 in regulating radiation responses. *Life (Basel, Switzerland)* 2022;**12**:1099.

Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. *Cold Spring Harb Perspect Biol* 2010;**2**:a001008.

Oren M, Prives C. p53: a tale of complexity and context. *Cell* 2024;**187**:1569–1573.

Owusu Obeng E, Rusciano I, Marvi MV *et al*. Phosphoinositide-dependent signaling in cancer: a focus on phospholipase C isozymes. *Int J Mol Sci* 2020;**21**:2581.

Palmieri M, Catimel B, Mouradov D *et al*. PI3Kα translocation mediates nuclear PtdIns(3,4,5)P_3 effector signaling in colorectal cancer. *Mol Cell Proteomics* 2023;**22**:100529.

Pedicone C, Meyer ST, Chisholm JD *et al*. Targeting SHIP1 and SHIP2 in cancer. *Cancers (Basel)* 2021;**13**:890.

Posor Y, Jang W, Haucke V. Phosphoinositides as membrane organizers. *Nat Rev Mol Cell Biol* 2022;**23**:797–816.

Razmara M, Heldin CH, Lennartsson J. Platelet-derived growth factor-induced Akt phosphorylation requires mTOR/Rictor and phospholipase C-γ1, whereas S6 phosphorylation depends on mTOR/Raptor and phospholipase D. *Cell Commun Signal* 2013;**11**:3.

Ren C, Carrillo ND, Cryns VL *et al*. Environmental pollutants and phosphoinositide signaling in autoimmunity. *J Hazard Mater* 2024;**465**:133080.

Rose HG, Frenster JH. Composition and metabolism of lipids within repressed and active chromatin of interphase lymphocytes. *Biochim Biophys Acta* 1965;**106**:577–591.

Russo A, Okur MN, Bosland M *et al*. Phosphatidylinositol 3-kinase, class 2 beta (PI3KC2β) isoform contributes to neuroblastoma tumorigenesis. *Cancer Lett* 2015;**359**:262–268.

Saji M, Vasko V, Kada F *et al*. Akt1 contains a functional leucine-rich nuclear export sequence. *Biochem Biophys Res Commun* 2005;**332**:167–173.

Sale E, Sale G. Protein kinase B: signalling roles and therapeutic targeting. *Cell Mol Life Sci* 2008;**65**:113–127.

Sarker D, Ang JE, Baird R *et al*. First-in-human phase I study of pictilisib (GDC-0941), a potent pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor, in patients with advanced solid tumors. *Clin Cancer Res* 2015;**21**:77–86.

Sbrissa D, Semaan L, Govindarajan B *et al*. A novel cross-talk between CXCR4 and PI4KIIIα in prostate cancer cells. *Oncogene* 2019;**38**:332–344.

Schill NJ, Anderson RA. Two novel phosphatidylinositol-4-phosphate 5-kinase type Igamma splice variants expressed in human cells display distinctive cellular targeting. *Biochem J* 2009;**422**:473–482.

Seok YM, Azam MA, Okamoto Y *et al*. Enhanced Ca^{2+}-dependent activation of phosphoinositide 3-kinase class IIα isoform-Rho axis in blood vessels of spontaneously hypertensive rats. *Hypertension* 2010;**56**:934–941.

Shen WH, Balajee AS, Wang J *et al*. Essential role for nuclear PTEN in maintaining chromosomal integrity. *Cell* 2007;**128**:157–170.

Sigalotti L, Covre A, Fratta E *et al*. Epigenetics of human cutaneous melanoma: setting the stage for new therapeutic strategies. *J Transl Med* 2010;**8**:1–22.

Sindić A, Aleksandrova A, Fields AP *et al*. Presence and activation of nuclear phosphoinositide 3-kinase C2β during compensatory liver growth. *J Biol Chem* 2001;**276**:17754–17761.

Singh B, Reddy PG, Goberdhan A *et al*. p53 regulates cell survival by inhibiting PIK3CA in squamous cell carcinomas. *Genes Dev* 2002;**16**:984–993.

Sinkala M. Mutational landscape of cancer-driver genes across human cancers. *Sci Rep* 2023;**13**:12742.

Smith CD, Wells W. Phosphorylation of rat liver nuclear envelopes. II. Characterization of *in vitro* lipid phosphorylation. *J Biol Chem* 1983;**258**:9368–9373.

Sone Y, Ito M, Shirakawa H *et al*. Nuclear translocation of phospholipase C-zeta, an egg-activating factor,

during early embryonic development. *Biochem Biophys Res Commun* 2005;**330**:690–694.
Song R, Tian K, Wang W *et al*. P53 suppresses cell proliferation, metastasis, and angiogenesis of osteosarcoma through inhibition of the PI3K/AKT/mTOR pathway. *International Journal of Surgery (London, England)* 2015;**20**:80–87.
Srinivasan S, Wang F, Glavas S *et al*. Rac and Cdc42 play distinct roles in regulating PI(3,4,5)P3 and polarity during neutrophil chemotaxis. *J Cell Biol* 2003;**160**:375–385.
Stallings JD, Tall EG, Pentyala S *et al*. Nuclear translocation of phospholipase C-δ_1 is linked to the cell cycle and nuclear phosphatidylinositol 4,5-bisphosphate. *J Biol Chem* 2005;**280**:22060–22069.
Stijf-Bultsma Y, Sommer L, Tauber M *et al*. The basal transcription complex component TAF3 transduces changes in nuclear phosphoinositides into transcriptional output. *Mol Cell* 2015;**58**:453–467.
Stuelten CH, Parent CA, Montell DJ. Cell motility in cancer invasion and metastasis: insights from simple model organisms. *Nat Rev Cancer* 2018;**18**:296–312.
Sun Y, Turbin DA, Ling K *et al*. Type I gamma phosphatidylinositol phosphate kinase modulates invasion and proliferation and its expression correlates with poor prognosis in breast cancer. *Breast Cancer Res* 2010;**12**:R6.
Sun Y, Isaji T, Oyama Y *et al*. Focal-adhesion kinase regulates the sialylation of N-glycans via the PI4KIIα-PI4P pathway. *J Biol Chem* 2023;**299**:105051.
Szivak I, Lamb N, Heilmeyer LM. Subcellular localization and structural function of endogenous phosphorylated phosphatidylinositol 4-kinase (PI4K92). *J Biol Chem* 2006;**281**:16740–16749.
Sztacho M, Sobol M, Balaban C *et al*. Nuclear phosphoinositides and phase separation: important players in nuclear compartmentalization. *Advances in Biological Regulation* 2019;**71**:111–117.
Tabellini G, Bortul R, Santi S *et al*. Diacylglycerol kinase-theta is localized in the speckle domains of the nucleus. *Exp Cell Res* 2003;**287**:143–154.
Tan X, Banerjee P, Pham EA *et al*. PI4KIIIβ is a therapeutic target in chromosome 1q-amplified lung adenocarcinoma. *Sci Transl Med* 2020;**12**:eaax3772.
Tanaka K, Horiguchi K, Yoshida T *et al*. Evidence that a phosphatidylinositol 3,4,5-trisphosphate-binding protein can function in nucleus. *J Biol Chem* 1999;**274**:3919–3922.
Thapa N, Chen M, Horn HT *et al*. Phosphatidylinositol 3-kinase signalling is spatially organized at endosomal compartments by microtubule-associated protein 4. *Nat Cell Biol* 2020;**22**:1357–1370.
Thapa N, Chen M, Cryns VL *et al*. A p85 isoform switch enhances PI3K activation on endosomes by a MAP4- and PI3P-dependent mechanism. *Cell Rep* 2024;**43**:114119.
Toulany M, Iida M, Lettau K *et al*. Targeting HER3-dependent activation of nuclear AKT improves radiotherapy of non-small cell lung cancer. *Radiother Oncol* 2022;**174**:92–100.
Tran CS, Kersten J, Yan J *et al*. Phosphatidylinositol 4-kinase III alpha governs cytoskeletal organization for invasiveness of liver cancer cells. *Gastroenterology* 2024;**167**:522–537.
Tribble EK, Ivanova PT, Grabon A *et al*. Quantitative profiling of the endonuclear glycerophospholipidome of murine embryonic fibroblasts. *J Lipid Res* 2016;**57**:1492–1506.
Turner N, Moretti E, Siclari O *et al*. Targeting triple negative breast cancer: Is p53 the answer? *Cancer Treat Rev* 2013;**39**:541–550.
Vallejo-Díaz J, Chagoyen M, Olazabal-Morán M *et al*. The opposing roles of PIK3R1/p85α and PIK3R2/p85β in cancer. *Trends in Cancer* 2019;**5**:233–244.
Vara JAF, Casado E, de Castro J *et al*. PI3K/Akt signalling pathway and cancer. *Cancer Treat Rev* 2004;**30**:193–204.
Vasko V, Saji M, Hardy E *et al*. Akt activation and localisation correlate with tumour invasion and oncogene expression in thyroid cancer. *J Med Genet* 2004;**41**:161–170.
Visnjic D, Crljen V, Curic J *et al*. The activation of nuclear phosphoinositide 3-kinase C2β in all-*trans*-retinoic acid-differentiated HL-60 cells. *FEBS Lett* 2002;**529**:268–274.
Wainstein E, Maik-Rachline G, Blenis J *et al*. AKTs do not translocate to the nucleus upon stimulation but AKT3 can constitutively signal from the nuclear envelope. *Cell Rep* 2022;**41**:111733.
Walerych D, Napoli M, Collavin L *et al*. The rebel angel: mutant p53 as the driving oncogene in breast cancer. *Carcinogenesis* 2012;**33**:2007–2017.
Walerych D, Lisek K, Del Sal G. Mutant p53: one, no one, and one hundred thousand. *Front Oncol* 2015;**5**:289.
Wang Y-H, Sheetz MP. When PIP2 meets p53: nuclear phosphoinositide signaling in the DNA damage response. *Front Cell Dev Biol* 2022;**10**:903994.
Wang Y, Helland A, Holm R *et al*. TP53 mutations in early-stage ovarian carcinoma, relation to long-term survival. *Br J Cancer* 2004a;**90**:678–685.
Wang Y, Kringen P, Kristensen GB *et al*. Effect of the codon 72 polymorphism (c.215G>C, p.Arg72Pro) in combination with somatic sequence variants in the TP53 gene on survival in patients with advanced ovarian carcinoma. *Hum Mutat* 2004b;**24**:21–34.
Wen T, Chen M, Cryns VL *et al*. Regulation of the poly(A) polymerase Star-PAP by a nuclear phosphoinositide signalosome. *bioRxiv* 2024:2024.07.01.601467.
Wong LH, Gatta AT, Levine TP. Lipid transfer proteins: the lipid commute via shuttles, bridges and tubes. *Nat Rev Mol Cell Biol* 2019;**20**:85–101.
Xu R, Sen N, Paul BD *et al*. Inositol polyphosphate multikinase is a coactivator of p53-mediated transcription and cell death. *Sci Signal* 2013;**6**:ra22.
Xue G, Hemmings BA. PKB/Akt–dependent regulation of cell motility. *J Natl Cancer Inst* 2013;**105**:393–404.
Yang Y, Lee M, Fairn GD. Phospholipid subcellular localization and dynamics. *J Biol Chem* 2018;**293**:6230–6240.
Yeudall WA, Wrighton KH, Deb S. Mutant p53 in cell adhesion and motility. *Methods Mol Biol* 2013;**962**:135–146.
Yoeli-Lerner M, Yiu GK, Rabinovitz I *et al*. Akt blocks breast cancer cell motility and invasion through the transcription factor NFAT. *Mol Cell* 2005;**20**:539–550.
Yoo SH, Huh YH, Huh SK *et al*. Localization and projected role of phosphatidylinositol 4-kinases IIα and IIβ in inositol

1,4,5-trisphosphate-sensitive nucleoplasmic Ca^{2+} store vesicles. *Nucleus* 2014;**5**:341–351.

Yue X, Zhang C, Zhao Y *et al*. Gain-of-function mutant p53 activates small GTPase Rac1 through SUMOylation to promote tumor progression. *Genes Dev* 2017;**31**:1641–1654.

Zhang X, Tang N, Hadden TJ *et al*. Akt, FoxO and regulation of apoptosis. *Biochim Biophys Acta* 2011;**1813**:1978–1986.

Zou J, Marjanovic J, Kisseleva MV *et al*. Type I phosphatidylinositol-4,5-bisphosphate 4-phosphatase regulates stress-induced apoptosis. *Proc Natl Acad Sci USA* 2007;**104**:16834–16839.