

Review

Current Study of CBX4 from Physiological Homeostasis to Tumorigenesis

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Abstract: CBX4 is a multifunctional chromatin regulator that integrates epigenetic silencing mediated by canonical polycomb repressive complex 1 (cPRC1) with post-translational modification mediated by its small ubiquitin-like modifier (SUMO) E3 ligase activity. Through these mechanisms, CBX4 governs diverse physiological processes, including lineage commitment, organogenesis, cellular reprogramming, senescence control, DNA damage response, and immune regulation. Dysregulation of CBX4 disrupts these homeostatic programs and promotes tumorigenesis through multiple routes. Beyond its canonical repressive roles, the interaction of CBX4 with other chromatin modifiers has emerged as a critical determinant of its oncogenic activity. This review synthesizes current evidence on how CBX4 coordinates epigenetic and post-translational regulation in physiological homeostasis and tumorigenesis, with emphasis on its context-dependent regulatory outputs and therapeutic implications.

Keywords: CBX4; SUMOylation; epigenetic regulation; physiological homeostasis; tumorigenesis

1. Introduction

Epigenetic modifications, including DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs (ncRNAs), constitute fundamental mechanisms that regulate gene expression. Dysregulation of these modifications drives aberrant biological processes encompassing uncontrolled cell division, impaired cell differentiation, dysfunctional immune responses and ultimately tumorigenesis. Canonical polycomb repressive complex 1 (cPRC1) is an essential chromatin-modifying complex that recognizes histone H3K27me₃-marked sites and represses gene transcription by depositing H2AK119ub1 [1]. Dysregulation or structural reconfiguration of cPRC1 broadly disrupts transcriptional homeostasis rather than simply repressing individual genes, thereby contributing to developmental abnormalities and oncogenesis across diverse tissue types [2].

Assembly of cPRC1 is a dynamic process mediated by functionally associated polycomb group (PcG) family proteins. These proteins primarily include RING1A/B, PCGF2/4 and chromobox (CBX) proteins [3]. CBX proteins share a highly conserved N-terminal chromodomain (CD) that forms a hydrophobic pocket, which enables CBX proteins to recognize and bind to methylated histone tails, thereby serving as readers of histone modifications [4]. Based on their C-terminal architecture, CBX proteins are divided into two groups: those containing a Pc box (the Pc group) and those containing a chromoshadow domain, referred to as the heterochromatin protein 1 (HP1) group. The HP1 group includes CBX1, CBX3 and CBX5 and is tightly involved in heterochromatin formation. The remaining CBX proteins belong to the Pc group, constitute cPRC1 components, and act as readers of H3K27me₃ [5]. The Pc box is essential for interaction with RING1A/B and for assembly of cPRC1 [6].

CBX4 is a notable member of the CBX family due to its role in epigenetic regulation and post-translational modification. While it facilitates cPRC1-mediated epigenetic silencing, CBX4 also functions as a SUMO E3



ligase, which enables it to regulate the function, localization, and stability of substrate proteins by attaching SUMO molecules to specific lysine residues [7,8]. Traditionally, CBX4 has been viewed as a transcriptional repressor acting through cPRC1. However, emerging evidence indicates that SUMOylation constitutes another key mechanism underlying CBX4-mediated transcriptional regulation [8–10]. Notably, beyond its classical repressive role, CBX4 can also promote transcriptional activation under specific circumstances [11,12]. To date, CBX4 has been implicated in multiple biological processes, such as stem cell fate, cellular senescence and DNA damage response [13–15]. Furthermore, the Wnt/ β -catenin signaling pathway is closely associated with CBX4 activity [16]. Therefore, it is not surprising that numerous studies have found that CBX4 dysfunction plays a pivotal role in various cancer types [8,10,11]. This review synthesizes current evidence on how CBX4 integrates epigenetic and post-translational regulation to maintain physiological homeostasis, and how disruption of these functions contributes to tumorigenesis.

2. The Normal Biological Functions of CBX4

Under physiological conditions, tightly regulated CBX4 activity is essential for maintaining cellular homeostasis. Several studies have collectively revealed that CBX4 plays a significant role in stem-cell fate, organogenesis, cellular reprogramming, cellular senescence, the DNA damage response, and immune homeostasis.

2.1. CBX4 in Stem Cell Fate Decisions

In mouse embryonic stem cells, cPRC1 governs the transition from pluripotency to lineage commitment. Undifferentiated embryonic stem cells express predominantly CBX7. The CBX7-containing cPRC1 complex binds to H3K27me₃-marked promoters of both CBX2 and CBX4, forming an autoregulatory loop that maintains the pluripotent state. Upon differentiation, newly expressed CBX2 and CBX4 replace CBX7 within cPRC1, and the reconfigured complex occupies the CBX7 promoter to reduce its expression. Deletion of CBX4 does not impair pluripotency maintenance but disrupts lineage commitment by altering germ layer composition [13].

In the haematopoietic system, overexpression of Cbx4 reduces self-renewal of haematopoietic stem and progenitor cells and prevents long-term haematopoietic reconstitution *in vivo*, suggesting that Cbx4 drives stem cells toward differentiation and exhaustion [17]. In keratinocytes, neuronal and other lineage-specific genes, including *Nefl*, *Neurog3*, *Mobp*, *En2*, and *Lhx4*, are repressed by cPRC1 containing CBX4. Meanwhile, CBX4 silences the transcription of genes associated with terminal differentiation including *Loricrin*, *Involucrin*, and *Filaggrin* through its SUMO E3 ligase activity. Further research indicates that p63, a major transcription factor in epidermal cells, serves as an upstream regulator of CBX4, highlighting the involvement of CBX4 in epidermal development [18]. Collectively, these findings have revealed that CBX4 acts as an important cell-fate decision maker in multiple stem cell compartments. Notably, the same mechanisms that enforce quiescence and lineage fidelity in normal stem cells can be co-opted to sustain cancer stemness and block differentiation in squamous malignancies.

2.2. CBX4 in Thymic Organogenesis

Organogenesis relies on differentiated cells to establish a coordinated tissue architecture, and its disruption can result in lethal developmental defects. A previous study showed that CBX4 is essential for thymic organogenesis. Cbx4-knockout mice exhibit a fatal thymic defect and die within one hour after birth. This defect originates from impaired proliferation and maturation of thymic epithelial cells. At embryonic day 18.5, the expression of markers for two distinct thymic epithelial cell populations declined by nearly half, and terminal-differentiation markers showed a similar reduction. Consistently, mRNA levels of key molecules involved in thymic epithelial development are reduced. However, the molecular mechanism by which CBX4 regulates this process remains unexplored [19]. This lethal phenotype highlights the indispensable, non-redundant role of CBX4 in epithelial tissue development. Such developmental essentiality raises the possibility that aberrant CBX4 activity in epithelial-derived tumors reflects the pathological co-option of a fundamental developmental program.

2.3. CBX4 in Cellular Reprogramming

Cellular reprogramming resets differentiated cells to a pluripotent state and is orchestrated by core transcription factors including Oct4, Sox2, Klf4, and c-Myc. CBX4 functions as a barrier to this process through the USP26-CBX4/CBX6-cPRC1 axis. USP26, a deubiquitinating enzyme, stabilizes CBX4 and CBX6 through K48-linked deubiquitination, preventing their proteasomal degradation. Stabilized CBX4 and CBX6 are then recruited to the promoters of Sox2 and Nanog, where increased H2AK119ub1 and H3K27me₃ indicate cPRC1-

mediated transcriptional silencing. This USP26-CBX4/CBX6-cPRC1 axis thus constitutes a negative regulatory mechanism that maintains somatic cell identity by repressing core pluripotency genes [20].

2.4. CBX4 in Cellular Senescence

Cellular senescence is a fundamental biological state characterized by a stable and permanent arrest of the cell cycle. It typically occurs after a limited number of cell divisions or in response to stimuli such as DNA damage, oxidative stress, oncogene activation, and chromatin disruption. The cyclin-dependent kinase inhibitor p16 is a critical senescence biomarker that indirectly blocks the G1-to-S phase transition. CBX4 counteracts senescence through at least two mechanistically distinct pathways, one dependent on p16 repression and the other involving nucleolar heterochromatin maintenance.

In WI-38 fibroblasts, CBX4 protein progressively declined during serial culture, falling by roughly 50% before the emergence of p16 and SA- β -gal, indicating that CBX4 loss is an early event in replicative senescence rather than a passive consequence. Consistently, CBX4 knockdown increased SA- β -gal activity and p16 protein and reduced EdU incorporation, whereas CRISPR-mediated activation of CBX4 decreased p16, DPP4, and SA- β -gal. Notably, CBX4 bidirectionally regulated CDKN2A transcription, and pathway analysis implicated DNA damage repair, cell-cycle control, and p53 signaling, consistent with PRC1-mediated repression of the p16 promoter [21]. A similar mechanism was identified in osteoarthritic chondrocytes, where mutation of the chromodomain upregulates p16 while deletion of the SUMO-interacting motifs increases secretion of senescence-associated secretory phenotype (SASP) factors. The combination of these two defects accelerates senescence beyond that caused by either defect alone [22].

Another distinct regulatory process operates independently of p16 and involves the maintenance of nucleolar heterochromatin. In human mesenchymal stem cells, CBX4 knockout results in decreased growth rate, upregulation of p16 and p21, and premature induction of SA- β -gal activity. RNA sequencing (RNA-seq) and ChIP-seq data revealed limited overlap between CBX4 binding sites and genes derepressed upon CBX4 loss, indicating a mechanism beyond direct transcriptional regulation. Immunoprecipitation-mass spectrometry identified fibrillarin (FBL), a nucleolar protein important for cellular homeostasis, and KRAB-associated protein 1 (KAP1), a co-repressor in heterochromatin formation, as CBX4 interaction partners. Decreased H3K9me3 at rDNA promoters further pointed to SUV39H1, a histone lysine methyltransferase, as an additional partner. Collectively, the CBX4-FBL-KAP1 axis recruits SUV39H1 to deposit H3K9me3 at rDNA promoters, thereby maintaining nucleolar heterochromatin, restricting ribosome biogenesis and protein synthesis, and counteracting senescence [14]. Because evasion of senescence is a hallmark of cancer, these CBX4-mediated protective mechanisms represent potential priming events for oncogenic transformation when dysregulated.

2.5. CBX4 in DNA Damage Response

Genomic DNA constantly faces exogenous and endogenous threats that generate mutations, and the DNA damage response (DDR) serves as a surveillance and repair system whose breakdown can lead to accelerated senescence, cell death, or tumorigenesis.

In addition to its role in senescence, CBX4 participates directly in genome maintenance through the DNA damage response. Following the induction of DNA double-strand breaks (DSBs), CBX4 is rapidly recruited to damage sites through direct binding to poly(ADP-ribose) (PAR) polymers, which are synthesized by poly(ADP-ribose) polymerase (PARP). Early DDR factors including H2AX, ATM, DNA-PKcs, RNF8, and BMI1 are not required for this recruitment. CBX4 knockout significantly reduces SUMOylation at damage sites. Combined knockout of CBX4 and the SUMO E3 ligases PIAS1 and PIAS4 revealed that CBX4 and PIAS1/4 mediate distinct DDR pathways. CBX4 SUMOylates BMI1 at K88, which promotes BMI1 recruitment to damage sites [15].

In addition to BMI1, CBX4-mediated SUMOylation also regulates DNA end resection, a critical prerequisite for homologous recombination. Among multiple SUMO E3 ligases tested, CBX4 depletion caused the most pronounced decrease in replication protein A (RPA) foci, mirroring the effect of losing CtIP, a key activator of DNA end resection. Further investigation demonstrated that CBX4 SUMOylates CtIP at K896, and a CtIP-SUMO1 fusion rescues the resection defect caused by CBX4 depletion, establishing a direct role for CBX4-mediated SUMOylation in DNA end resection [23]. CBX4-mediated SUMOylation also engages the non-homologous end joining machinery. Upon DNA damage, HDAC8 removes the crotonyl group from Ku80 K568, licensing CBX4 to SUMOylate the same residue; this crotonylation-to-SUMOylation conversion promotes DNA-PK complex assembly and DNA-PKcs autophosphorylation, thereby facilitating DSB repair. While essential for genomic integrity, this same repair activity may inadvertently confer radioresistance and mutagenic tolerance in the tumor

context. Conversely, disrupting this modification sensitizes tumor cells to radiotherapy, linking CBX4-dependent repair to cancer radioresistance [24].

2.6. CBX4 in Immune Homeostasis

CBX4 influences immune function through SUMOylation-dependent modulation of T cell metabolism and inflammatory cytokine production. In CD8-positive T cells, CBX4 suppresses antitumor function by reprogramming glycolytic metabolism. Mechanistically, CBX4 promotes SUMOylation of the transcription factors specificity protein 1 (SP1) and Krüppel-like factor 3 (KLF3), thereby upregulating Aldob, a key enzyme in glucose metabolism, leading to impaired glycolysis and reduced ATP synthesis [25]. Conversely, CBX4 has also been reported to sustain T cell-mediated antitumor immunity by epigenetically repressing the inhibitory receptor PD-1. T cell-specific deletion of *Cbx4* in mice upregulates *Pdcd1* across peripheral T cell subsets, impairs effector cytokine production, and accelerates tumor growth. Mechanistically, CBX4 represses *Pdcd1* transcription by promoting PRC1-dependent H2AK119ub1 deposition and PRC2-dependent H3K27me3 deposition at conserved regulatory regions of its promoter [26]. These seemingly contradictory findings indicate that CBX4 can exert opposing effects on T cell antitumor immunity. It suppresses effector function through SUMOylation-driven metabolic reprogramming in CD8⁺ T cells, yet sustains it through PRC1/PRC2-mediated epigenetic silencing of PD-1, underscoring the context- and mechanism-dependent nature of CBX4 in immune regulation. Beyond T cells, CBX4 also regulates inflammatory cytokine expression. BRD4, an epigenetic reader of the inflammatory response, is stabilized by CBX4-mediated SUMOylation at K1111. This modification prevents BRD4 ubiquitination and proteasomal degradation, resulting in increased transcription of the pro-inflammatory cytokines IL-1 β , TNF- α , and IL-6. SUMOylated BRD4 also recruits TRMT112, a component of multiple RNA translation regulatory complexes, to stabilize the pre-mRNAs of these cytokines. However, the mechanism underlying this mRNA stabilization remains largely unknown [27]. Thus, CBX4 operates as a double-edged sword in immune regulation: its homeostatic functions can be subverted to generate an immunosuppressive microenvironment that favors tumor progression.

The diverse physiological functions of CBX4 underscore its modular regulatory capacity, a feature that becomes further amplified and co-opted in tumorigenesis. This transition from homeostasis to malignancy reflects not a simple loss of function but a pathological redirection of CBX4's modular activities. The stem-cell identity and lineage fidelity enforced by CBX4 in normal tissues (Section 2.1) can be hijacked to sustain cancer stemness and block differentiation; its suppression of cellular senescence through p16 repression and nucleolar heterochromatin maintenance (Section 2.4) removes a critical barrier to oncogenic transformation; its coordination of DNA damage repair (Section 2.5), while protective under physiological conditions, can confer radioresistance and mutagenic tolerance in tumors; and its immune-regulatory functions (Section 2.6) can be subverted to generate an immunosuppressive or metabolically compromised microenvironment. While CBX4's roles in thymic organogenesis (Section 2.2) and as a barrier to reprogramming (Section 2.3) are essential for normal development, their direct mechanistic links to tumorigenesis remain less defined. Collectively, these observations indicate that the physiological modules with established cancer-relevant conceptual frameworks constitute double-edged swords: when amplified, redirected, or released from normal regulatory constraints, the very mechanisms that preserve tissue homeostasis become drivers of tumor initiation, adaptation, and therapy resistance.

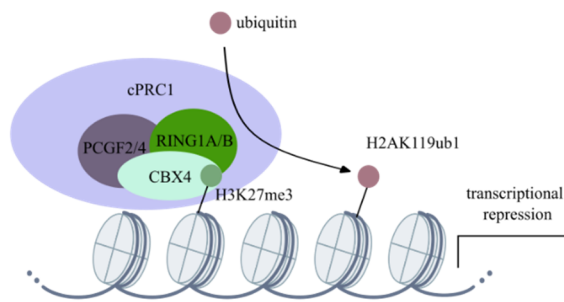
3. CBX4 in Cancer: Multifaceted Mechanisms Driving Tumorigenesis

Tumorigenesis arises from the combined dysregulation of oncogenes and tumor suppressor genes. Given that CBX4 primarily mediates transcriptional repression, one might expect it to function as a tumor suppressor. However, CBX4 is consistently upregulated in multiple primary cancers, including gastric cancer, hepatocellular carcinoma (HCC), lung cancer, osteosarcoma (OS), and colon cancer [9,11,16,28,29]. This apparent contradiction suggests that CBX4 drives malignancy via mechanisms that extend beyond transcriptional silencing.

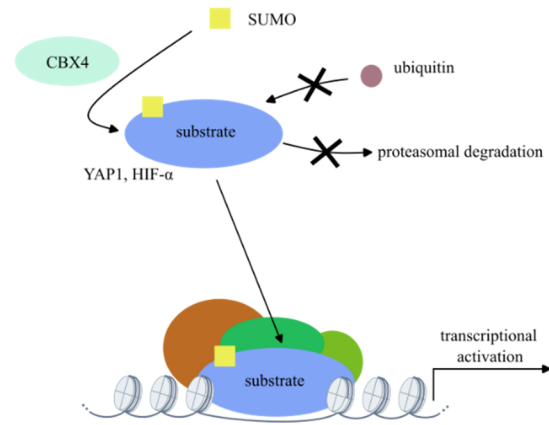
3.1. CBX4 as a cPRC1 Component: Reading H3K27me3 and Depositing H2AK119ub1

As a core component of cPRC1, CBX4 binds H3K27me3-marked sites via its chromodomain and represses transcription by depositing H2AK119ub1. In lung cancer, CBX4 recruits other cPRC1 members to the ZEB2 promoter; cPRC1-mediated deposition of H2AK119ub1 suppresses ZEB2 transcription, thus restraining metastasis [12] (Figure 1a).

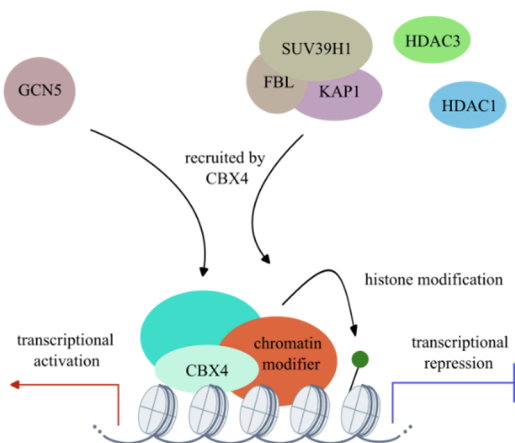
(a) cPRC1 mediated repression



(b) SUMOylation



(c) interaction with chromatin modifiers



(d) upstream and agents of CBX4

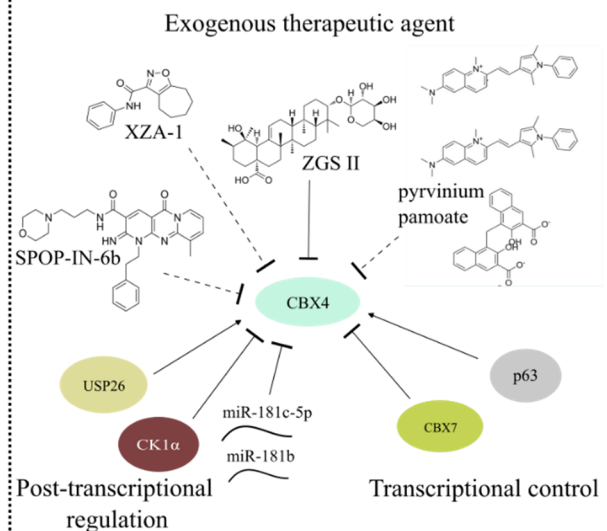


Figure 1. Major regulatory mechanisms of CBX4. (a) CBX4 promotes transcriptional repression by recognizing H3K27me3 and participating in cPRC1 assembly. (b) CBX4 SUMOylates substrates to regulate their function and stability. (c) CBX4 acts as a scaffold that recruits distinct chromatin modifiers to establish transcriptionally active or repressive chromatin states. (d) Upstream regulators and pharmacological agents targeting CBX4.

While cPRC1 exists in multiple forms, certain variants prove unexpectedly critical in particular contexts. In diffuse midline glioma (DMG), CBX4 and PCGF4, another cPRC1 component, are necessary for cell survival. Although CBX4-PCGF4-cPRC1 constitutes less than 5% of total cPRC1, PRC2 target genes are activated following CBX4 knockdown, whereas knockdown of CBX2 or PCGF2 has little detectable effect. The central region of CBX4 is critical for its interaction with PCGF4, and its deletion alters the interaction pattern of CBX4. These findings indicate that a minor yet essential cPRC1 subspecies, defined by CBX4-PCGF4 pairing, sustains the oncogenic gene expression program in this malignancy [30]. These examples collectively demonstrate that the oncogenic relevance of CBX4 cannot be predicted simply from its abundance within total cPRC1 pools; rather, specific protein-protein interactions dictate its tumorigenic potential in a context-dependent manner.

Beyond protein-coding genes, CBX4-mediated repression also extends to endogenous retroelements, with important implications for tumor immunity. *In vivo* CRISPR screens in mouse tumor models treated with immune checkpoint blockade (ICB) identified CBX4 as a key epigenetic regulator of cancer immunotherapy. CBX4 silences H3K9me3- and H3K27me3-marked retrotransposons, and its loss derepresses these elements, activating cytosolic RNA-sensing pathways and the type I interferon response. The resulting inflamed tumor microenvironment enhances the infiltration and cytotoxic activity of CD8⁺ T cells and NK cells, thereby sensitizing tumors to ICB. Consistently, high CBX4 expression in both tumor cells and immunosuppressive tumor-associated

macrophages correlates with anti-PD-1 non-response, supporting CBX4 as a promising epigenetic immune regulator in cancer [31].

3.2. CBX4 as a SUMO E3 Ligase: Modifying Substrates to Drive Oncogenic Pathways

Beyond its role within cPRC1, CBX4 acts as a SUMO E3 ligase that attaches SUMO molecules to specific substrates, altering their function, localization, or stability. This enzymatic activity, conferred by its SUMO-interacting motifs, is co-opted in multiple malignancies to drive oncogenic signaling.

In hepatocellular carcinoma, CBX4 controls a distinct SUMOylation axis that promotes angiogenesis. As tumor growth outpaces oxygen diffusion, hypoxia induces the transcription factor HIF-1 α , which drives the expression of pro-angiogenic factors. CBX4 enhances HIF-1 α -mediated transcription by SUMOylating HIF-1 α at K391 and K477, elevating VEGF expression and consequently promoting angiogenesis [10] (Figure 1b).

CBX4 also targets the Hippo pathway transcriptional co-activator YAP1. In gastric cancer, CBX4 is identified as a poor prognostic marker. Clinical data shows that gastric cancer patients with high CBX4 expression have shorter overall survival [28]. Mechanistically, CBX4 SUMOylates the Hippo pathway transcriptional co-activator YAP1 at K97 and K280, competitively inhibiting phosphorylation at S127. This post-translational modification enhances YAP1 stability and promotes its nuclear translocation (Figure 1b). Consequently, CBX4 overexpression attenuates cellular senescence and desensitizes gastric cancer cells to cisplatin [8]. A parallel mechanism operates in HCC, where CBX4 similarly induces YAP1 nuclear translocation and upregulates downstream targets including CTGF, SOX2, OCT4, and NANOG [9]. However, the relationship between CBX4 and YAP1 is not strictly linear. In embryonic fibroblasts from Cbx4-knockout KrasG12D mice, Cbx4 deletion paradoxically augmented YAP1 nuclear translocation despite the absence of CBX4-mediated SUMOylation [32]. This discrepancy warrants deeper critical evaluation. In the KrasG12D-mutant background, Cbx4 loss induces profound genomic instability and chromosome mis-segregation due to defective DNA damage repair, resulting in massive apoptosis of the majority of cells. Notably, only a minor subpopulation survives this genetic crisis, and these surviving cells exhibit secondary YAP1 nuclear accumulation [32]. Therefore, rather than a direct transcriptional or epigenetic consequence of CBX4 loss, this paradoxical YAP1 activation may represent an adaptive survival response selected under conditions of profound chromosomal instability. To determine whether CBX4 loss directly regulates YAP1, the specific impact of CBX4 depletion on YAP1 regulation must be independently validated under non-lethal, genome-stable conditions. Collectively, these contrasting findings do not negate the direct SUMOylation-dependent role of CBX4 in YAP1 activation in certain cancers, but rather highlight that the functional output of CBX4 is highly context-dependent, shaped by tumor lineage, genomic background, and the cellular stress environment.

CBX4-mediated SUMOylation has also been linked to circadian clock regulation in colon cancer. CBX4 has been proposed to enhance the transcriptional activity of the CLOCK:ARNTL complex through SUMOylation, leading to the accumulation of downstream products such as PER1, PER3, and CRY2, which subsequently exert negative feedback inhibition on CLOCK:ARNTL-mediated transcriptional activity [29]. Nevertheless, direct evidence within the tumor context remains to be established.

Across these malignancies, a common theme emerges: CBX4-mediated SUMOylation frequently redirects transcription factor localization and activity toward pro-tumorigenic programs. Yet the precise mechanism by which SUMOylation enhances substrate function, whether through steric hindrance of phosphorylation, altered protein-protein interactions, or protection from degradation, remains insufficiently dissected. Moreover, the contrasting, and occasionally paradoxical, effects of CBX4 on shared substrates such as YAP1 across different genetic backgrounds underscore that the oncogenic output of CBX4 cannot be deduced from its SUMO E3 ligase activity alone; rather, it is profoundly shaped by tumor lineage, genomic integrity, and the cellular stress environment.

3.3. An Emerging Role: CBX4 as a Chromatin Scaffold beyond PRC1 and SUMOylation

Beyond its classical roles in cPRC1 formation and SUMO E3 ligase activity, recent studies have discovered that CBX4 can serve as a chromatin scaffold that recruits distinct histone modifiers to establish transcriptionally active or repressive chromatin marks (Figure 1c).

In osteosarcoma (OS), CBX4 interacts with the histone acetyltransferase GCN5 to deposit H3K27ac at the Runx2 promoter, enhancing migration and metastasis. CBX4 relies on its chromodomain for this function but acts independently of cPRC1 activity [11]. Similarly, in lung cancer, CBX4 recruits GCN5 to the PHGDH promoter; the resulting H3K27ac deposition drives PHGDH transcription and downstream serine synthesis to promote proliferation. Thus, the CBX4-GCN5-H3K27ac axis represents a chromodomain-dependent, cPRC1-independent route to transcriptional activation.

In colorectal cancer, CBX4 recruits HDAC3 to remove H3K27 acetylation at the Runx2 promoter, inhibiting migration and metastasis [33]. A related mechanism was identified in adamantinomatous craniopharyngioma (ACP), where CBX4 stabilizes HDAC3 nuclear localization, thereby restraining Runx2 activation and osteoblastic differentiation [34]. In clear cell renal cell carcinoma (ccRCC), CBX4 suppresses the tumor-suppressor gene KLF6 through interaction with HDAC1 at the KLF6 promoter, an interaction independent of both the chromodomain and the SUMO-interacting motif [35]. A related repressive scaffolding function operates in acute monocytic leukemia (AML-M5), where CBX4 is markedly overexpressed and recruits histone deacetylase activity to the Runx1 promoter; the resulting reduction in H3K27 acetylation suppresses Runx1 expression, skews hematopoiesis toward the monocyte/macrophage lineage, and promotes AML-M5-like disease in zebrafish models [36].

In synovial sarcoma, CBX4 has also been identified as an interacting partner of SS18::SSX, the fusion oncoprotein that defines this malignancy. Although the functional consequences of this interaction remain largely unknown, this finding raises the possibility that CBX4 may contribute to fusion oncoprotein-directed chromatin dysregulation [37].

Taking these findings together, the comparative evidence across cancer contexts (Table 1), together with the contrasting YAP1 findings, indicates that the functional output of CBX4 is not intrinsically oncogenic or tumor-suppressive but is shaped by several intersecting molecular variables. First, tumor lineage and differentiation state may influence the available targets and co-regulators, as reflected by CBX4-dependent regulation of Runx1, Runx2, KLF6, and PHGDH in different cancers. Second, complex composition influences local chromatin output: CBX4-PCGF4 forms a tumor-critical cPRC1 subtype, whereas CBX4-GCN5 increases H3K27ac and CBX4-HDAC1/HDAC3 reduces promoter histone acetylation. Third, genomic background can alter CBX4 function: CBX4-mediated SUMOylation promotes YAP1 activity in gastric cancer and hepatocellular carcinoma, whereas Cbx4 deletion paradoxically increases YAP1 nuclear translocation in KrasG12D embryonic fibroblasts, indicating an alternative, context-dependent route of YAP1 regulation. Fourth, substrate-related post-translational modification status provides an additional layer of control, as illustrated by CBX4-mediated YAP1 SUMOylation, which competitively antagonizes S127 phosphorylation of YAP1. Finally, local chromatin state may determine whether CBX4 engages H3K27me3-marked repressive regions or promoters undergoing H3K27ac remodeling; whether locus accessibility further contributes remains to be determined. Thus, context-dependent CBX4 function reflects the combined influence of tumor lineage, genomic background, complex composition, modification status, chromatin state, and CBX4 abundance and stability, rather than a single invariant activity.

3.4. Upstream Regulation and Therapeutic Targeting of CBX4

The diverse oncogenic mechanisms driven by CBX4 have prompted exploration of therapeutic strategies. In addition to direct oncogenic effects, CBX4 overexpression confers resistance to multiple antitumor agents. In gastric cancer, CBX4 reduces cisplatin sensitivity, whereas in HCC, CBX4 inhibition restores sorafenib susceptibility [8,9]. Clinical data further support the prognostic relevance of CBX4 in HCC: elevated CBX4 expression predicts poor outcome and serves as an independent biomarker for transarterial chemoembolization (TACE) following hepatic resection [38]. These findings suggest that targeting CBX4 may hold clinical value both as a standalone strategy and as a means to overcome drug resistance.

At the transcriptional level, CBX4 expression is directly controlled by upstream regulators (Figure 1d). In embryonic stem cells, CBX7-containing cPRC1 represses CBX4 transcription by binding H3K27me3-marked promoters, forming an autoregulatory loop that maintains pluripotency [13]. The transcription factor p63 directly promotes CBX4 expression as an upstream regulator in epidermal cells [18].

Beyond transcriptional control, CBX4 abundance is further shaped by post-transcriptional and protein-level mechanisms (Figure 1d). USP26 stabilizes CBX4 protein through K48-linked deubiquitination, preventing proteasomal degradation [20]. Conversely, CK1 α -mediated phosphorylation of CBX4 at T437 triggers CHIP-dependent ubiquitination and subsequent proteasomal degradation [12]. Additionally, miRNA-dependent regulation provides an additional layer of post-transcriptional control. miR-181c-5p directly targets CBX4 mRNA in non-small cell lung cancer, and SNHG5 sponges miR-181c-5p, thereby derepressing CBX4 and activating NF- κ B signaling [39]. Similarly, miR-181b directly targets CBX4, as demonstrated in adamantinomatous craniopharyngioma, where Bmp2-driven upregulation of miR-181b reduces CBX4 levels, relieving CBX4-mediated stabilization of nuclear HDAC3 and permitting osteoblastic differentiation [34].

Table 1. CBX4-associated molecular events across cancer contexts: functional modules, upstream regulation, and pharmacological targeting.

CBX4 Module	Cancer/Model	Factor Type/Name	PTM/Chromatin/Signaling Effect	Transcription/ Expression Effect	Biological Output
cPRC1	Lung adenocarcinoma	Target gene: ZEB2	H2AK119ub1 ↑	ZEB2 transcription ↓	Metastasis ↓
	Diffuse midline glioma	Interactor: PCGF4	CBX4–PCGF4–cPRC1 assembly	PRC2-target transcription ↓	Tumor-cell survival ↑
	Multiple tumor models	Target: retrotransposons	Retrotransposon chromatin repression	Retrotransposon transcription ↓	Immune evasion ↑
SUMO E3 ligase	Hepatocellular carcinoma	SUMO substrate: HIF-1 α	HIF-1 α SUMOylation ↑	VEGF transcription ↑	Angiogenesis ↑
	Hepatocellular carcinoma	SUMO substrate: YAP1	YAP1 SUMOylation and nuclear localization ↑	CTGF, SOX2, OCT4, NANOG ↑	Sorafenib resistance ↑
	Gastric cancer	SUMO substrate: YAP1	YAP1 SUMOylation and stability ↑; S127 phosphorylation ↓	NR	Cisplatin resistance ↑
	Colon cancer	SUMO substrate: CLOCK	CLOCK SUMOylation ↑	PER1, PER3, CRY2 ↑	Potential Oncogenic Effect
	Multiple tumor models	SUMO substrate: Ku80	Ku80 SUMOylation ↑; NHEJ ↑	NR	Radioresistance ↑
Chromatin scaffold	Lung adenocarcinoma	Interactor: GCN5	H3K27ac ↑	PHGDH transcription ↑	Proliferation ↑
	Osteosarcoma	Interactor: GCN5	H3K27ac ↑	Runx2 transcription ↑	Metastasis ↑
	Colorectal cancer	Interactor: HDAC3	H3K27ac ↓	Runx2 transcription ↓	Metastasis ↓
	Adamantinomatous craniopharyngioma	Interactor: HDAC3	HDAC3 nuclear localization ↑	Runx2 transcription ↓	Calcification ↓
	Clear cell renal cell carcinoma	Interactor: HDAC1	NR	KLF6 transcription ↓	Oncogenesis ↑
	Acute monocytic leukemia	Interactor: HDAC	H3K27ac ↓	Runx1 transcription ↓	Leukemia development ↑
Upstream regulation	Non-small cell lung cancer	Upstream: lncRNA: SNHG5	NF- κ B signaling ↑	CBX4 expression ↑	Progression ↑
Pharmacological targeting	Hepatocellular carcinoma	Drug: XZA-1	CBX4 acetoacetylation ↑; HIF-1 α activity ↓	NR	Angiogenesis ↓
	Osteosarcoma	Drug: ZGS II	CBX4 abundance ↓; Wnt/ β -catenin signaling ↓	EMT-related genes ↓	Metastasis ↓
	Osteosarcoma	Drug: pyrrvinium pamoate	CBX4 degradation ↑; YAP1 SUMOylation ↓	p16/p21 pathway ↑	Senescence ↑; metastasis ↓
	Melanoma	Drug: SPOP inhibitor	CBX4 degradation ↑ STING activation ↑	NR	Immunotherapy efficacy ↑

NR: not reported.

Exogenous therapeutic agents target CBX4 through direct and indirect mechanisms (Figure 1d). ZGS II, a natural triterpene glycoside with reported antitumor activity across multiple cancer types, shows preclinical promise against metastatic osteosarcoma. Molecular docking predicts a direct interaction between ZGS II and CBX4, and the downregulation of CBX4 following ZGS II treatment supports its functional involvement; CBX4 knockout produces a pattern similar to ZGS II treatment, characterized by inhibition of Wnt/ β -catenin signaling and suppression of epithelial-mesenchymal transition (EMT) [40]. Notably, CBX4 has also been reported to upregulate Wnt/ β -catenin signaling in lung adenocarcinoma, although the precise molecular interface remains to be elucidated [16]. The small-molecule activator XZA-1 binds 3-hydroxyacyl coenzyme A dehydrogenase (HADH) to increase cellular acetoacetyl-CoA levels. Acetoacetylation of CBX4 at lysine 106 subsequently impairs its SUMO E3 ligase activity and inhibits HIF-1 α -induced angiogenesis [41]. Targeted protein degradation represents an emerging alternative strategy. Small-molecule inhibitors of the E3 ligase SPOP act as molecular glues that redirect SPOP toward neosubstrates including CBX4, and the resulting CBX4 degradation increases DNA damage and activates STING-dependent innate immunity, thereby synergizing with immune checkpoint blockade and CAR-T cell therapy in melanoma models [42]. Pharmacological activation of upstream kinases offers another indirect route to lower CBX4 levels. In osteosarcoma, a pH-responsive self-assembling peptide nanoplatform delivering the CK1 α activator pyrvinium pamoate promotes ubiquitin-dependent degradation of CBX4, which in turn suppresses YAP1 SUMOylation and nuclear translocation, induces p16- and p21-dependent cellular senescence, and inhibits tumor growth and lung metastasis without obvious systemic toxicity [43].

Collectively, these studies reveal that CBX4 drives tumorigenesis through multiple distinct mechanisms. As a cPRC1 component, CBX4 facilitates H2AK119ub1 deposition at selected loci; the resulting tumor-promoting or tumor-suppressive outcome depends on both the repressed target genes and the cancer context. As a SUMO E3 ligase, it modifies YAP1 and HIF-1 α to activate oncogenic signaling and angiogenesis. In addition to these enzymatic roles, CBX4 serves as a chromatin scaffold that recruits either activating or repressive complexes in a locus-specific manner, generating bidirectional transcriptional outputs. These diverse mechanisms have motivated therapeutic strategies targeting either CBX4 SUMO E3 ligase activity or CBX4 protein abundance, with potential utility in restoring chemosensitivity and suppressing tumor progression.

4. Summary

CBX4 has traditionally been regarded as a transcriptional repressor acting through canonical polycomb repressive complex 1 (cPRC1). By recognizing H3K27me3-marked chromatin, CBX4-containing cPRC1 promotes H2AK119ub1 deposition and transcriptional repression (Figure 1a). In lung cancer, this mechanism represses ZEB2 and restrains metastasis. In diffuse midline glioma, CBX4 and PCGF4 are required for tumor-cell survival, and CBX4 knockdown leads to the activation of PRC2 target genes. These findings indicate that the biological consequences of CBX4-associated transcriptional repression depend on the target locus and cancer context. CBX4 also functions as a small ubiquitin-like modifier (SUMO) E3 ligase that regulates substrate stability, subcellular localization, and activity (Figure 1b). Reported substrates include YAP1, HIF-1 α , BMI1, CtIP, SP1, KLF3, and BRD4. In cancer cells, CBX4-mediated SUMOylation of YAP1 and HIF-1 α promotes oncogenic signaling, angiogenesis, and therapeutic resistance. In non-malignant cells, CBX4-mediated SUMOylation of BMI1 and CtIP contributes to DNA damage repair, whereas modification of SP1, KLF3, and BRD4 regulates immune and inflammatory responses.

Beyond cPRC1-mediated repression and SUMOylation, CBX4 interacts with additional chromatin regulators and can function as a chromatin scaffold (Figure 1c). CBX4 recruits GCN5 to establish H3K27ac and activate Runx2 or PHGDH transcription, whereas its interactions with HDAC1 or HDAC3 are associated with transcriptional repression at the KLF6 and Runx2 promoters. In normal mesenchymal stem cells, CBX4 also cooperates with fibrillarin, KAP1, and SUV39H1 to maintain nucleolar heterochromatin. These findings indicate that CBX4 can participate in either transcriptional activation or repression, depending on its interacting proteins and target loci. CBX4 expression and activity are also regulated at multiple levels (Figure 1d). Its transcription can be controlled by p63 and CBX7-containing cPRC1, whereas miR-181c-5p represses CBX4 post-transcriptionally. At the protein level, USP26 stabilizes CBX4 through deubiquitination, while CK1 α -mediated phosphorylation promotes CHIP-dependent ubiquitination and degradation. CBX4 acetoacetylation can also inhibit its SUMO E3 ligase activity. Preclinical studies suggest that XZA-1 and ZGS II can interfere with CBX4-dependent pathways, but their broader applicability and clinical potential remain to be determined.

In summary, CBX4 is a multifunctional chromatin regulator involved in cPRC1-mediated repression, SUMO-dependent post-translational modification, and scaffold-mediated recruitment of chromatin regulators. Further studies are needed to clarify how CBX4 engages distinct protein partners at specific genomic loci and how CBX4-dependent pathways can be targeted while preserving its normal physiological functions.

Author Contributions

H.T.: investigation, writing—original draft preparation, visualization; K.Z.: writing—reviewing and editing, visualization; S.W.: investigation; Y.Z.: conceptualization, writing—reviewing and editing, supervision. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No datasets were generated or analyzed during the current study.

Conflicts of Interest

Given the role as Deputy Editor-in-Chief of *Gene Regulation and Signaling*, Yue Zhao had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

Abbreviations

ACP	Adamantinomatous craniopharyngioma
CBX	Chromobox
ccRCC	Clear cell renal cell carcinoma
CD	Chromodomain
cPRC1	Canonical polycomb repressive complex 1
DDR	DNA damage response
DMG	Diffuse midline glioma
DSB	DNA double-strand break
FBL	Fibrillarin
HADH	3-hydroxyacyl coenzyme A dehydrogenase
HCC	Hepatocellular carcinoma
HP1	Heterochromatin protein 1
KAP1	KRAB-associated protein 1
KLF3	Krüppel-like factor 3
ncRNA	Non-coding RNA
OS	Osteosarcoma
PcG	Polycomb group
PAR	Poly (ADP-ribose)
PARP	Poly (ADP-ribose) polymerase
RPA	Replication protein A
SASP	Senescence-associated secretory phenotype
SIM	SUMO-interacting motif
SP1	Specificity protein 1
TACE	Transarterial chemoembolization

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