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Review

CIP2A in Cancer: Molecular Mechanisms, Signalling Networks and Clinical Implications

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Abstract

Cancerous inhibitor of protein phosphatase 2A (CIP2A) is an oncoprotein that is frequently overexpressed in many cancers and can be associated with cancer progression, poor prognosis, and treatment resistance. CIP2A was initially characterised as an inhibitor of protein phosphatase 2A (PP2A), thereby inhibiting the dephosphorylation and degradation of the transcription factor c-Myc. However, more recent evidence suggests that CIP2A has broader functions in cell cycle progression, genomic stability, and DNA damage repair. CIP2A is regulated at multiple levels, including transcriptional, post-transcriptional and post-translational mechanisms, allowing integration with several oncogenic signalling pathways. Elevated CIP2A expression has been reported in numerous haematological and solid malignancies, where it is frequently associated with poor clinical outcomes. Growing evidence supports the use of CIP2A as a prognostic biomarker, and its central role in tumour biology has established the CIP2A-PP2A interaction as a promising therapeutic target. Although challenges remain, including incomplete structural characterisation and the absence of clinically approved CIP2A-targeted therapies, continued research in biomarker development and drug discovery highlights the potential of CIP2A in personalised cancer treatment to improve patient outcomes.

Keywords: CIP2A; protein phosphatase 2A; cancer; oncogenic signalling; biomarker

1. Introduction

Cancer remains one of the leading causes of mortality worldwide. Estimates suggest that >2.1 million new cancer cases and >626,000 cancer-related deaths are projected for 2026 [1]. Despite substantial advances made in cancer diagnosis and treatment, many cancers are still associated with poor clinical outcomes. The development and progression of cancer can be attributed to several hallmarks, including apoptosis resistance, angiogenesis, metastasis, and dysregulation of metabolism [2]. Many of these adaptations are a result of mutations or overexpression of protein kinases, phosphatases and other cell signalling molecules [3].

Protein Phosphatase 2A (PP2A) is one of the most abundant serine/threonine phosphatases in human cells and functions as a key tumour suppressor. By inhibiting kinase activity, PP2A regulates major signalling pathways, including the Wnt and MAPK/ERK pathways. PP2A is essential for controlling the cell cycle, including mitotic progression and the G1/S and G2/M transitions. Through these functions, PP2A suppresses oncogenic signalling by dephosphorylating substrates such as c-Myc, β-catenin, and key regulators of cell cycle progression and apoptosis, thereby maintaining cellular homeostasis [4–6].

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Inhibition of PP2A is recognised as a common feature of many cancers, often through inhibitor proteins such as Cancerous inhibitor of PP2A (CIP2A) [7], SET/IPP2A [8] and PME-1 [9]. While several PP2A inhibitors have been implicated in cancer development, this review focuses specifically on CIP2A. Originally known as KIAA1524 or P90 due to its size (90 kDa), CIP2A is an oncoprotein found on human chromosome 3q13.13 [10]. CIP2A promotes tumorigenesis by inhibiting PP2A-mediated dephosphorylation of c-Myc at serine 62, resulting in stabilisation of c-Myc and sustained oncogenic signalling [7]. Beyond its accepted role as an inhibitor of PP2A-mediated tumour suppressor activity, there is accumulating evidence suggesting that CIP2A has several PP2A-independent functions, one of which is the regulation of mitosis. CIP2A has been shown to interact directly with the polo-box domain of polo-like kinase 1 (PLK1), promoting mitotic progression [11]. Furthermore, CIP2A interacts with another serine/threonine kinase, NEK2, promoting its activity and thus promoting centrosome separation and mitotic spindle formation [12]. Early evidence demonstrates a link between CIP2A and tumour progression in murine models, with CIP2A depletion associated with reduced tumour size and weight. Minimal levels of CIP2A protein were detected in non-malignant human cell lines when compared to cell lines derived from human head-and-neck squamous cell carcinomas (HNSCC) [7]. Remarkably, CIP2A overexpression can be seen in over 70% of cancers, and its expression levels may be used as a predictor for clinical outcome [13]. These findings highlight the potential importance of CIP2A in tumour development and progression and provide a rationale for further investigating its molecular functions across different cancer types.

This review examines CIP2A in malignancies, in particular its relevance as a prognostic biomarker and potential therapeutic target. This review first outlines the structure and regulation of CIP2A, then examines its effects on PP2A-dependent and PP2A-independent signalling pathways. It subsequently considers evidence across haematological and solid malignancies before evaluating the current clinical evidence for CIP2A as a biomarker and therapeutic target.

2. Structure and Regulation of CIP2A

2.1. CIP2A Structure

Despite its well-established oncogenic role, the structural details of CIP2A are limited. Localised within the cytoplasmic and perinuclear region, CIP2A is made up of 905 amino acids and is encoded by a gene spanning 38.8 kb and consisting of 21 exons [10]. Computational models suggest that the N-terminal domain of CIP2A adopts an armadillo repeat fold, which can form a superhelical structure with a positively charged central groove. This is likely to be where CIP2A can interact with key regulators such as PP2A and c-Myc. The structural model supports the idea that CIP2A functions as a scaffold protein, engaging multiple partners through a common binding groove. The armadillo domain groove is predicted to bind short linear peptide motifs, which are common in transcription factors like c-Myc [14]. Other regions of the protein include heat repeats and a leucine zipper, as shown in Figure 1 [15].

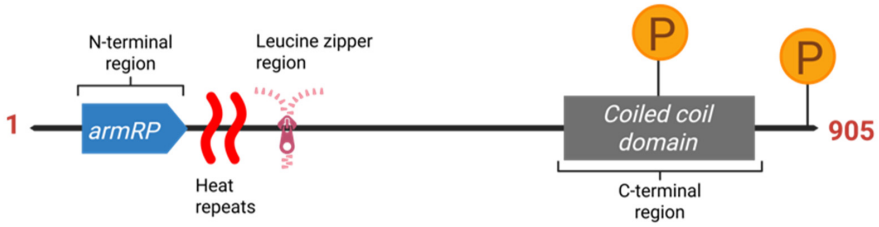


Figure 1. Schematic diagram of the CIP2A protein structure, created based on information from Ref. [15]. The protein structure includes an N-terminal region consisting of an armadillo repeat and a C-terminal region consisting of a coiled-coil domain. Other domains include HEAT repeats, a leucine zipper region, and phosphorylation sites. Created with BioRender.com.

2.2. CIP2A Normal Function

CIP2A is minimally expressed in healthy tissues, and despite the extensive research about CIP2A's role in cancer, comparatively little is known about its role in normal cellular function [16]. One of the earliest discoveries about CIP2A in non-cancerous cells was in neural progenitor cells, where CIP2A was found to promote self-renewal and c-Myc-dependent proliferation [17]. Subsequent studies also demonstrated a link between CIP2A and spermatogonial progenitor cells (SPCs) in the testis. CIP2A was shown to promote SPC proliferation and self-renewal, upstream of the promyelocytic leukaemia zinc finger (PLZF). In mice where CIP2A expression was knocked out, no major developmental abnormalities or reductions in lifespan were observed. These findings support the potential of CIP2A as a therapeutic target; however, constitutive loss of CIP2A may permit developmental compensation that would not necessarily occur following pharmacological inhibition. Furthermore, reduced CIP2A expression impaired spermatogenesis and sperm production, suggesting that CIP2A may have a role in supporting fertility and sperm production [18]. These findings highlight the need to consider the functions of CIP2A in specific proliferative compartments when evaluating its therapeutic potential and safety.

More recent evidence has further explored the physiological role of CIP2A during normal development, particularly within the central nervous system. CIP2A deficiency has been shown to impair neuronal dendritic development through altered PP2A-AKT signalling, and CIP2A also contributes to the regulation of neural progenitor cell self-renewal and proliferation [19]. These findings suggest that CIP2A has context-dependent functions during normal cellular development, proliferation, and differentiation. In addition, CIP2A has been associated with the prevention of chromosomal fragmentation in the early stages of embryonic development, highlighting an additional role in genomic stability [20]. Collectively, these findings indicate that although CIP2A expression is relatively low in most healthy tissues, it has important physiological functions in specific cell types and developmental contexts.

2.3. CIP2A Regulation

Given its oncogenic function, CIP2A is tightly regulated at multiple levels, including transcriptional, post-transcriptional, and post-translational. These mechanisms control CIP2A expression and function, influencing the downstream signalling pathways involved in proliferation and cell survival [21]. At the transcriptional level, CIP2A is regulated by several transcription factors, with c-Myc being one of the best characterised. c-Myc promotes CIP2A transcription, while CIP2A, in turn, contributes to the stabilisation and activity of c-Myc, forming a positive feedback loop that promotes oncogenic signalling. Under normal circumstances, PP2A dephosphorylates c-Myc at Ser^{62}, promoting its degradation. Inhibition of PP2A therefore causes an increase in Ser^{62} phosphorylation and c-Myc stability [22].

In gastric cancer cells, CIP2A was shown to inhibit PP2A-mediated dephosphorylation of c-Myc, thereby promoting c-Myc stabilisation. In turn, stabilised c-Myc can promote increased transcription of CIP2A, forming a positive feedback loop [23]. Similarly, in cervical cancer cells there is evidence of a multidirectional positive feedback loop between CIP2A and transcription factor E2F1 [24]. Evidence from patients with chronic myeloid leukaemia (CML) further supports the relationship between CIP2A and E2F1. The silencing of CIP2A, c-Myc, or E2F1 reactivates PP2A activity, supporting the existence of a CIP2A-c-Myc-E2F1 positive feedback loop that promotes cell proliferation [25].

The transcription factor ATF2 binds to the CIP2A promoter region and promotes the transcription of CIP2A upon activation by Ras-activated JNK2 [26]. This mechanism is demonstrated in gastric cancer cells, where infection with *Helicobacter pylori* was shown to

activate JNK2 and ATF2, which leads to increased CIP2A expression and thus increased cellular proliferation [27]. Similarly, ATF6 can bind to the CIP2A promoter region and increase CIP2A transcription.

In colorectal cancer cells, this occurs in response to endoplasmic reticulum stress [28]. Ets1 and Elk1 have also been identified as regulators of CIP2A expression. Both transcription factors are required to bind to the CIP2A promoter region to promote CIP2A transcription. Ets1 links EGFR–MEK–ERK signalling to CIP2A expression, highlighting the integration of growth factor signalling pathways in the regulation of CIP2A [29]. Additionally, the transcription factor Oct4 has been shown to positively regulate CIP2A expression in testicular cancer cells but also in embryonic stem cells [30]. Epigenetic modifications also play a part in the regulation of CIP2A transcription. The inhibition of histone deacetylase HDAC1 in colorectal cancer cell lines has been shown to reduce CIP2A expression and reactivate PP2A. The reactivation of PP2A then led to dephosphorylation of GSK-3β, leading to degradation of β-catenin and suppression of Wnt/β-catenin signalling [31].

In addition to its transcriptional regulation, CIP2A is also regulated post-transcriptionally. MicroRNAs (miRNAs) represent a major component of this aspect of CIP2A regulation. Several miRNAs have been identified as direct regulators of CIP2A, including miR-375 [32], miR-218 [33], and miR-383 [34]. Through binding to complementary sequences within CIP2A mRNA, these miRNAs suppress CIP2A expression and consequently inhibit downstream oncogenic signalling pathways, resulting in reduced cellular proliferation [35]. Across various cancers, miR-218, miR-383-5P and miR-548B have all demonstrated their ability to target CIP2A's 3′ UTR to negatively regulate CIP2A expression and thus c-Myc stabilisation [33,36,37]. Conversely, miR-375 exerts its ability to negatively regulate CIP2A by binding to five conserved target sites within CIP2A's coding region [32]. Pan-cancer bioinformatics analysis also revealed several 5′ and 3′ UTR variants predicted to alter CIP2A gene regulation [38].

Another important determinant of cellular CIP2A levels is its post-translational protein stability. There is evidence that a loss of CIP2A protein stability will reactivate PP2A activity, thereby suppressing CIP2A's oncogenic effects. Stabilisation is often achieved through interactions with other proteins, specifically PP2A [39]. One mechanism regulating CIP2A degradation is through the ubiquitin–proteasome system (UPS), in which ubiquitination targets CIP2A for degradation. In hepatocellular carcinoma, degradation of CIP2A via the UPS was induced by Gambogenic acid, resulting in reduced proliferation signalling [40]. On the other hand, UCHL1 can act as a deubiquitinating enzyme for its downstream target CIP2A. Evidence suggests that knockdown of UCHL1 in gastric cancer cells increases CIP2A degradation, thereby decreasing c-Myc signalling [41].

Subcellular localisation may also contribute to the regulation of CIP2A. CIP2A is predominantly localised in the cytoplasm, although a small fraction of CIP2A protein is retained at the inner nuclear membrane during interphase, where it can interact with Ser62-phosphorylated c-Myc [42]. In melanoma, CIP2A has also been detected in both the cytoplasm and nucleus, with its prognostic significance differing according to cellular localisation and melanoma subtype [43]. These findings suggest that the subcellular distribution of CIP2A may contribute to its context-dependent functions in tumour cells.

Collectively, CIP2A regulation occurs at multiple levels, involving various transcription factors, epigenetic regulators, and miRNAs (Figure 2). Given CIP2A's role in oncogenic signalling, dysregulation of these mechanisms can lead to increased cell proliferation, survival, and therapeutic resistance. As many of these regulatory mechanisms are themselves controlled by growth factors, stress-response and DNA damage signalling pathways, CIP2A occupies a central position within several signalling pathways that contribute to tumour development and progression.

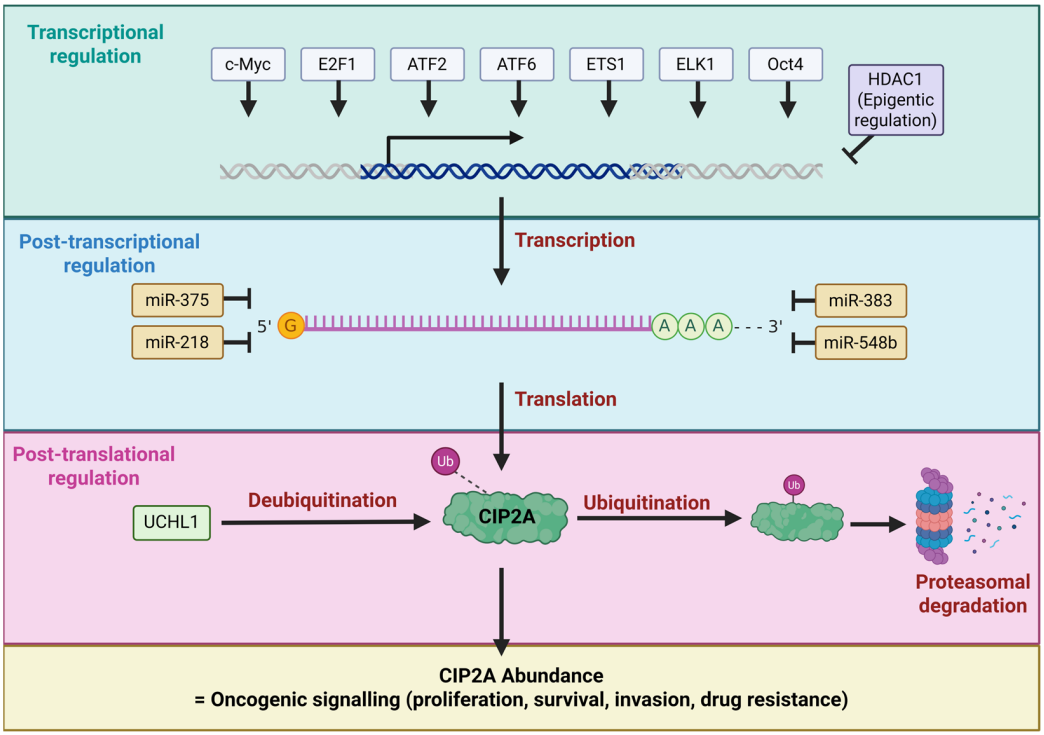


Figure 2. Multi-level regulation of CIP2A expression and stability. CIP2A expression can be regulated at multiple levels. At the transcriptional level, c-Myc, E2F1, ATF2, ATF6, ETS1, ELK1 and Oct4 can regulate CIP2A expression, while HDAC1 does this epigenetically. Post-transcriptional regulation involves various miRNAs, including miR-375, miR-218, miR-383 and miR-548b. At the post-translational level, ubiquitin–proteasome-mediated degradation reduces CIP2A abundance, whereas UCHL1 promotes CIP2A stability through deubiquitination. Collectively, these mechanisms determine CIP2A levels and influence downstream oncogenic signalling. Created with BioRender.com.

3. CIP2A-Mediated Molecular Mechanisms

While the regulatory mechanisms described above govern CIP2A expression, its oncogenic functions arise from its ability to regulate multiple cellular signalling pathways. The most well-characterised function of CIP2A is its inhibition of PP2A, resulting in the stabilisation of key oncogenic proteins and alterations to signalling pathways involved in proliferation and cell survival [39].

3.1. PP2A-Dependent Mechanisms

The serine/threonine protein phosphatase PP2A is a key tumour suppressor. PP2A is trimeric in structure, consisting of a structural (A) subunit, regulatory (B) subunit, and a catalytic (C) subunit, all of which have multiple different isoforms. All combinations of PP2A subunits could make more than 75 different trimeric holoenzyme complexes [44]. The tumour-suppressive role of PP2A was initially supported by studies using the PP2A inhibitor okadaic acid, which demonstrated tumour-promoting activity in two-stage carcinogenesis models [45]. Since then, PP2A has been shown to regulate multiple stages of the cell cycle, including progression through the G1/S transition, DNA replication, mitosis, and chromosomal segregation [46]. Highlighting PP2A's role in maintaining cellular function is its involvement in embryogenesis, where PP2A dephosphorylation is essential [47]. Additionally, PP2A can control apoptosis through negative regulation of the PI3K/AKT pathway, β-Catenin dephosphorylation, and modulation of Bcl-2 family proteins [48–50]. Given that PP2A functions as a tumour suppressor, inhibition of PP2A by CIP2A can greatly alter cellular proliferation and survival.

CIP2A was originally identified as a cancer-associated inhibitor of PP2A through its ability to prevent PP2A-mediated dephosphorylation of c-Myc at Ser62 [7]. CIP2A interacts directly with the PP2A-B56α holoenzyme and occupies the B56α substrate-binding groove, thereby blocking substrate access and preventing PP2A-mediated dephosphorylation of its targets [51]. This inhibition of PP2A activity contributes to the loss of its tumour-suppressive functions [51]. One of the best characterised consequences of PP2A inhibition by CIP2A is the stabilisation of the oncogenic transcription factor c-Myc. Under normal conditions, PP2A dephosphorylates c-Myc at Ser62, a modification that promotes its proteasomal degradation. By inhibiting PP2A activity, CIP2A prevents dephosphorylation of Ser62, thereby maintaining c-Myc phosphorylation and increasing protein stability. The stabilisation of c-Myc leads to increased cell proliferation [7]. When c-Myc levels increase, CIP2A activity also increases, leading to further c-Myc stabilisation and further cell proliferation; this forms a positive feedback loop [23]. In gastric cancer, it was found that when c-Myc is silenced, CIP2A mRNA and protein expression were decreased, providing evidence that c-Myc directly promotes CIP2A transcription [23]. In addition to preventing PP2A-mediated degradation of c-Myc, CIP2A in colorectal cancer cells has been shown to regulate c-Myc translation through its 5′UTR, suggesting CIP2A has multiple methods to enhance c-Myc expression [52]. Similarly to c-Myc, E2F1 has been shown to demonstrate a similar relationship. Upon TP53 downregulation, E2F1 levels increase, leading to increased CIP2A transcription. Increased CIP2A can then go on to inhibit PP2A activity, which leads to the phosphorylation of E2F1 at Ser364, forming another positive feedback loop [53].

Beyond c-Myc and E2F1, CIP2A-mediated inhibition of PP2A influences several additional signalling pathways involved in cancer development. One major pathway is PI3K/AKT/mTOR signalling [54]. AKT signalling is active in many tumours and promotes cell proliferation and survival. A key regulator of AKT is PP2A; PP2A negatively regulates AKT by dephosphorylating AKT at threonine 308 and serine 473, therefore suppressing AKT activity and limiting downstream pro-survival and anti-apoptotic signalling [55]. In hepatocellular carcinoma, increased CIP2A expression leads to increased phosphorylation and, therefore, to active AKT [56]. Similarly, in oral squamous cell carcinoma, there is evidence of interaction between CIP2A and AKT, with CIP2A shown to interact with and regulate AKT, promoting proliferation and cell survival. CIP2A-mediated activation of AKT enhances inhibitory phosphorylation of GSK-3β at Ser9, thereby reducing GSK-3β activity and promoting β-catenin signalling. These findings suggest that CIP2A contributes to tumour progression through the AKT/GSK-3β/β-catenin pathway [57]. In addition to regulating AKT activity, CIP2A has been shown to regulate mTORC1, a key kinase that regulates autophagy and cellular growth. There is evidence to suggest that CIP2A acts as an allosteric inhibitor of mTORC1-associated PP2A, preventing dephosphorylation of mTORC1 substrates and therefore enhancing mTORC1 growth signalling. As a result, CIP2A can promote protein synthesis and cellular proliferation while suppressing autophagy. Furthermore, inhibition of mTORC1 activity leads to CIP2A ubiquitination and degradation, thereby reducing c-Myc stability and decreasing oncogenic signalling. This demonstrates a regulatory feedback loop between CIP2A and mTORC1 [58]. Together, these findings suggest that CIP2A not only promotes PI3K/AKT signalling but also influences downstream pathways, such as Wnt/β-catenin signalling, thereby promoting cancer cell proliferation and survival.

Evidence from JAK2V617F-mutant cells demonstrated a role for CIP2A in regulating STAT5 signalling. In these cells, inhibition of the PI3K/AKT/mTOR pathway reduced CIP2A expression, thereby reactivating PP2A. Increased PP2A activity subsequently promoted dephosphorylation of STAT5, thereby reducing STAT5-mediated transcriptional activity. These findings suggest that CIP2A contributes to sustained activation of the JAK/STAT path-

way by suppressing PP2A activity [59]. Another significant aspect of CIP2A in oncogenic signalling is its regulation by the MAPK/ERK pathway. In gastric epithelial cells, upon *Helicobacter pylori* infection, CIP2A expression is increased through the virulence factor CagA. This upregulation was dependent on CagA phosphorylation and activation of the MEK/ERK signalling pathway [60]. In cancerous cells, CIP2A expression is highly sensitive to the inhibition of the EGFR/MEK/ERK pathway. Silencing MEK1/2 has been shown to reduce CIP2A protein expression, highlighting the importance of MEK/ERK signalling when maintaining CIP2A expression levels [61]. Upstream of the MEK/ERK pathway is KRAS, which has recently been associated with increased CIP2A in pancreatic cancer. KRASG12D-induced upregulation of CIP2A leads to a decrease in PP2A-B56α, and as a result, c-Myc is stabilised and promotes oncogenic activity [62]. These studies demonstrate that CIP2A is both a downstream target and an important effector of MAPK/ERK signalling. Activation of the EGFR–MEK–ERK pathway promotes CIP2A expression, which in turn enhances oncogenic signalling by inhibiting PP2A and stabilising key oncogenic proteins such as c-Myc.

Finally, CIP2A is also implicated in cellular stress and DNA damage mechanisms. In glioblastoma, CHK1 activity was shown to positively regulate CIP2A expression through forming a positive feedback loop with pSTAT3. Inhibition of CIP2A expression induced cellular senescence and impaired tumour growth, highlighting the importance of the CHK1–STAT3–CIP2A loop in maintaining oncogenic signalling [63]. Moreover, inhibition of CHK1 reduced CIP2A transcription, resulting in reactivation of PP2A tumour suppressor activity and the destabilisation of c-Myc [64].

3.2. PP2A-Independent Mechanisms

Recent evidence expands CIP2A's functionality beyond PP2A inhibition. There is increasing evidence of CIP2A's role in phosphorylation signalling, mitosis, and the DNA damage response in cancerous cells, thereby exploiting more of the key hallmarks of cancer [65]. CIP2A has been shown to interact with the DNA damage response protein TOPBP1 (DNA Topoisomerase II-Binding Protein 1), which is responsible for G2/M checkpoint signalling [66]. More recently, CIP2A has been shown to form a complex with TOPBP1 during mitosis, thereby maintaining chromosome stability in BRCA1/2-deficient cells. The CIP2A–TOPBP1 complex prevents mis-segregation of damaged chromosomes, enhancing the survival of mutated cancer cells [67]. Furthermore, CIP2A can directly interact with the polo-box domain of PLK1, leading to PLK1 stabilisation and thus the maintenance of PLK1 levels and its kinase activity. Decreased CIP2A levels led to delayed mitotic progression, highlighting CIP2A's role in cell cycle regulation [11]. In addition to PLK1, CIP2A can interact directly with NEK2, enhancing its activity related to centrosome separation during the G2/M checkpoint [12]. Together, these PP2A-independent mechanisms demonstrate that CIP2A can influence multiple cellular processes beyond PP2A inhibition, including mitotic progression, centrosome regulation, and responses to genomic instability. Consequently, CIP2A occupies a central position within diverse oncogenic signalling networks that govern proliferation and survival.

The ability of CIP2A to coordinate these various signalling pathways contributes to proliferation, survival, metabolic adaptation and therapeutic resistance, highlighting its importance in tumour initiation and progression. Consequently, aberrant CIP2A expression has been identified across a wide range of human malignancies, where it is frequently associated with aggressive disease and poor clinical outcomes [16]. An overview of the molecular mechanisms underlying CIP2A-mediated signalling is presented in Figure 3.

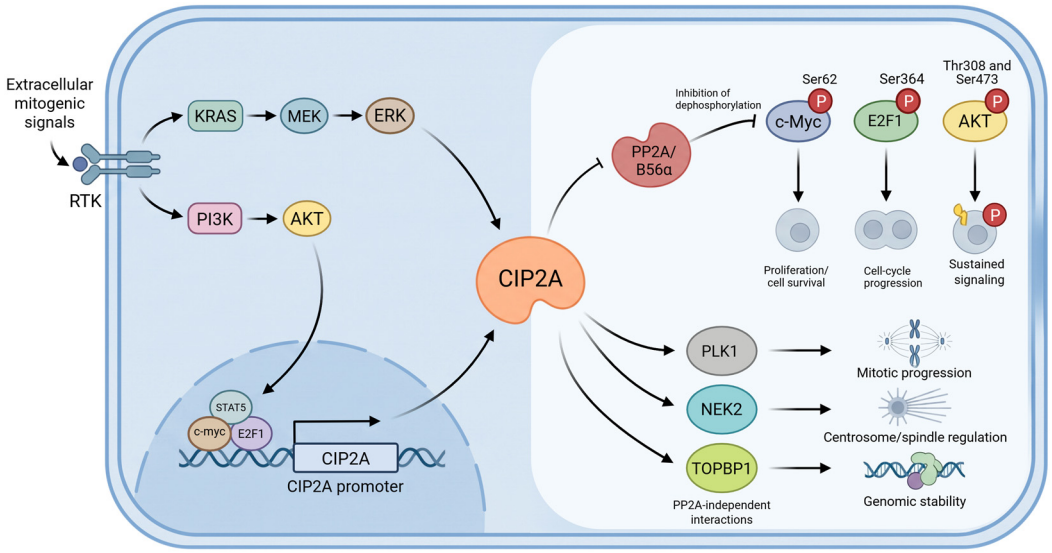


Figure 3. CIP2A-mediated molecular mechanisms and downstream oncogenic signalling. Upstream receptor tyrosine kinase (RTK) signalling promotes CIP2A expression, while CIP2A-mediated PP2A inhibition maintains phosphorylation of c-Myc, E2F1 and AKT, promoting oncogenic signalling. PP2A-independent interactions with PLK1, NEK2 and TOPBP1 contribute to mitotic progression, centrosome regulation and genomic stability. Created with BioRender.com.

4. CIP2A in Cancer

Given CIP2A's extensive involvement with oncogenic signalling, it is unsurprising that CIP2A overexpression is reported in many cancers. Elevated CIP2A has been reported in both solid and haematological malignancies, where it is shown to contribute to poor prognosis, tumour progression and treatment resistance [68]. The variety of cancers in which CIP2A is involved, along with any cancer-specific mechanism, is summarised in Table 1.

Table 1. CIP2A in cancer. Summary table of CIP2A's main function and clinical significance in a variety of cancers.

Cancer Type	Main Finding	Additional Mechanisms *	Reference
CML	Overexpressed at diagnosis; predicts progression to blast crisis	BCR::ABL1 signalling	[69]
AML	Overexpressed in newly diagnosed and relapsed disease; potential relapse biomarker	Impaired differentiation	[70]
Diffuse large B-cell lymphoma (DLBCL)	Promotes proliferation, migration and metastasis	Wnt/β-catenin signalling; EMT	[71]
Multiple myeloma	Promotes proliferation and inhibits apoptosis	PI3K/AKT/mTOR signalling	[72]
Gastric	Overexpressed; induced by Helicobacter pylori infection	CagA/Src/MEK/ERK signalling	[60]
Oesophageal squamous cell carcinoma (ESCC)	Associated with tumour progression and poor clinical outcome	Not reported	[73]
Colon	Independent predictor of poor prognosis and reduced survival	Not reported	[74]
Hepatocellular carcinoma (HCC)	Associated with tumour progression, recurrence and poor prognosis	AKT activation	[75]

Table 1. *Cont.*

Cancer Type	Main Finding	Additional Mechanisms *	Reference
Pancreatic ductal adenocarcinoma (PDAC)	Promotes EMT and aggressive tumour behaviour	EMT; KRAS-CIP2A axis	[76]
Renal cell carcinoma (RCC)	Associated with reduced patient survival	Not reported	[77]
Prostate	Associated with disease progression; potential biomarker	Not reported	[78]
Ovarian	Associated with poor prognosis and reduced survival	Not reported	[79]
Endometrioid adenocarcinoma	Contributes to tumour progression	Ets1/Elk1-mediated regulation	[80]
Cervical	Implicated in cervical carcinogenesis	Not reported	[81]
Breast	Enriched in aggressive subtypes; associated with poor prognosis	Not reported	[82]
Triple negative breast cancer (TNBC)	Promotes proliferation, survival, migration and invasion	AKT/mTOR/p70S6K signalling	
Non-small cell lung cancer (NSCLC)	Correlates with poor prognosis and reduced overall survival	Not reported	[83]
Head and neck squamous cell carcinoma (HNSCC)	Promotes radio resistance in TP53-mutant tumours	mTOR signalling	[84]
Osteosarcoma	Promotes tumour progression	Not reported	[85]
Glioblastoma	High expression predicts poor survival; depletion induces senescence	CHK1/pSTAT3-CIP2A positive feedback loop	[63]
Medulloblastoma	Promotes leptomeningeal dissemination	PP2A/AKT signalling; NF-κB signalling	[86]
Papillary thyroid carcinoma (PTC)	Associated with poor prognosis; potential diagnostic biomarker	Not reported	[87]
Bladder urothelial carcinoma	Predicts poor patient survival	Not reported	[88]
Cutaneous malignant melanoma	Expression increases with tumour progression; associated with poor survival	Not reported	[89]
Oral squamous cell carcinoma (OSCC)	Associated with aggressive disease and poor survival	AKT/GSK3β/β-catenin signalling	[90]

* "Not reported" indicates that no additional CIP2A-mediated mechanism was identified in the studies included in this review. Across the cancers discussed, CIP2A exerts its oncogenic effects predominantly through inhibition of PP2A and subsequent stabilisation of oncogenic proteins, including c-Myc.

4.1. CIP2A in Haematological Malignancies

One of the most extensively studied cancers in relation to CIP2A is CML; this is perhaps due to the links made between PP2A and the driver of CML, BCR::ABL. PP2A is a key target of BCR::ABL, and treatment with the tyrosine kinase inhibitor imatinib inhibits BCR::ABL while reactivating PP2A [69,91]. CIP2A has been validated as an independent prognostic biomarker for progression to blast crisis in CML. In CML patients, increased CIP2A expression was associated with increased PP2A phosphorylation at Tyr307, an inhibitory modification that reduces PP2A activity, alongside increased c-Myc expression [69]. CIP2A has also been associated with the development of an antiapoptotic phenotype in CML through decreased proapoptotic BCL-2 family members, including BIM, PUMA, and

HRK, and upregulation of the antiapoptotic protein BCL-XL [92]. Additionally, a CIP2A splice variant has been identified (NOCIVA), which is further associated with poor clinical outcomes in both CML and acute myeloid leukaemia (AML). It is proposed that this variant could inform therapeutic decision-making [93]. This is particularly important given the growing evidence linking CIP2A expression to treatment failure and resistance [94].

Similarly to CML, CIP2A is frequently overexpressed in AML. Cristóbal et al. (2011) reported that PP2A activity was reduced in 78% of their cohort of AML patients, indicating that PP2A inactivation is a common feature of the disease [95]. Mechanistically, PP2A reactivation inhibited AML cell growth, induced apoptosis, and suppressed ERK1/2 and AKT signalling [95]. Likewise, Wang et al. (2011) found CIP2A expression in the bone marrow of more than 70% of the newly diagnosed/relapsed AML patients included in their study [70]. This was in comparison to 2.86% CIP2A expression in healthy participants [70]. Functional studies in HL60 cells demonstrated that CIP2A depletion reduced proliferation while promoting cellular differentiation. These effects were accompanied by reactivation of PP2A and a decrease in c-Myc expression, supporting a central role for the CIP2A-PP2A-c-Myc loop in maintaining the leukemic phenotype [70]. Lucas et al. (2018) reported that PP2A inhibition occurs in AML by 2 different pathways: CIP2A in normal karyotype patients and SETBP1 in adverse karyotype patients [96]. These findings have been more recently supported by independent patient cohorts which also demonstrate CIP2A overexpression in AML [97].

Beyond myeloid leukaemias, CIP2A overexpression has also been reported in mature B-cell malignancies. In multiple myeloma, CIP2A promotes tumour growth through activation of the PI3K/AKT/mTOR pathway, with depletion of CIP2A reducing proliferation and inducing apoptosis [98]. Clinically, elevated CIP2A expression in multiple myeloma is associated with poorer overall survival, while suppression of CIP2A can restore sensitivity to dexamethasone and is downregulated by bortezomib treatment, highlighting a role in therapeutic response [72,99]. Increased CIP2A expression has similarly been observed in lymphoid malignancies. There is evidence that increasing expression of CIP2A is related to increasing clinical aggressiveness of lymphoma [100]. CIP2A drives proliferation, migration and epithelial–mesenchymal transition (EMT) through Wnt/β-catenin signalling, whereas its inhibition suppresses tumour growth and metastatic potential [71]. Together, these findings demonstrate that CIP2A contributes to the pathogenesis and disease progression of several haematological malignancies through the promotion of cell proliferation, cancer aggressiveness and treatment resistance, highlighting its potential as a biomarker to predict clinical outcome and a therapeutic target.

4.2. CIP2A in Solid Tumours

4.2.1. CIP2A in Gastrointestinal Malignancies

Evidence displaying the role of CIP2A in cancer prognosis extends beyond just haematological cancers, as seen in Table 1; a broad range of gastrointestinal cancers are also affected. Across multiple gastrointestinal malignancies, elevated CIP2A expression is associated with adverse clinical outcomes and reduced survival. However, the mechanisms underlying these observations differ substantially between tumour types [23,73,75,76,101]. Gastric cancer was one of the first solid tumours to be associated with CIP2A. Functional studies showed that reducing CIP2A reduced c-Myc expression, thereby impairing the transforming capacity of gastric cancer cells. Additionally, CIP2A inhibition induced senescence in AGS gastric cancer cells, suggesting that CIP2A may promote malignant transformation and tumour growth [102]. Both CIP2A and c-Myc have been shown to promote gastric cancer cell proliferation, with CIP2A doing so by stabilising c-Myc and thereby enhancing its oncogenic activity [23,102]. There is also a relationship between CIP2A and *Helicobacter*

pylori infections. Evidence shows that CIP2A expression depends on phosphorylation of the bacterial virulence factor CagA. CagA-mediated upregulation of CIP2A occurred through activation of Src and Ras/MEK/ERK signalling pathways and decreased CIP2A, leading to partially attenuated *H. pylori*-induced c-Myc stabilisation [60].

CIP2A expression was also found in both oesophageal squamous cell carcinoma (ESCC) and oesophageal adenocarcinoma, and similar PP2A-c-Myc-dependent mechanisms have been observed. In ESCC, CIP2A promotes tumour growth through c-Myc expression, while its silencing reduces both c-Myc levels and cell proliferation [73]. In oesophageal adenocarcinoma, most tumours exhibited moderate to strong CIP2A expression, which positively correlated with c-Myc expression. However, unlike observations seen in other cancer types, in oesophageal adenocarcinoma, CIP2A expression was not correlated with differences in patient survival outcomes [103]. This suggests that in this cancer type, CIP2A may only play a role in the development of the tumour and is not a reliable predictor of poor prognosis. While oesophageal cancer studies primarily highlight the relationship between CIP2A and c-Myc expression, colorectal cancer studies have revealed a more direct role for CIP2A in c-Myc translational regulation. CIP2A expression correlates with c-Myc expression in colorectal cancer, and CIP2A has been shown to enhance MYC mRNA translation through its 5′ UTR [52]. While some studies have made a connection between CIP2A expression and prognosis, the relationship remains inconsistent across colorectal cancer cohorts. Böckelman et al. (2012) found that while most patients had moderate to strong levels of CIP2A, this was not correlated with survival outcomes [101]. On the other hand, there is evidence to show that increased CIP2A expression can be used as an independent biomarker for poor prognosis in patients with wild-type KRAS metastatic colorectal cancer following a liver metastasectomy [104]. Interestingly, in colorectal cancer, the use of CIP2A as a biomarker for poor prognosis was improved when used in combination with the neutrophil-to-lymphocyte ratio (NLR) [105].

4.2.2. CIP2A in Hepatobiliary and Pancreatic Malignancies

CIP2A also contributes to hepatobiliary malignancies through distinct signalling pathways. In hepatocellular carcinoma (HCC), CIP2A may serve as a biomarker to predict both overall and disease-free survival [75]. In addition to its prognostic significance, CIP2A may represent a therapeutic target in HCC. Bortezomib-induced downregulation of CIP2A restores PP2A activity and suppresses AKT signalling, thereby increasing apoptosis in HCC cells [56]. A key mechanism underlying CIP2A-mediated oncogenesis in HCC involves the PP2A-AKT signalling pathway. Decreasing CIP2A was shown to increase PP2A activity, thereby reducing AKT phosphorylation and inducing apoptosis [56]. Furthermore, it has been demonstrated that loss of CIP2A expression can lead to cell-cycle arrest and senescence in HCC [106]. More recently, CIP2A has been implicated in treatment resistance, where the DUBR-E2F1-CIP2A feedback loop was shown to promote self-renewal and oxaliplatin resistance [107]. Evidence from both clinical and experimental studies suggests that CIP2A plays a role in the progression of pancreatic ductal adenocarcinoma (PDAC). High CIP2A expression is associated with altered expression of EMT markers, which correlates with poor prognosis and metastatic progression [76]. Additionally, KRAS signalling has been shown to upregulate CIP2A expression, leading to suppression of the tumour suppressor PP2A-B56α complex and promoting pancreatic cancer initiation [62]. Moreover, CIP2A has been shown to contribute to chemoresistance in PDAC, and decreasing CIP2A increases sensitivity to gemcitabine [108].

4.2.3. CIP2A in Genitourinary Malignancies

Consistent with observations made in other cancer types, CIP2A dysregulation has also been reported in several genitourinary and gynaecological cancers. Although the mechanism behind this varies between cancer types, elevated CIP2A expression is consistently associated with cancer progression and poor clinical outcomes [77–81]. More specifically, in clear cell renal cell carcinoma (ccRCC), CIP2A overexpression has been linked to the promotion of EMT and vasculogenic mimicry, both of which are associated with increased invasiveness and metastatic potential [109,110]. Interestingly, downregulation of CIP2A also led to decreased angiogenesis in ccRCC, suggesting that CIP2A contributes not only to cancer progression but also to the maintenance of a supportive tumour microenvironment [111]. Finally, in renal cancers, CIP2A is also implicated in chemoresistance, where suppression of CIP2A leads to enhanced cisplatin sensitivity [112]. In prostate cancer, CIP2A is overexpressed and associated with aggressive disease [78]. Functional papers have demonstrated that CIP2A can promote tumour progression through regulation of Wnt/β-catenin, PLK1 and ERK signalling pathways [113], contributing to EMT, invasion and increased proliferation [114]. Additionally, CIP2A in prostate cancer has been linked to genomic instability through the promotion of chromosomal segregation defects and aneuploidy [115]. From a therapeutic perspective, decreasing CIP2A increases the sensitivity of prostate cancer cells to docetaxel [116].

4.2.4. CIP2A in Gynaecological Malignancies

Among the gynaecological cancers, the role of CIP2A has been particularly well characterised in ovarian cancer. Similarly to cancers already discussed, in ovarian cancer, CIP2A is highly expressed and correlates with aggressive cancer types [79]. CIP2A also contributes to cisplatin resistance, while its suppression sensitises ovarian cancer cells to chemotherapy [117]. More recently, CIP2A expression has been proposed as a biomarker for therapeutic stratification by predicting APR-246 responsiveness, as ovarian tumours with low CIP2A expression exhibit increased sensitivity to APR-246 [118]. Interestingly, analysis of ovarian cancer datasets identified a potentially functional R530T mutation in CIP2A, predicted to disrupt CIP2A dimerisation and alter protein stability, highlighting a possible role for CIP2A genetic alterations in ovarian tumorigenesis [119]. In endometrial cancer, CIP2A contributes to tumour progression through promoting proliferation while suppressing apoptosis [80]. Descriptive studies have further demonstrated associations between elevated CIP2A expression and adverse characteristics, including advanced tumour stage, grade and HER2 positivity [120]. Mechanistically, in endometrial cancer, CIP2A expression is regulated by the transcription factors Ets1 and Elk1 [29]. Cervical cancer provides a unique example of CIP2A dysregulation through viral oncogenesis. Multiple studies have shown that CIP2A expression is elevated in cervical cancer [81] and that this can be directly upregulated by the human papillomavirus (HPV) 16 E7 oncoprotein [121]. CIP2A contributes to HPV-driven carcinogenesis through interactions with E2F1, promoting cell proliferation [122] and enabling G1/S cell-cycle progression [123]. A regulatory feedback loop between HPV E7, E2F1 and CIP2A has also been identified, suggesting that sustained activation of this pathway contributes to cervical tumour progression and may have prognostic significance [24]. CIP2A has also been shown to cooperate with H-Ras to promote EMT, contributing to cervical cancer progression [124]. More recently, CIP2A has been implicated in regulating the DNA damage response through interactions with TOPBP1 during HPV infection, further highlighting CIP2A's role in HPV-associated tumour biology [125]. CIP2A has also been implicated in treatment resistance in cervical cancer by upregulating MDR1 expression, leading to increased P-glycoprotein-mediated drug

efflux, thereby reducing the intracellular accumulation of chemotherapy drugs (cisplatin, paclitaxel, and doxorubicin) [126].

4.2.5. CIP2A in Breast Cancer

Among solid tumours, the role of CIP2A has been extensively investigated in breast cancer. In breast cancer, CIP2A is associated with tumour aggressiveness and contributes to disease progression through regulation of the PP2A-AKT pathway [82,127]. The importance of CIP2A appears particularly significant in triple-negative breast cancer (TNBC), where elevated CIP2A expression correlates with invasion, autophagy and tumour survival, suggesting a role in maintaining aggressive disease phenotypes. The mechanism behind this in TNBC is said to be via regulation of a PP2A/c-Myc/p27Kip1 pathway [128] and the maintenance of CIP2A expression via a positive feedforward loop involving CIP2A, PP2A, pERK and pELK-1 [129]. Apart from its effects on proliferation, CIP2A also contributes to basal-like breast cancer through interaction with TOPBP1 and activation of mTORC1 [58,66]. The CIP2A-TOPBP1 axis prevents the mis-segregation of damaged chromosome fragments that arise in BRCA-deficient cells. Therefore, disruption of the CIP2A-TOPBP1 axis was highly toxic to BRCA1- and BRCA2-mutated tumour cells, highlighting the pathway as a promising therapeutic target [67]. In addition to its role in tumour progression, CIP2A contributes to therapeutic resistance in breast cancer. Increased CIP2A expression has been linked to resistance to tamoxifen [130], doxorubicin [131] and everolimus [132], while therapeutic strategies that suppress CIP2A signalling, includingbortezomib treatment [133], restore PP2A activity, induce apoptosis, and enhance treatment sensitivity, particularly in TNBC.

4.2.6. CIP2A in Thoracic Malignancies

Lung cancer represents another malignancy in which CIP2A has been extensively investigated. Although numerous studies have associated elevated CIP2A expression with tumour aggressiveness and poor prognosis in non-small cell lung cancer (NSCLC), its biological significance extends beyond prognostic value [83,134]. There is evidence suggesting that CIP2A does so via regulation of multiple pathways, including AKT and JNK signalling [135,136]. CIP2A expression can also be influenced by the tumour microenvironment. In lung adenocarcinoma, the inflammatory cytokine IL-10 promotes tumour aggressiveness by transcriptional upregulation of CIP2A, thereby linking inflammatory signalling to CIP2A-mediated oncogenesis [137]. Recent studies have demonstrated that CIP2A drives metabolic reprogramming by inducing arginine biosynthesis, regulating LDH-A expression and lactate production, maintaining redox homeostasis, and promoting oxidative phosphorylation via PKM2 activation, thereby supporting tumour growth and survival [138,139]. CIP2A can also promote CREB phosphorylation indirectly, likely through PP2A-regulated kinases such as AKT, p90RSK, and p38 MAPK, thereby linking PP2A-dependent signalling pathways to metabolic reprogramming and tumour progression [140]. CIP2A has also been implicated in resistance to conventional chemotherapy in NSCLC. Overexpression of CIP2A reduced sensitivity to cisplatin by activating the AKT signalling pathway [141]. On the other hand, several drugs have demonstrated anti-tumour activity through targeting the CIP2A-PP2A axis in NSCLC. Specifically, celastrol, ethoxysanguinarine and the erlotinib derivative TD-19 suppress CIP2A expression or promote its degradation, leading to PP2A reactivation and induction of apoptosis in lung cancer cells [142–144].

4.2.7. CIP2A in Other Solid Malignancies

Although less extensively studied than breast, lung or the haematological malignancies, CIP2A has also been implicated in the progression of several additional solid tumours in-

cluding oral cancer and head and neck cancers, where dysregulated expression contributes to tumour growth and treatment resistance [84,145]. In glioblastoma, CIP2A promotes tumour cell survival through PP2A-dependent regulation of oncogenic and DNA damage response pathways such as activation of CHK1 and STAT3 signalling [63,146]. In medulloblastoma, suppression of PP2A activity contributes to tumour progression, and pharmacological reactivation of PP2A has been shown to overcome metastatic spread in Group 3 medulloblastoma [86]. Likewise, in osteosarcoma, CIP2A is overexpressed, and this overexpression is also seen more in advanced-stage osteosarcoma patients [85]. The plant-derived compound, Tenuigenin, was shown to inhibit the CIP2A-PP2A-NF-κB pathway and therefore suppress tumour growth in osteosarcoma [147].

Taken together, these studies demonstrate the significance of CIP2A expression in cancer and its role in tumour progression, therapeutic resistance and metastasis. Although the mechanisms and pathways involved vary from cancer to cancer, the consistent role of CIP2A in promoting aggressive tumour phenotypes highlights its importance in cancer biology. As a result, there is increasing attention towards the clinical use of CIP2A as both a diagnostic/prognostic biomarker and a therapeutic target.

5. Clinical Significance of CIP2A

The consistent dysregulation of CIP2A across multiple cancers highlights its clinical relevance. Beyond its role in cancer biology, evidence suggests that CIP2A may serve as a prognostic biomarker, potentially informing treatment decisions. One of the first papers to explore the use of CIP2A as a prognostic biomarker was in gastric cancer, where CIP2A expression was associated with reduced overall survival in a subgroup of patients with tumours 5 cm or less and/or P53 immunopositive tumours. In this paper, CIP2A was recognised as an independent predictor of survival [23]. Conversely, in ovarian cancer, cytoplasmic expression of CIP2A was associated with poor overall and progression-free survival; however, after multivariate analysis, they revealed that CIP2A adds no independent prognostic value [79]. High CIP2A expression was also associated with poor clinical outcome in breast cancer, although the authors suggest that CIP2A's prognostic value may be limited and likely dependent on additional factors [127]. The use of CIP2A in combination with other biomarkers was studied in colorectal cancer, where CIP2A, together with an established inflammatory marker, NLR, was used to predict clinical outcomes. It was found that the combination of serum CIP2A levels and NLR yielded the greatest accuracy compared with either marker alone. Patients with both elevated CIP2A and NLR had the poorest clinical outcomes [105]. Another biomarker combination is CIP2A and the anti-apoptotic protein BCL-XL. Both CIP2A and BCL-XL expression levels have been described as biomarkers of disease progression in CML, and their combination improved prognostic accuracy compared with either marker alone. It has been identified that CIP2A and BCL-XL expression levels could help identify patients with a lower likelihood of achieving successful treatment-free remission (TFR) following tyrosine kinase inhibitor discontinuation. The findings support the use of a combined CIP2A/BCL-XL diagnostic toolkit for risk stratification and to guide therapeutic decision-making in CML [147]. The use of CIP2A as a biomarker for disease progression and therapeutic resistance has been validated in CML. CIP2A expression levels were found to be independent of established prognostic scoring systems in CML, such as the Sokal score. CML patients with increased CIP2A expression have a significantly increased risk of treatment failure, demonstrating how CIP2A could be used to inform treatment decision-making [94]. Beyond its role in prognosis and treatment stratification, CIP2A also shows potential as a diagnostic biomarker. Recent advances in biosensor technology have enabled the development of a rapid, transistor-based platform

for highly sensitive detection of CIP2A in oral cancer samples, highlighting the feasibility of incorporating CIP2A into future point-of-care diagnostic approaches [148].

In addition to its role as a prognostic/diagnostic biomarker, CIP2A has the potential to be a strong therapeutic target. Several compounds have demonstrated their ability to target CIP2A and thereby cause increased anti-tumour activity [56,142,144,149]. For example, compounds including ethoxysanguinarine and celastrol have been shown to reduce CIP2A expression in lung cancer cells, with celastrol additionally enhancing the anti-tumour effects of cisplatin [142,144]. Tenuigenin has also been reported to suppress CIP2A, leading to increased PP2A activity and reduced NF-κB signalling in osteosarcoma cells [149]. The anti-cancer drug bortezomib may provide another approach to targeting the CIP2A–PP2A axis. Bortezomib has been reported to suppress CIP2A transcription, resulting in reduced AKT phosphorylation and increased apoptosis in breast cancer cells [133]. Bortezomib has also been shown to enhance PP2A activity in hepatocellular carcinoma [56], further supporting its potential to exert anti-tumour effects through modulation of the CIP2A–PP2A pathway. Another way to counteract the effects of CIP2A is by reactivating PP2A directly. Preclinical analysis investigated the anticancer potential of small-molecule PP2A activators in neuroblastoma. The PP2A reactivators ATUX-792 and DBK-1154 inhibited neuroblastoma cell growth and reduced CIP2A expression [150]. Targeting the CIP2A-PP2A axis may be particularly valuable in overcoming treatment resistance, as CIP2A has been implicated in resistance to a range of chemotherapies including platinum-based chemotherapy (cisplatin and oxaliplatin), endocrine therapies and targeted agents such as erlotinib and gefitinib [117,141,143,151]. Structural analysis of CIP2A identified potential protein-ligand interaction sites that could be targeted by small-molecule inhibitors. This supports the potential of directly targeting CIP2A, rather than indirect approaches or restoring PP2A activity [152]. Collectively, these findings highlight CIP2A as a promising therapeutic target and support the continued development of CIP2A-targeted therapies for clinical application.

A major challenge to the clinical translation of CIP2A as a biomarker is the heterogeneity in sample types and analytical methods used to measure CIP2A. Studies have used methods such as serum protein measurement by ELISA [105], bone marrow transcript analysis [70], tumour-tissue protein expression by immunohistochemistry [74], RT-qPCR [75], and Western blotting [72]. More recently, transistor-based biosensor technology has also been explored for CIP2A detection [148]. These approaches assess CIP2A at different biological levels and in different sample types and therefore cannot be considered directly interchangeable. Standardisation and independent validation of clinically relevant assays, including the definition of appropriate cut-off values, will therefore be important before CIP2A can be reliably implemented as a clinical biomarker.

Future Directions

Despite the growing body of evidence linking CIP2A to cancer and the current understanding of its biology, several important questions remain regarding its use in clinical practice. It is known that CIP2A is a 905-amino-acid protein, and the crystal structure of the N-terminal region has been determined up to 560 amino acids [39]. However, the full-length structure has not yet been determined; in particular, the C-terminal region is completely uncharacterised. This limits the understanding of CIP2A function and hinders drug development. Nevertheless, the recent structural analysis by Ibitoye et al. (2023), which identified potential ligand-binding sites within CIP2A, represents an important step towards the development of CIP2A-targeted therapies and highlights the value of future structural studies [152].

The development of pharmacological inhibitors targeting CIP2A also remains an important area for future research. Several compounds have been reported to reduce CIP2A expression or promote its degradation, including gambogenic acid [40], ethoxysanguinarine [151] and celastrol [144]. However, most of these compounds are not selective CIP2A inhibitors and have not progressed to clinically validated CIP2A-targeted therapies [153]. An alternative approach is to indirectly counteract the effects of CIP2A by restoring PP2A activity. McClinch et al. (2018) demonstrated that small-molecule activators of PP2A (SMAPs), which directly bind the PP2A Aα subunit and activate PP2A, exerted anti-tumour effects in preclinical models of castration-resistant prostate cancer, including inhibition of tumour growth in xenograft models [154]. Further investigation is required to determine whether these approaches can be developed into selective and clinically applicable strategies. Validation of the ligand-binding sites identified by Ibitoye et al. (2023) and the development of compounds capable of disrupting critical CIP2A interactions with PP2A or other binding partners may provide a basis for the development of direct CIP2A-targeted therapies [152].

CIP2A may also have considerable value in personalised medicine approaches. Increasing evidence suggests that combining CIP2A with additional biomarkers can improve accuracy as a prognostic biomarker. For example, the use of CIP2A and NLR in colorectal cancer, BCL-XL in CML, and low CIP2A expression as a marker of APR-246 sensitivity in ovarian cancer [105,118,147]. Future studies should investigate if these biomarkers can be translated into clinically actionable diagnostic tools. Validation of these tools could be beneficial across many cancers, facilitating more personalised treatment strategies and improving patient outcomes.

Furthermore, CIP2A has an emerging role in genomic stability and DNA damage [67,125,146]. Continued investigation into these lesser-researched functions may prove important for identifying novel therapeutic targets. Addressing these gaps will be essential to fully characterise CIP2A and establish its potential as both a biomarker and therapeutic target across a range of cancers.

6. Conclusions

CIP2A is a key regulator of tumour development and progression across a range of both haematological and solid tumours. By inhibiting the tumour suppressor PP2A and stabilising oncogenic proteins such as c-Myc, CIP2A can promote increased cell proliferation, survival, metastasis, and therapeutic resistance. More recent studies have also shown that CIP2A plays roles in mitotic progression, genomic stability, and DNA damage.

The overexpression of CIP2A in multiple cancer types and its frequent association with poor clinical outcomes highlights its use as a prognostic biomarker, particularly when used in combination with other markers. Additionally, CIP2A's ability to influence a patient's response to chemotherapy, targeted therapies, and endocrine treatments has established it as an attractive therapeutic target.

However, there are still gaps in the literature to address, including the structural characterisation of CIP2A and the lack of approved CIP2A-targeting therapies. Research into CIP2A's structural biology, PP2A reactivation strategies, and biomarker-guided decision-making continues to advance the use of CIP2A as a promising predictive biomarker and therapeutic target, with the potential to improve outcomes for cancer patients.

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