Clinical Epigenetics

REVIEW

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Epigenetic regulatory protein chromobox family regulates multiple signalling pathways and mechanisms in cancer

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Abstract

Signal transduction plays a pivotal role in modulating a myriad of critical processes, including the tumour microenvironment (TME), cell cycle arrest, proliferation and apoptosis of tumour cells, as well as their migration, invasion, and the epithelial–mesenchymal transition (EMT). Epigenetic mechanisms are instrumental in the genesis and progression of tumours. The Chromobox (CBX) family proteins, which serve as significant epigenetic regulators, exhibit tumour-specific expression patterns and biological functionalities. These proteins are influenced by a multitude of factors and could modulate the activation of diverse signalling pathways within tumour cells through alterations in epigenetic modifications, thereby acting as either oncogenic agents or tumour suppressors. This review aims to succinctly delineate the composition, structure, function, and expression of CBXs within tumour cells, with an emphasis on synthesizing and deliberating the CBXs-mediated activation of intracellular signalling pathways and the intricate mechanisms governing tumourigenesis and progression. Moreover, a plethora of contemporary studies have substantiated that CBXs might represent a promising target for the diagnosis and therapeutic intervention of tumour patients. We have also compiled and scrutinized the current research landscape concerning inhibitors targeting CBXs, aspiring to aid researchers in gaining a deeper comprehension of the biological roles and mechanisms of CBXs in the malignant evolution of tumours, and to furnish novel perspectives for the innovation of targeted tumour therapeutics.

Keywords Chromobox family proteins, Epigenetic mechanisms, Tumour signalling pathways, Tumour prognostic marker, Tumour targeted therapy

Background

Cancer represents a complex evolutionary process marked by the dynamic interplay of diverse cellular subsets. Unravelling the pivotal factors and mechanisms underlying tumourigenesis and malignant progression, as well as identifying effective therapeutic strategies, remains a formidable challenge and a critical frontier in humanity's quest to conquer cancer. Extensive research has corroborated that aberrations in epigenetic mechanisms are prevalent in tumours and play a significant role in propelling tumour evolution. These epigenetic alterations endow cancer cells with phenotypic heterogeneity, foster the proliferation and metastasis of tumour cells, augment the anti-tumour immune response, and enhance immune evasion capabilities, thereby accelerating the malignant progression of tumours [1].

The Chromobox (CBX) family proteins are pivotal epigenetic regulators that modulate gene expression by either suppressing transcription or recruiting

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transcriptional coactivators to promoter regions. This is achieved through various epigenetic modifications, including DNA/RNA methylation and histone methylation/acetylation, which in turn influence the chromatin state to either activate or inactivate the transcription of target genes. In mammalian genomes, eight CBX-encoding genes (CBX1-8) have been identified. Among these, CBX2, CBX4, CBX6, CBX7, and CBX8 are categorized within the polycomb group (PcG) protein family [2], whereas CBX1, CBX3, and CBX5 are associated with the heterochromatin protein 1 (HP1) protein family [3]. The aberrant expression or functional impairment of CBX proteins in tumours is mediated through a complex interplay of mechanisms, including epigenetic modifications, nuclear translocations, interactions with non-coding RNAs, transcriptional regulation, post-translational modifications (PTMs), protein–protein interactions (PPIs), signal transduction, and metabolic reprogramming. These mechanisms enable CBX proteins to act as oncogenic or tumour suppressor factors, influencing the malignant progression of tumours and serving as biomarkers for tumour diagnosis and prognosis [4]. Recent studies have elucidated that CBX proteins could modulate a variety of signalling pathways, such as Wnt/β-catenin [5], Hippo [6], PI3K/AKT/mTOR [7], NF-κB [8], TGF-β [9], MAPK [10], Notch [11], and HIF-1α [12], thereby affecting critical tumour processes including proliferation, cell cycle, apoptosis, EMT, and chemotherapy resistance. Despite the extensive literature detailing the roles of CBX family members in tumour biology, there remains a lack of specificity in the description of how CBX proteins mediate different signalling pathways across various tumour types. This review aims to provide a comprehensive summary and discussion on the regulatory roles and specific mechanisms of different CBX family members in various tumour signalling pathways. By delving deeper into the epigenetic mechanisms through which CBX proteins regulate these pathways, we could gain a better understanding of their significant role in tumour evolution. Furthermore, this review seeks to offer valuable insights for the clinical diagnosis, treatment, drug development, and prognosis prediction of tumours, with a focus on targeting tumour epigenetics.

Structure and function of CBXs

The CBX 1–8 proteins exhibit chemical similarities, particularly in their aminoterminal regions, which harbour the chromatin domain (CD). This domain plays a crucial role in regulating heterochromatin formation, gene expression, and developmental processes. Based on the structural similarities of their carboxyl-terminal domains, the CBX proteins could be categorized into two distinct families: PcG protein family and the HP1 protein family [4]. Specifically, the carboxyl-terminal regions of CBX2/4/6/7/8 contain conserved multivalent repressor protein motifs, classifying them as members of the PcG protein family. Additionally, the regions adjacent to the CD in these CBX proteins (CBX2/4/6/7/8) are characterized by the presence of DNA-binding motifs and AT-hook motifs (in CBX2) or AT-hook-like motifs (in the other CBXs) [2] (Fig. 1A). On the other hand, the carboxyl-terminal regions of CBX 1/3/5 are distinguished by the presence of a chromoshadow domain (CSD), which places them within the HP1 protein family [3] (Fig. 1B).

PcG protein mainly forms Polycomb repressive complex 1/2 (PRC1/2), which is involved in transcriptional inhibition, and collaborates with histone post-translational modification to transcriptionally silence the expression of target genes. PRC1 is mainly composed of Sex Combs Extra (Sce), Polycomb (Pc), Posterior Sex Combs (Psc), Polyhomeotic (Ph), and Sex Comb on Midleg (Scm) [13], which is divided into canonical PRC1 (cPRC1) and non-canonical PRC1 (ncPRC1). PRC1 could catalyse the mono-ubiquitination of histone H2A at lysine K119 (H2AK119ub) [14–16]. PRC2 mainly contains four core subunits: enhancer of zeste homolog 1/2 (EZH1/2), embryonic ectoderm development (EED), suppressor of zeste 12 (SUZ12), and retinoblastoma protein-associated proteins 46/48 (RBAP46/48). It could catalyse the methylation of histone H3 at lysine K27 (H3K27me1/2/3), where H3K27me3 acts as a marker of transcriptional inhibition [17–19]. CBX 2/4/6/7/8 is one of the important components of cPRC1, with polyhomeoproteins (PHC1/2/3) and SCM proteins (SCML1/2 or SCMH1) around the catalytic core of RING1A/B and Polycomb group RING finger proteins (PCGF2/4) to assemble cPRC1 [20]. CBX 2/4/6/7/8 possess histone methylation reader functions, enabling them to recognize H3K27me3, a mark catalysed by PRC2. These CBX proteins, in conjunction with the H3K24/K36 demethylase KDM2B, facilitate the recruitment of cPRC1 to target gene loci that are preferentially occupied by PRC2. This recruitment allows the RING proteins within cPRC1 to catalyse the H2AK119ub1, leading to chromatin structural abnormalities, transcriptional repression, and downregulation of target gene expression. This mechanism is commonly referred to as the classical PRC1-dependent pathway [21] (Fig. 2A). In addition to their role in recognizing histone modifications, CBX2 contains a disordered region rich in positively charged amino acids, which could directly induce chromatin compaction and contribute to the transcriptional silencing of target genes [21]. Although CBX 2/4/6/7/8 share the ability to recognize H3K27me3, their affinities for this mark vary. Moreover, some CBX proteins could also recognize other histone modifications. For instance, the chromatin domains of CBX2

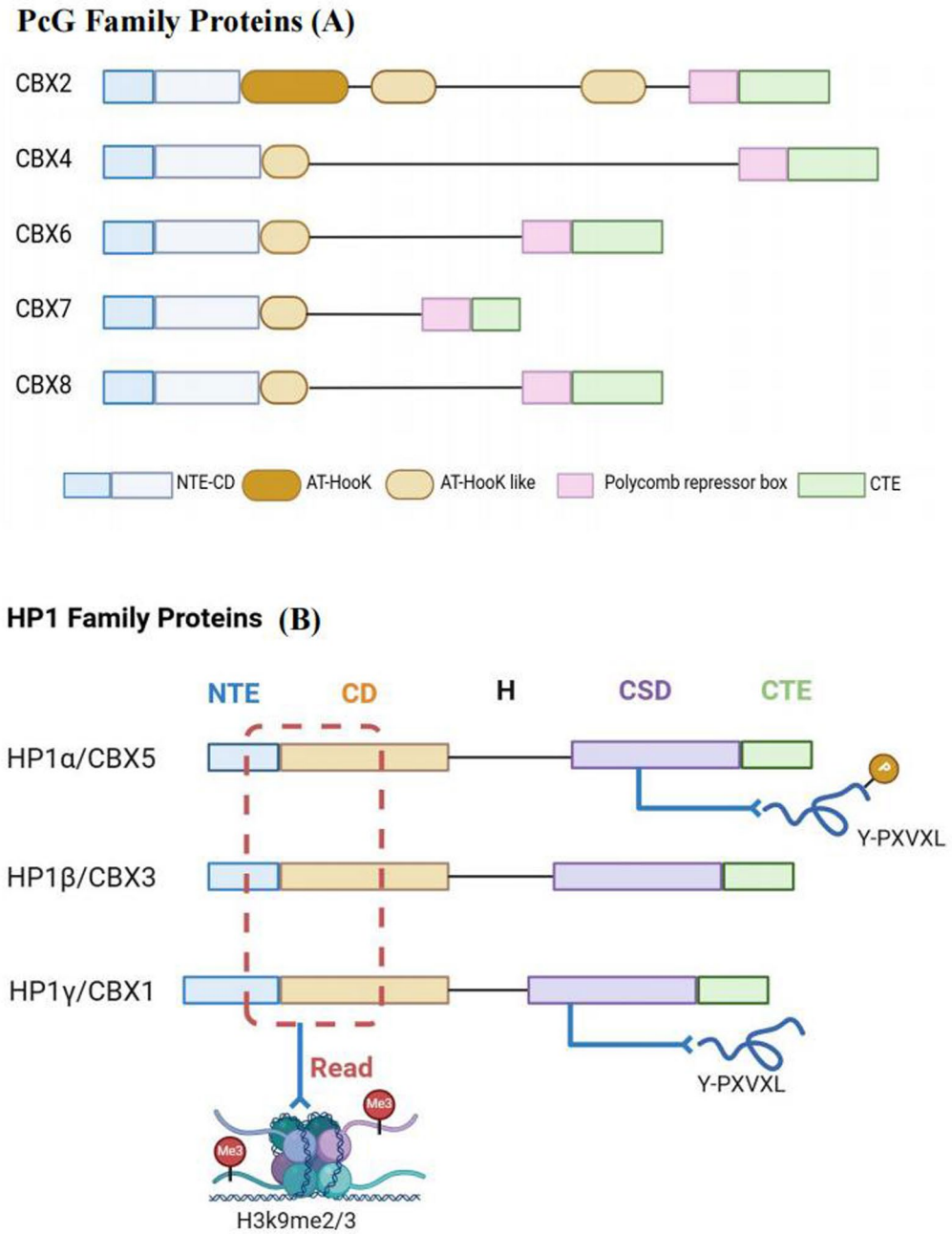

Fig. 1 Structure of CBXs family proteins. (**A**) CBX2, CBX4, CBX6, CBX7 and CBX8 belong to the polycomb group (PcG) protein family. Both of these amino terminal regions carry the chromatin domain (CD), the regions adjacent to CD carry DNA-binding motifs and AT-hook motifs (CBX2) or AT-hook-like motifs (CBX4/6/7/8). The carboxyl-terminal region of CBX 2/4/6/7/8 carried conserved multi-comb repressor protein boxes. (**B**) HP1α/CBX5, HP1β/CBX1, HP1γ/CBX3 belong to HP1 family. Their structure contains the amino terminal chromatin domain (CD) and the carboxyl-terminal chromatin shadow domain (CSD), which are connected by a hinge domain (H) that imparts nucleic acid binding activity. CD acts as a "reader" and is responsible for recognizing the methylated histone H3 at lysine K9 (H3K9me2/3) and interacting with the methylated histone tail-specific CHD, and the higher the H3K9me2/3 level, the affinity between HP1 and methylated histone tail CHD was stronger. CSD contains homologous and heterodimer domains, and is mainly responsible for forming a dimerization interface for recruiting specific ligands. In addition, the CSD of HP1α and γ interacts with two tyrosine 41 (Y41) residues located upstream of the PxVxL pentapeptide motifs. Thease residues bind to the PxVxL pentapeptide mootifs on the αn1-helix of H3. However, the binding of HP1α to the PxVxL pentapeptide motifs in H3 is inhibited by the phosphorylation of Y41

and CBX7 exhibit a strong affinity for H3K27me3, while CBX4 shows a pronounced preference for methylated histone H3 at lysine K9 (H3K9me3). CBX6, on the other hand, displays a weaker affinity for both H3K27me3 and H3K9me3 [22]. Emerging research has identified the existence of ncPRC1 complexes, which are formed by the association of non-classical PRC1 genes such as BCOR, PCGF1, KDM2B, SKP1, and USP7 with certain PRC1 subunits. These ncPRC1 complexes could perform functions analogous to those of canonical PRC1, including the catalysis of H2AK119ub1, a hallmark of transcriptional repression. For instance, in diffuse large B cell lymphoma (DLBCL), CBX8 has been shown to retain its role as a reader of H3K27me3, a mark deposited by PRC2. However, instead of recruiting canonical PRC1, CBX8 facilitates the recruitment of the non-canonical PRC1-BCOR complex to the promoter regions of downstream target genes. This recruitment leads to the catalysis of H2AK119ub1 and subsequent transcriptional repression of target genes, operating through a non-classical PRC1-independent pathway [23]. Additionally, studies have demonstrated that CBX4/7/8 could exert transcriptional regulatory effects independently of the classical PRC1-dependent pathway. These CBX proteins could mediate transcriptional repression or even activation through mechanisms involving SUMO E3 ligase activities, interactions with histone deacetylases (HDAC2/3), and modulation of H3K4 methyltransferase activity (Wdr5) [24–26]. In mammals, the HP1 family comprises three major homologs: HP1α, HP1β, and HP1γ, encoded by the CBX5, CBX1, and CBX3 genes, respectively. HP1α (CBX5) and HP1β (CBX3) are predominantly associated with heterochromatin regions, such as centromeres and telomeres, where they contribute to the transcriptional suppression of genes. In contrast, HP1γ (CBX1) is primarily located in euchromatin regions and is involved in transcriptional elongation and RNA processing [27]. Structurally, HP1 proteins are characterized by two conserved domains: the amino-terminal CD and the carboxyl-terminal CSD. These domains are connected by a hinge region (H) that confers nucleic acid binding activity. The CD functions as a "reader" module, specifically recognizing and binding to H3K9me2/3. This interaction is mediated through the methylated histone tail-specific chromodomain (CHD), with the binding affinity of HP1 to the methylated histone tail increasing in proportion to the levels of H3K9me2 /3 [28]. The CSD of HP1 proteins contains homologous and heterodimerization interfaces, which are primarily responsible for forming dimerization structures and recruiting specific ligands. One critical function of the CSD is the recruitment of SUV39H1, a histone methyltransferase that catalyses the methylation of H3K9me3. This recruitment creates new binding sites for additional HP1 molecules, establishing a positive feedback loop that propagates the H3K9me3 mark along specific chromosomal regions. As a result, a large number of proteins are recruited to these regions, leading to the formation and spread of heterochromatin. This process induces chromatin compaction and gene silencing, effectively rendering the associated genes transcriptionally inactive [3] (Fig. 2B). The interplay between HP1 and SUV39H1 also extends to DNA methylation. Both HP1 and SUV39H1 could recruit DNA methyltransferases, facilitating the methylation of DNA. In some cases, histone H3K9 methylation precedes DNA methylation, supporting the notion that these molecules are integral to a cyclical recruitment process during gene silencing. Interestingly, HP1 proteins are not solely involved in transcriptional repression. HP1α (CBX5), HP1β (CBX1), and HP1γ (CBX3) have also been shown

(See figure on next page.)

Fig. 2 The main function of CBXs family proteins. (**A**) CBX 2/4/6/7/8, integral components of the canonical Polycomb Repressive Complex 1 (cPRC1), collaborate with Polyhomeotic proteins (PHC1/2/3) and SCM proteins (SCML1/2 or SCMH1) to form a complex around the catalytic core composed of RING1A/B and Polycomb group RING finger proteins (PCGF2/4). These CBX proteins serve as histone methylation readers, specifically recognizing the methylation of histone H3 at lysine K27 (H3K27me3) mark catalysed by Polycomb repressive complex 2 (PRC2), which mainly contains four core subunits: enhancer of zeste homolog 1/2 (EZH1/2), embryonic ectoderm development (EED), suppressor of zeste 12 (SUZ12), and retinoblastoma protein-associated proteins 46/48 (RBAP46/48). The H3K24/K36 demethylase KDM2B directs cPRC1 to genomic loci pre-marked by PRC2. Within this complex, the RING proteins catalyse the ubiquitination of histone H2A at lysine 119 (H2AK119ub1), leading to chromatin compaction, transcriptional repression, and the downregulation of target gene expression. This mechanism is recognized as the classical PRC1-dependent pathway. (**B**) HP1 contains the amino terminal chromatin domain (CD) and the carboxyl-terminal chromatin shadow domain (CSD), which are connected by a hinge domain (H) that imparts nucleic acid binding activity. CD acts as a "reader" and is responsible for recognizing the methylated histone H3 at lysine K9 (H3K9me2/3) and interacting with the methylated histone tail-specific CHD, and the higher the H3K9me2/H3K9me3 level, The affinity between HP1 and methylated histone tail CHD was stronger. CSD contains homologous and heterodimer domains, and is mainly responsible for forming a dimerization interface for recruiting specific ligands, recruiting SUV39H1 (an inhibitor of H3K9 methyltransferase) to methylate neighbouring nucleosomes, creating new binding sites for other HP1s to form a positive feedback loop, leading to the formation of inhibitory H3K9me3 markers along specific chromosome regions, with a large number of proteins recruited and inserted into genes that cannot be transcribed, thus inducing heterochromatin formation and spread, resulting in chromatin structure compression and gene silencing.

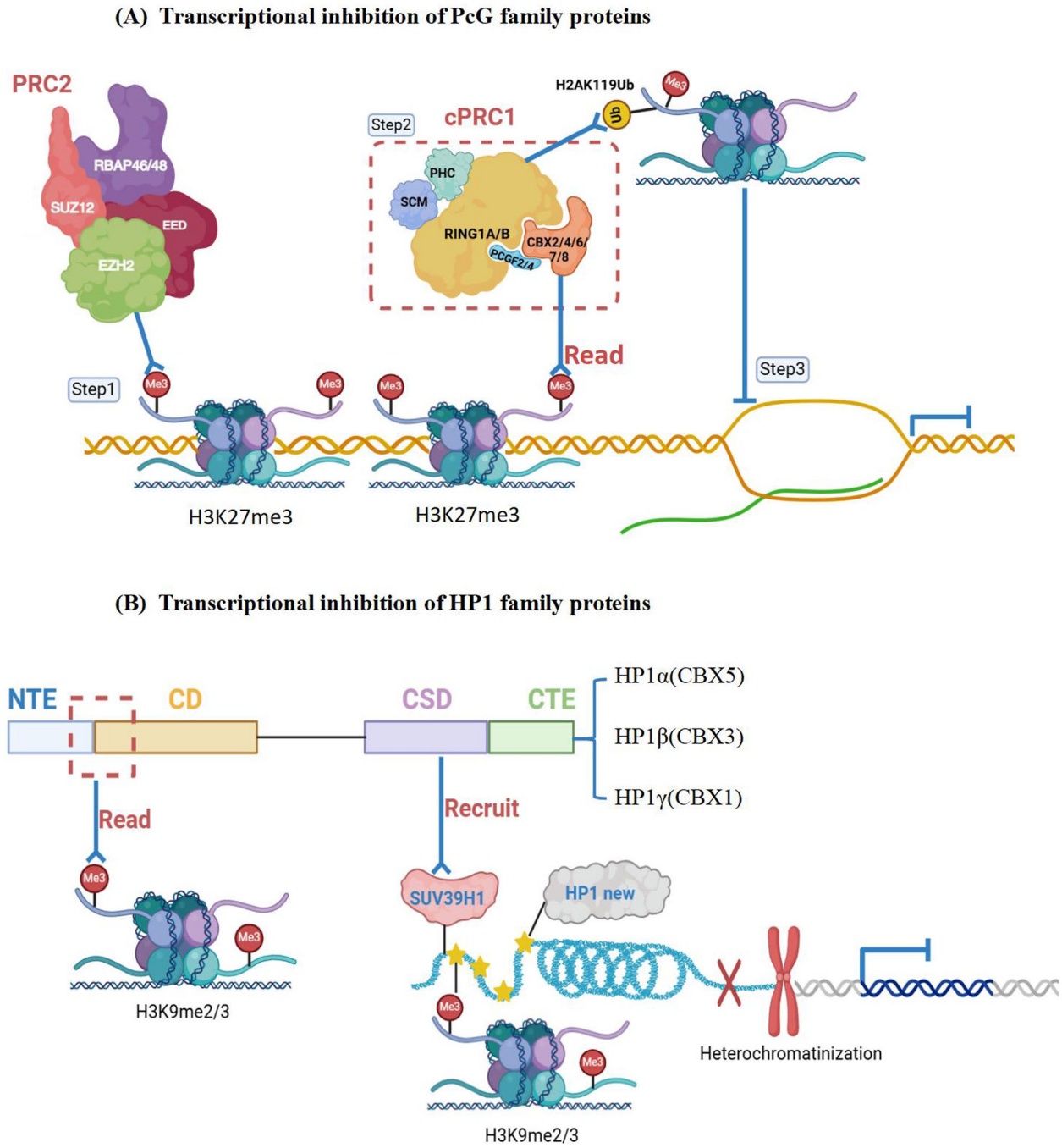

Fig. 2 (See legend on previous page.)

to exert transcriptional activation effects. In euchromatin regions, these proteins could promote gene activation by participating in co-transcriptional splicing processes [29–32].

Expression levels and roles of CBXs in different tumours

The expression and biological role of CBX family members in tumours are tumour-specific (Table 1). CBX1

Table 1 CBX proteins's expression and signalling pathways in different tumours and their function

CBX	Signalling pathway	Tumour	Expression level	Function		Reference
CBX1	Wnt/β-catenin	HCC	H	Carcinogenic factor	Tumour cell proliferation, migration	[96]
CBX2	Wnt/β-catenin	GC	H	Carcinogenic factor	Tumour cell proliferation, migration, invasion	[97]
	Hippo	HCC	H	Carcinogenic factor	Tumour cell proliferation, apoptosis	[98]
	PI3K/AKT/mTOR	BC,GBM	H	Carcinogenic factor	Tumour cell proliferation ,migration, invasion	[99, 100]
	ERK/MAPK	AML	H	Carcinogenic factor	Tumour cell proliferation, migration, invasion	[10]
CBX3	Wnt/β-catenin	CRC	H	Carcinogenic factor	Tumour cell proliferation, cycle, apoptosis	[101]
	PI3K/AKT/mTOR	ccRCC,PCa	H	Carcinogenic factor	Tumour cell angiogenesis, immunological disorders, proliferation, migration, invasion	[102, 103]
	TGF-β	PC	H	Carcinogenic factor	Tumour cell proliferation,migration, invasion	[9]
	P53-P21-RB	ESCC,TSCC,CRC	H	Carcinogenic factor	Tumour cell proliferation, cycle	[104, 105]
	Rho-ROCK	LUAD	H	Carcinogenic factor	Tumour cell proliferation,migration, invasion	[106]
CBX4	Wnt/β-catenin	LUAD	H	Carcinogenic factor	Tumour cell proliferation, cycle	[107]
	Hippo	LUAD (KrasG12D mutations)	L	Carcinogenic factor	Tumour cell apoptosis	[81]
	NF-κB	NSCLC,OS	H	Carcinogenic factor	Tumour cell proliferation, migration, invasion	[108, 109]
	Notch	BC	H	Carcinogenic factor	Tumour cell proliferation, migration	[77]
	HIF-1α	HCC,OS	H	Carcinogenic factor	Tumour cell proliferation, apoptosis, migration, invasion, angiogenesis	[12, 110]
CBX5	E2F1/BIRC5	LUAD	L	Carcinogenic factor	Tumour cell proliferation, apoptosis, cycle, chemoresistance	[82]
CBX6	NF-κB	HCC BC	H L	Carcinogenic factor Tumour suppressor	Tumour cell proliferation,cycle, migration, invasion	[111, 112]
CBX7	Wnt/β-catenin	UBC,HCC,BC	L	Tumour suppressor	Tumour cell proliferation,cycle, migration, invasion	[5, 113, 114]
	Hippo	GBM	L	Tumour suppressor	Tumour cell proliferation, apoptosis, migration, invasion	[6]
	PI3K/AKT/mTOR	UBC	L	Tumour suppressor	Tumour cell proliferation, migration, invasion, chemoresistance	[115]
	NF-κB	ccRCC PC GC	L L H	Tumour suppressor Tumour suppressor Carcinogenic factor	Tumour cell proliferation, migration, chemoresistance, stem cell-like properties	[116, 117, 8]
	TGF-β	CCA	L	Tumour suppressor	Tumour cell proliferation, apoptosis, migration, invasion	[118]
	ERK/MAPK	UBC,NSCLC	L	Tumour suppressor	Tumour cell proliferation, cycle,migration, invasion, stem cell-like properties	[119, 120]
	P53-P21	Thyroid cancer,Lung cancer,Glioma	L	Tumour suppressor	Tumour cell proliferation, cycle, apoptosis ,migration, invasion	[121–123]

Table 1 (continued)

CBX	Signalling pathway	Tumour	Expression level	Function		Reference
CBX8	Wnt/β-catenin	LSCC	H	Carcinogenic factor	Tumour cell proliferation, apoptosis, migration, invasion	[124]
	PI3K/AKT/mTOR	PC	H	Carcinogenic factor	Tumour cell proliferation	[7]
	ERK/MAPK	HCC	H	Carcinogenic factor	Tumour cell proliferation, migration, invasion, stem cell-like properties	[125]
	Notch	BC	H	Carcinogenic factor	Tumour cell proliferation, stem cell-like properties	[11]
	P53-P21	UBC,HCC	H	Carcinogenic factor	Tumour cell proliferation, cycle	[126, 127]
	Rho-ROCK	GBM,BC,Lung cancer	H	Carcinogenic factor	Tumour cell proliferation, migration, invasion	[128]
	PRDM1/c-FOS	UBC	H	Carcinogenic factor	Tumour cell proliferation, apoptosis,migration, invasion	[129]

Expression Level: High/Low (H/L)

could be highly expressed in breast cancer (BC), colorectal cancer (CRC), oesophageal cancer (EC), gastric cancer (GC), hepatocellular carcinoma (HCC), head and neck squamous cell carcinoma (HNSCC), lung adenocarcinoma (LUAD), non-small cell lung cancer (NSCLC), pancreatic adenocarcinoma (PAAD), low expressed in clear cell renal cell carcinoma (ccRCC), and CBX1 could be highly or low expressed in ovarian cancer (OC) [33–51]. CBX2 could be highly expressed in BC, CRC, EC, GC, glioma, HCC, HNSCC, LUAD, NSCLC, OC, skin cutaneous melanoma (SKCM), acute myelocytic leukaemia (AML), while low expression of CBX2 has not been found in tumours [33–37, 39–43, 45, 46, 48, 51–65]. CBX3 could be highly expressed in BC, ccRCC, CRC, EC, oesophageal squamous cell carcinoma (ESCC), GC, glioma, HCC, HNSCC, LUAD, NSCLC, OC, osteosarcoma (OS), PAAD, pancreatic cancer (PC), prostate carcinoma (PCa), SKCM, TSCC, urinary bladder cancer (UBC), while low expression of CBX3 has not been found in tumours [33–38, 40–48, 50, 51, 53–55, 59, 60, 62, 64, 66–75]. CBX4 could be highly expressed in BC, ccRCC, CRC, EC, GC, HCC, HNSCC, LUAD, NSCLC, OS [33, 35, 37, 39–43, 45–48, 50, 59, 60, 69, 76–80] and other studies have shown that CBX4 could be low expressed in KrasG12D-mutated LUAD [81]. CBX5 could be highly expressed in BC, CRC, EC, GC, glioma, HCC, NSCLC, PAAD, SKCM, low expression in ccRCC [33–37, 39–48, 50, 53, 54, 64, 69], CBX5 could be high in LUAD or low expression in EGFR-mutated LUAD [82]. CBX6 could be highly expressed in HCC, HNSCC, SKCM, low expressed in BC, ccRCC, CRC, glioma, NSCLC, OC, and high or low expressed in GC [33, 34, 40, 45, 46, 48, 50, 53, 54, 60, 62, 64, 73, 74, 83–85]. CBX7 could be highly expressed in HCC, low expressed in cervical carcinoma (CCA), ccRCC, CRC, EC, GC, glioma, HNSCC, LUAD, NSCLC, OC, PAAD, PC, SKCM, UBC, and high or low expressed in BC and GC [33–36, 38–43, 45, 46, 48, 50, 52–54, 59, 60, 62–64, 69, 73, 74, 86–89]. CBX8 could be highly expressed in BC, ccRCC, CEC, EC, ESCC, GC, glioma, HCC, HNSCC, LSCC, LUAD, OC, PAAD, PC, TSCC, UBC and low expressed in SKCM [33–35, 37, 38, 41–48, 50, 53, 54, 59, 64, 69, 74, 86, 88, 90–95]. The results of relevant biogenic analysis and experimental articles also indicate that the expression of some CBXs (high/low) might be closely related to the shortened overall survival and poor prognosis of patients, and some of them have even been confirmed as biological markers of tumour diagnosis and prognosis. (Please see Table 2 for more details)

We could see from the above expression of CBXs in various tumours that CBX 1/2/3/4/5/8 is highly expressed in most tumours. Although some studies have found that CBX4 is low expressed in LUAD cells with KrasG12D mutation, many studies have confirmed that CBX4 is highly expressed in LUAD cells with KrasG12D mutation [81]. Regardless of the expression of CBX 1/2/3/4/5/8 in tumours, CBX itself mostly exists as a carcinogenic factor, regulating tumour TME and tumour metabolism, affecting the cycle, proliferation, apoptosis, migration and invasion, chemotherapy or radiotherapy sensitivity and other processes, and playing an active role in promoting the proliferation and malignant progression of tumour cells. It could also be used as a biomarker of poor prognosis. However, some researchers have found that CBX5 could be low expressed in LUAD cells with epidermal growth factor receptor (EGFR) mutation and

Table 2 The expression of CBXs in different tumours and its effect on OS reduction

CBXs	High expression in tumours	Low expression in tumours	OS reduce with poor prognosis	References
CBX1	BC,CRC,EC,GC,HCC,HNSCC LUAD,NSCLC,OC,PAAD,Sarcoma	ccRCC,OC	(H):LUAD,GC,HCC,OC,Sarcoma (L):ccRCC	[33–51]
CBX2	AML,BC,CRC,EC,GC,Glioma,HCCH NSCC,LUAD,NSCLC,OC,SKCM	NONE	(H):BC,HCC,OC (L):PAAD	[33–35, 35–37, 39–43, 35, 35, 36, 51–65]
CBX3	BC,ccRCC,CRC,EC,ESCC,GC Glioma,HCC,HNSCC,LUAD NSCLC,OC,OS,Osteosarcoma,PAA DPC,PCa,Sarcoma,SKCM,TSCC UBC	NONE	(H):BC,CRC,EC,GC,Glioma,HCC,HN SCC,OC,Osteosarcoma,Sarcoma (L):GC	[14, 33–35, 67, 33, 40–44, 46–48, 69, 70, 53–55, 43, 62, 44, 46, 66–70, 75, 50, 51]
CBX4	BC,ccRCC,CRC,EC,GC HCC,HNSCC,LUAD,NSCLC,OS Osteosarcoma Sarcoma	KrasG12D-mutated LUAD	(H):BC,CRC,EC,GC,HCC,LUAD (L):LUAD	[81, 76, 33, 39–43, 45–48, 40–43, 76–81]
CBX5	BC,CRC,EC,Glioma,GC,HCC LUAD,NSCLC,PAAD,Sarcoma SKCM	ccRCC,EGFR-mutated LUAD	(H):BC,CRC,GC,HCC,LUAD,Sarco ma,SKCM (L):ccRCC,HNSCC	[33–37, 39–48, 45–47, 64, 48, 50]
CBX6	GC,HCC,HNSCC,Sarcoma,SKCM	BC,ccRCC,CRC,Glioma,GC,NSCL C,OC	(H):CRC,GC,HCC (L):BC,ccRCC,Glioma,PAAD	[53, 54, 33, 34, 83, 60, 40, 62, 45, 46, 73, 74, 64, 48, 83–85]
CBX7	BC,GC,HCC	BC,CCA,ccRCC,CRC,EC,GC,Glioma, HNSCC,LUAD NSCLC,OC,PAAD,PC,SKCM,UBC	(H):GC (L):BC,CCA,ccRCC,EC,GC,Glioma,H CC,LUAD,PAAD,Sarcoma	[33–36, 38–43, 38, 69, 39, 40, 52–54, 62, 45, 62–64, 74, 63, 64, 86–89]
CBX8	BC,ccRCC,CEC,EC,ESCC,GC Glioma,HCC,HNSCC,LSCC,LUADO C,PAAD,PC,Sarcoma,TSCC,UBC	SKCM	(H):BC,ccRCC,CRC,EC,GC,Glioma, HCC,YBC (L):LUAD,PAAD	[33–35, 34, 59, 41–48, 43, 44, 91, 92, 45, 46, 93, 47, 74, 90–95]

OS overall survival, *H* high expression, *L* low expression

could be used as a tumour-suppressive factor, which helps to improve the sensitivity of tumour patients to EGFRi treatment [82]. The expression of CBX6 is different in different tumours, but it usually exists as an oncogene to promote the occurrence and development of tumours. Some studies have also shown that CBX6 could play a role as a tumour suppressor in BC, and its expression is inhibited and downregulated in the process of tumour development. CBX7 is mostly expressed at a low level in tumours. Although it has been confirmed that CBX7 is beneficial to the prognosis of patients as a tumour suppressor in most tumours, some studies have found that CBX7 plays a role as a carcinogenic factor in HCC, promoting the proliferation, migration, and invasion of tumour cells and other malignant progression [4].

CBXs and signalling transduction in tumours

CBX 1/2/3/4/7/8 regulates Wnt/β-catenin signalling pathway

The Wnt signalling pathway represents an evolutionarily conserved intercellular signalling cascade, initiated by lipid-modified proteins secreted from the Wnt family. This pathway, pivotal throughout biological evolution [130], bifurcates into two principal categories: the canonical pathway, exemplified by the Wnt/β-catenin signalling pathway, and the non-canonical pathways, such as the Wnt/Ca^{2+} pathway. These pathways intricately interconnect, forming a regulatory network that governs cellular processes. The canonical Wnt/β-catenin pathway predominantly orchestrates cell proliferation, whereas its non-canonical counterparts are instrumental in modulating cell polarity and migration [5]. A growing body of research, bolstered by clinical evidence, underscores the critical role of dysregulation within the canonical Wnt/β-catenin signalling pathway in the malignant progression of various cancers, including CRC, HCC, and SKCM. Such dysregulation is intricately linked to tumourigenesis, the onset of EMT, and the facilitation of cancer cell migration and invasion [131]. Emerging studies reveal that the activation of Wnt/β-catenin signalling pathway in tumour cells could be regulated by epigenetic regulatory factor CBX1/2/3/4/7/8, which could promote or inhibit the malignant progression of tumour cells (Fig. 3A).

Existing research has established that CBX1 and CBX3 function as transcriptional activators in HCC and CRC, respectively. Although the precise mechanisms remain to be fully elucidated, these proteins upregulate the expression of downstream target genes, thereby enhancing the activation of the Wnt/β-catenin signalling pathway and contributing to tumour promotion. In contrast, the roles of CBX2/4/8 in GC, LUAD, and LSCC are less understood. It remains unclear through which transcriptional regulatory mechanisms these CBXs overactivate the Wnt/β-catenin signalling pathway, thereby acting as oncogenic drivers in these cancers.

The High mobility group A2 (HMGA2) protein serves as an upstream regulator, targeting and modulating key signalling pathways such as Wnt/β-catenin and mTOR in tumour cells. This regulation mediates the induction of EMT in HCC cells [132]. Intriguingly, CBX1 and HMGA2 co-localize within the nucleus of HCC cells, where CBX1 transcriptionally activates the ectopic expression of HMGA2. This activation enhances HMGA2-mediated phosphorylation of β-catenin at Ser552, further promoting the activation of the Wnt/β-catenin signalling pathway. Consequently, this cascade induces EMT, accelerates the malignant proliferation, migration, and invasion of HCC cells, and ultimately leads to poor patient prognosis [96]. Additionally, Yes-associated protein (YAP), a downstream effector of the Hippo signalling pathway, has been shown to positively regulate the expression of β-catenin protein. This regulation further facilitates the activation of the Wnt/β-catenin signalling pathway in tumour cells, contributing to tumour progression [133]. CBX2 has been identified as a key regulator of the YAP/β-catenin signalling pathway, playing a significant role in tumour promotion [97]. In GC, CBX2 inhibits the activation of the Hippo signalling pathway, thereby reducing the nuclear translocation and phosphorylation of its downstream effector, YAP. This inhibition leads to the upregulation of YAP protein expression, which in turn promotes the expression of β-catenin and its downstream targets, including the cell cycle-related proteins c-myc and cyclin D1. Concurrently, CBX2 suppresses the expression of DKK-1, a negative regulator of β-catenin, further activating the Wnt/β-catenin signalling pathway. This activation inhibits cell cycle arrest in GC cells, facilitating tumour cell proliferation, migration, and invasion. In CRC, the expression of Non-structural Maintenance of Chromosomes (SMC) Condensin I Complex Subunit G (NCAPG) is significantly elevated, positioning it as both an oncogenic factor and a prognostic biomarker [134]. CBX3 interacts with the promoter region of NCAPG in CRC, acting as a transcriptional activator to upregulate NCAPG expression. This upregulation enhances the expression of Wnt/β-catenin signalling-related proteins, such as Wnt3a and β-catenin, thereby promoting the activation of the Wnt/β-catenin signalling pathway and inducing EMT in tumour cells. Consequently, CBX3-mediated activation of this pathway enhances the migration and invasion capabilities of tumour cells, promotes their proliferation, inhibits cell cycle arrest and apoptosis, and accelerates the malignant progression and metastasis of CRC [101]. CBX4 has been shown to positively regulate the expression of β-catenin and its downstream targets, c-myc and cyclin D1, at both the mRNA and protein levels in LUAD cells. This regulation promotes the activation of the Wnt/β-catenin signalling pathway, accelerates tumour cell proliferation, and is associated with poor patient prognosis [107]. In LSCC, dysregulation of the Wnt/β-catenin signalling pathway is closely linked to the induction of EMT and might directly contribute to tumour progression and metastasis [135]. Specifically, CBX8 in LSCC cells upregulates the expression of the CTNNB1 gene, which encodes β-catenin, as

(See figure on next page.)

Fig. 3 Details of CBX members regulate Wnt/β-catenin, Hippo, MARK signalling pathways in tumours and mechanism. (**A**) CBX1 and CBX3, respectively, play a transcriptional activation role in HCC and CRC (the specific mechanism of action is not yet clear), could upregulate the expression of downstream target genes to promote the activation of Wnt/β-catenin signalling pathway and play a tumour promotion role. However, it is not clear CBX2/4/8 through what transcriptional regulatory mechanism overactivates the Wnt/β-catenin signalling pathway in GC/LUAD/LSCC cells to play the role of carcinogenic factors. CBX7 could act as a methylation reader to identify H3K27me3 on the promoter of downstream target genes, silence the expression of downstream target genes through classical PRC1-dependent transcriptional pathway, inhibiting the activation of Wnt/β-catenin signalling pathway, and act as a cancer suppressor. However, although CBX7 also exists as a tumour suppressor in BC cells, it exerts transcriptional activation independently of the classical PRC1-dependent pathway, upregulates the expression of downstream target genes, and inhibits the activation of Wnt/β-catenin signalling pathway. (**B**) CBX2 in HCC might be independent of the classical PRC1-dependent pathway, playing a role in transcriptional activation (the specific mechanism is not clear), upregulating the expression of downstream target genes, inhibiting the activation of Hippo signalling pathway, and playing a role in tumour promotion. However, the transcriptional regulatory mechanism of oncogenic factor CBX4 in inhibiting Hippo signalling pathway activation in LUAD cells in the context of KrasG12D mutation remains unclear. In GBM, CBX7 could inhibit the expression of downstream target genes through classical PRC1-dependent pathway transcription, promote the activation of tumour suppression-related Hippo signalling pathway, inhibit the activation of EMT-related SAPK/JNK signalling pathway, and play a role as a cancer suppressor, which is conducive to patients' prognosis. CBX2 could inhibit the expression of downstream target genes through classical PRC1-dependent pathway transcription, promote the activation of MAPK signalling pathway in AML, and play a role as a carcinogenic factor. Although CBX8 could recognize H3K27me3 in HCC cells, it transcriptionally activating the expression of downstream target genes through other mechanisms independent of the classical PRC1-dependent pathway, promoting the activation of MAPK signalling pathway, and playing a role as a carcinogenic factor. The transcriptional regulation mechanism of oncogenic factor CBX7 in promoting the activation of MAPK signalling pathway in OC cells remains unclear. CBX7 could silence the expression of downstream target genes through classical PRC1-dependent transcriptional pathway, inhibit the activation of MAPK signalling pathway in UBC, and act as a tumour-suppressive factor. However, it is not clear whether the transcriptional regulation mechanism of CBX7 is involved in the regulation of ERK/MAPK signalling pathway activation in NSCLC cells.

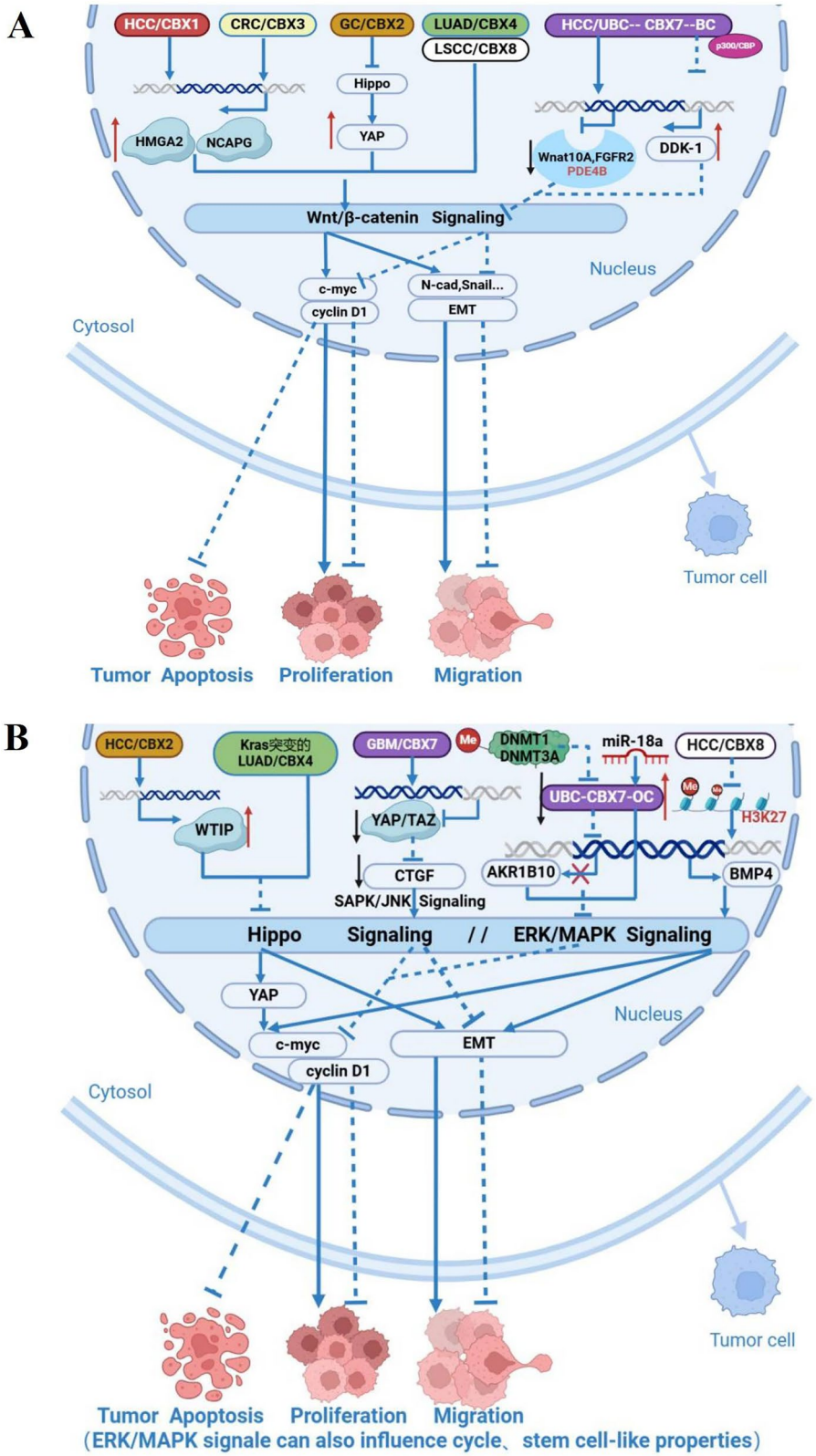

Fig. 3 (See legend on previous page.)

well as EMT-related proteins such as N-cadherin and Snail1. Concurrently, CBX8 downregulates the expression of negative regulators of the Wnt signalling pathway, including DKK-1 and GSK3β, and modulates apoptosis-related proteins such as Bax and Bcl2. These changes result in the overactivation of the Wnt/β-catenin signalling pathway, induction of EMT, promotion of LSCC cell proliferation and migration, inhibition of apoptosis, and acceleration of tumour malignant progression [124].

CBX7, a key component of PRC1, functions as a methylation reader by recognizing H3K27me3 marks on the promoters of downstream target genes. Through the classical PRC1-dependent transcriptional repression pathway, CBX7 silences the expression of these target genes, thereby inhibiting the activation of the Wnt/β-catenin signalling pathway and acting as a tumour suppressor in UBC and HCC. Interestingly, in BC cells, CBX7 also exhibits tumour-suppressive properties, but its mechanism of action diverges from the classical PRC1-dependent pathway. Instead of repressing gene expression, CBX7 exerts transcriptional activation, upregulating the expression of downstream target genes, still resulting in the inhibition of the Wnt/β-catenin signalling pathway.

Phosphodiesterase 4B (PDE4B) plays a role in regulating various intracellular signalling pathways [136] and has been implicated as an oncogenic factor [137, 138]. In UBC cells, CBX7 functions as a methylation reader, recognizing H3K27me3 marks catalysed by PRC2 in the promoter region of the downstream PDE4B gene. CBX7 recruits PRC1 to bind to the PDE4B promoter, enabling the core RING protein of PRC1 to catalyse the H2AK119ub1. This results in chromatin structural changes and transcriptional silencing of PDE4B in a classical PRC1-dependent manner. Consequently, this process inhibits the activation of the Wnt/β-catenin signalling pathway, reduces the expression of the EMT-related transcription factors Twist1/2 downstream of PDE4B, and increases the expression of E-cadherin. These changes hinder the occurrence of EMT, thereby delaying the malignant progression of UBC tumours [5]. Various endogenous non-coding small RNAs (miRNAs/miRs) could either activate or inhibit the classical Wnt/β-catenin signalling pathway in different types of tumours [139, 140]. Specifically, miR-181a has been shown to induce EMT and is recognized as a key driver in the initiation and progression of HCC [141]. In HCC cells, the expression of CBX7 is negatively regulated by the upstream target miR-181ab1. This regulation likely occurs through the classical PRC1-dependent pathway, where CBX7 transcriptionally silences the expression of downstream target genes such as Wnt10a and FGFR2, thereby inhibiting the activation of the Wnt/β-catenin signalling pathway. Then, upregulating the expression of cyclin E1 protein related to cell cycle induces cell cycle arrest, inhibiting malignant proliferation of HCC cells, to function as a cancer suppressor [113]. The Wnt/β-catenin signalling pathway is a critical regulator of cancer stem cell (CSC) properties, including tumour cell spheroid formation, migration, invasion, and chemotherapy resistance [142, 143]. Although chromatin immunoprecipitation (ChIP) assays revealed that CBX7 is closely bound to the distal promoter region of DKK-1, a negative regulator of the Wnt signalling pathway, the levels of H3K27me3 and H2AK119ub1 remained unchanged. This suggests that CBX7 in BC does not mediate transcriptional repression through the classical PRC1-dependent pathway. Further studies have demonstrated that CBX7 could directly interact with p300 acetyltransferase in BC cells, recruiting p300/CBP histone acetyltransferase (HAT) to the distal promoter region of DKK-1. This interaction catalyses the acetylation of histone 3 (H3AC) and inhibits the deacetylation activity of HDAC, thereby promoting transcriptional activation and upregulating the expression of DKK-1. Consequently, the Wnt/β-catenin/TCF signalling pathway is suppressed, leading to decreased expression of cell proliferation, cell cycle-related proteins such as c-Myc and cyclin D. This process inhibits the self-renewal, proliferation, migration, and invasion of CSCs, ultimately delaying the malignant progression of BC [114].

CBX 2/4/7 regulates Hippo signalling pathway

The Hippo signalling pathway, a highly conserved pathway throughout biological evolution, plays a pivotal role in regulating a wide range of physiological and pathological processes. Its activity is largely mediated by the downstream key effectors YAP and transcriptional coactivator with PDZ-binding motif (TAZ). Activation of the Hippo signalling pathway promotes the phosphorylation of YAP, preventing its nuclear translocation and leading to its degradation in the cytoplasm [144]. While the Hippo pathway primarily functions as a tumour suppressor, it is frequently dysregulated during the malignant progression of tumours [144]. Recent studies have revealed that epigenetic regulatory factors CBX2/4/7 could modulate the activation of the Hippo signalling pathway in tumour cells, acting either as oncogenic or tumour-suppressive factors (Fig. 3B).

Current studies have confirmed that CBX2 in HCC might function independently of the classical PRC1-dependent pathway, acting as a transcriptional activator (although the specific mechanism remains unclear). It upregulates the expression of downstream target genes, inhibits the activation of the Hippo signalling pathway, and promotes tumour progression. However, the transcriptional regulatory mechanism by which the

oncogenic factor CBX4 suppresses the activation of the Hippo signalling pathway in LUAD cells, particularly in the context of KrasG12D mutation, remains poorly understood and requires further investigation.

Studies have demonstrated that CBX2 exhibits transcriptional activation in HCC. It enhances the transcriptional activities of WT1-interacting proteins (WTIP) [145, 146], which are among the antagonists of the Hippo signalling pathway. This action inhibits the activation of the Hippo signalling pathway, leading to reduced phosphorylation and degradation of the downstream effector YAP. Consequently, the expression of YAP is increased, promoting the proliferation and metastasis of HCC cells, inhibiting apoptosis, and accelerating the malignant progression of the tumour [98]. The mutation of KrasG12D, a membrane protein with GTPase activity, regulates the expression of apoptosis-related genes and enhances the proliferation and invasion capabilities of tumour cells. It is frequently utilized as a tumour model in lung cancer studies [147]. Recent research has revealed that a subset of LUAD patients with KrasG12D mutations exhibit low expression of CBX4 in tumour cells, yet CBX4 still functions as an oncogenic factor. In KrasG12D-mutant LUAD cells, CBX4 inhibits the activation of the Hippo signalling pathway, leading to increased expression of the downstream signalling molecule YAP. This upregulation enhances the proliferation and invasion abilities of tumour cells. Additionally, low expression of CBX4 affects chromosomal stability, modulates the expression of apoptosis-related genes, and contributes to poor patient prognosis [81]. Researchers have also identified the involvement of the Wnt signalling pathway in this context. It is hypothesized that the loss of CBX4 might regulate multiple genes and signalling pathways in tumour cells through complex mechanisms, enabling a small population of KrasG12D-mutant LUAD cells to survive genomic instability and acquire enhanced proliferative and invasive capabilities. However, the specific mechanisms underlying these processes remain to be fully elucidated and require further investigation.

In glioblastoma (GBM), CBX7 exerts its tumour-suppressive functions through multiple mechanisms. It inhibits the expression of downstream target genes via the classical PRC1-dependent transcriptional pathway, promoting the activation of the tumour-suppressive Hippo signalling pathway while concurrently suppressing the EMT-associated SAPK/JNK signalling pathway activation.

In GBM, the majority of PRC1 and PRC2 components exhibit dysregulation, contributing to the enhancement of CSC properties and radioresistance, thereby facilitating GBM progression [148–150]. The expression of CBX7, a key regulatory component, is frequently suppressed in malignant GBM through hypermethylation of its promoter region, which consequently impairs its PRC1-dependent transcriptional regulatory functions. Connective tissue growth factor (CTGF) is highly expressed in GBM in a manner dependent on YAP/TAZ transcriptional activity, where it functions as an oncogene to promote GBM progression. However, under non-malignant conditions, the expression of CBX7 in GBM is not downregulated despite promoter hypermethylation, allowing it to maintain sufficient levels and properly integrate into the PRC1 complex. As a methylation reader, CBX7 recognizes the H3K27me3 mark in the promoter regions of downstream target genes, recruiting PRC1 to these sites. This recruitment catalyses the H2AK119ub1, leading to the formation of heterochromatin. Through this classical PRC1-dependent pathway, the transcriptional activity of YAP/TAZ downstream effectors of the Hippo signalling pathway—and their target gene CTGF are suppressed. Consequently, this inhibition promotes the activation of the Hippo signalling pathway while attenuating the activation of SAPK/JNK and other kinases mediated by CTGF. As a result, the SAPK/JNK signalling pathway is downregulated, EMT is impeded, and the malignant progression of GBM cells including proliferation, migration, and invasion is significantly delayed [6]. In addition, somatic and germline mutations rarely impact the Hippo signalling pathway. Therefore, the inactivation of this pathway in certain tumour cells is primarily attributed to molecular events other than somatic mutations, underscoring the critical role of the epigenetic regulatory protein CBX7. Specifically, CBX7 could modulate the activation of the Hippo signalling pathway by disrupting YAP/TAZ-dependent transcriptional activity in GBM, thereby inhibiting the malignant progression of GBM.

CBX 2/3/7/8 regulates PI3K/AKT/mTOR (PAM) signalling pathway

The PI3K and AKT proteins are the primary functional components of the PAM signalling pathway, with AKT and mTOR serving as its main effectors. This pathway is highly conserved throughout biological evolution and plays a critical role in promoting cell survival, growth, and cell cycle progression in response to external stimuli [151]. Approximately 50% of tumour cases are associated with the activation of membrane receptors (RTK or GPCR), induction of upstream PI3K oncogenes, mutations or amplifications of kinases like PIK3CA, and dysregulation or mutations in multiple components of the PAM signalling pathway [152, 153]. The PAM signalling pathway is one of the most frequently activated pathways in tumour cells, driving malignant processes such as tumour cell proliferation, EMT, migration, invasion,

and chemotherapy resistance [154]. Notably, epigenetic regulatory factors CBX2/3/7/8 have been found to transcriptionally regulate the activation of the PAM signalling pathway in tumour cells, functioning as either oncogenic or tumour-suppressive factors (Fig. 4A).

The current research has yet to substantiate that CBX2 transcriptionally modulates the activation of the PI3K/AKT signalling pathway in BC and GBM through the canonical PRC1-dependent mechanism to exert its oncogenic influence, suggesting the potential existence of alternative regulatory mechanisms. Moreover, investigations have revealed that CBX8 recognizes the H3K27me3 mark on downstream target genes within PC cells; however, it does not function as a transcriptional repressor. Instead, it appears to facilitate the transcriptional activation of these target genes via unidentified mechanisms, thereby modulating the PI3K/AKT signalling pathway and contributing to tumour progression. Similarly, CBX3 has been observed to possess transcriptional activation properties in ccRCC and PCa, enhancing the transcriptional activity of downstream target genes, which in turn regulates the PI3K/AKT signalling pathway activation and promotes tumourigenesis (the specific mechanism is still unclear).

CBX2 has been demonstrated to enhance the phosphorylation of PIK3CA and PIK3CD, key proteins within the PI3K/AKT signalling pathway, as well as downstream mTOR proteins in BC cells. This action positively regulates the activation of the PI3K/AKT signalling pathway and amplifies the activity of the mTORC1 signalling pathway, thereby promoting the proliferation, migration, and invasion of BC cells and accelerating their malignant progression [99]. Additionally, CBX2 might facilitate the activation of the PI3K/AKT signalling pathway in GBM cells by upregulating the phosphorylation of core pathway proteins AKT and GSK-3β. This upregulation leads to increased expression of EMT marker proteins, such as N-cadherin, Slug, and Snail, thereby inducing EMT and driving the malignant proliferation and metastasis of GBM cells [100]. CBX3 might initiate gene modification in ccRCC, functioning as a transcriptional activator. It upregulates the expression of the PI3Kγ complex component PIK3R6, thereby promoting the activation of the PI3K/AKT signalling pathway. This activation increases the expression of EMT-related proteins, such as E-cadherin, N-cadherin, and vimentin, and induces EMT. Consequently, CBX3 drives malignant progression, including the proliferation, migration, and invasion of ccRCC cells, acting as an oncogenic factor [102]. Notably, deficiencies in the PI3K-γ complex have been linked to abnormal DC migration. Furthermore, the PI3K-γ complex is found to be overactivated in highly immunogenic malignancies like ccRCC, influencing multiple processes, including tumour immunity, and accelerating the malignant progression of tumours. The PI3K signalling pathway plays a pivotal role in the proliferation of tumour B lymphocytes and their mediated immune responses [155, 156]. Consequently, CBX3-mediated transcriptional activation of PIK3R6 not only promotes the activation of the PI3K/AKT signalling pathway but also triggers immune dysregulation in ccRCC cells, altering the tumour immune microenvironment and facilitating neovascularization. Additionally, studies have revealed that ccRCC patients with high CBX3 expression exhibit sensitivity to immune checkpoint inhibitors (ICIs) and cyclin-dependent kinase (CDK) inhibitors. However, these patients demonstrate resistance to inhibitors targeting the PAM signalling pathway, such as LY-3023414,

(See figure on next page.)

Fig. 4 Details of CBX members regulate PI3K/AKT/mTOR, NF-κB signalling pathways in tumours and mechanism. (**A**) CBX2 could transcriptionally regulate PI3K/AKT signalling pathway activation in BC and GBM through classical PRC1-dependent pathway, playing a role in tumour promotion, other mechanisms might exist. In addition, it was found that CBX8 recognized H3K27me3 of downstream target genes in PC cells, but did not play a transcriptional inhibitory role, there were other ways to transcriptionally activate the expression of downstream target genes (the specific mechanism is still unclear) to regulate the activation of PI3K/AKT signalling pathway and play a role in tumour promotion. CBX3 has transcriptional activation in ccRCC/PCa (the specific mechanism is still unclear), which could increase the transcriptional activity of downstream target genes, regulate the activation of PI3K/AKT signalling pathway, and play a role in tumour promotion. In UBC, CBX7 could transcriptively silence the expression of downstream target genes in a classical PRC1-dependent manner, inhibit the activation of PI3K-AKT signalling pathway, play a role as a tumour-suppressive factor, and delay the malignant progression of tumours. (**B**) The transcriptional regulation mechanism of oncogenic factor CBX4 is involved in the regulation of NF-κB signalling pathway activation in NSCLC/OS cells. CBX6 could exert transcriptional activation independently of the classical PRC1-dependent pathway (the specific mechanism is not yet clear), upregulate the expression of downstream target genes, promote the activation of NF-κB signalling pathway in HCC, and play a role as a carcinogenic factor. Although CBX7 acts as a carcinogenic factor in GC, it could still play a transcriptional inhibitory role and promote the activation of NF-κB signalling pathway in GC, but the specific regulatory mechanism is unknown. CBX6 and CBX7 could inhibit the activation of NF-κB signalling pathway in BC/ccRCC cells by silencing the expression of downstream target genes through classical PRC1-dependent transcriptional pathway, thus acting as a tumour suppressor. CBX7 could transcribe and activate the expression of downstream target genes in PC cells independently of the classical PRC1-dependent pathway, and the NF-κB signalling pathway is activated to act as a tumour suppressor.

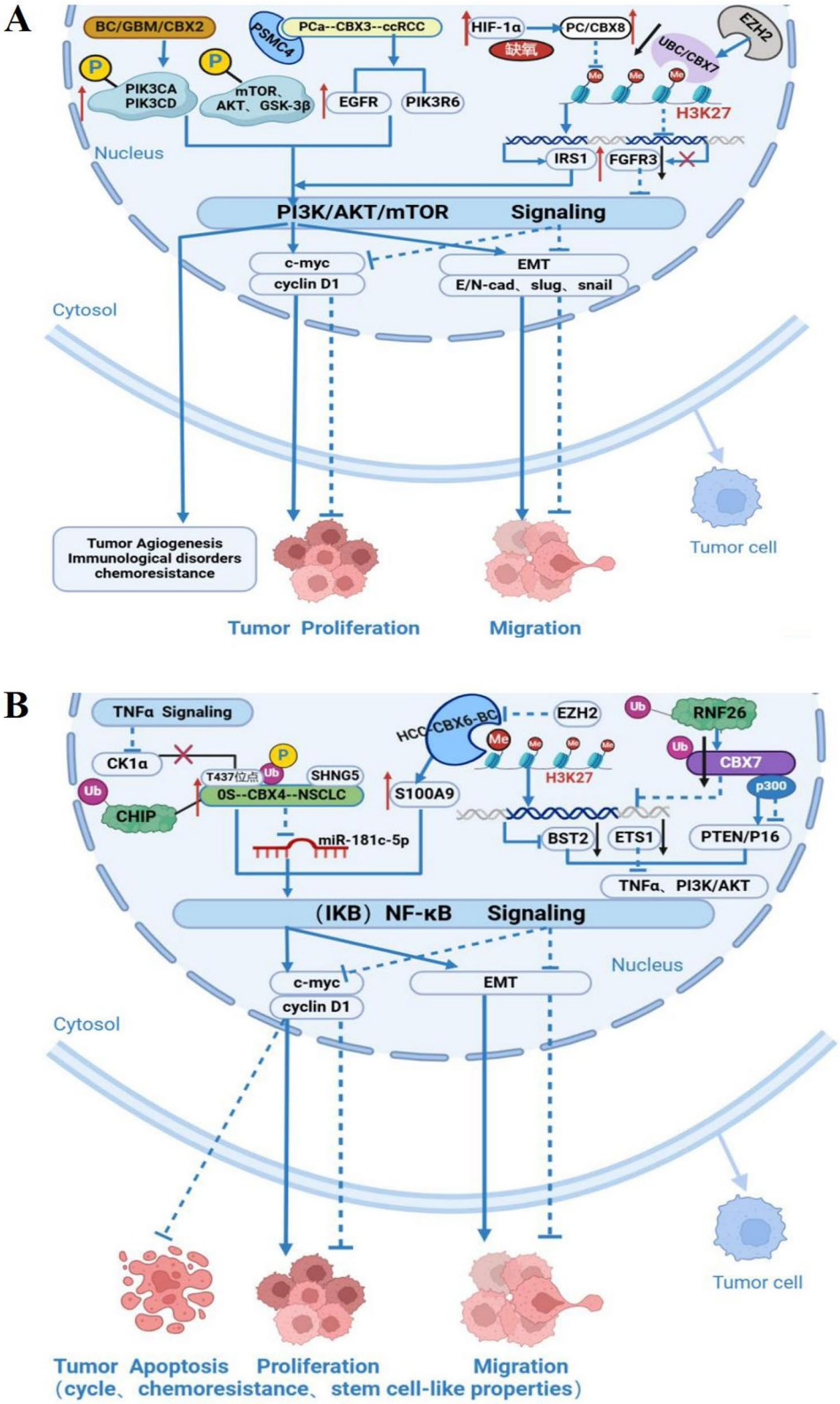

Fig. 4 (See legend on previous page.)

PQR-620, INK-128, and everolimus [157, 158]. Therefore, research into CBX3 inhibitors might enhance the sensitivity of ccRCC patients to PAM signalling pathway inhibitors, offering novel strategies for clinical treatment and improving patient prognosis. Proteasome 26S subunit ATPase 4 (PSMC4) plays a critical role in regulating proteasome assembly and influencing the initiation and progression of various cancers, including BC [159] and PCa [160]. Notably, CBX3 has been found to transcriptionally regulate the expression of EGFR, thereby promoting the activation of the PAM signalling pathway in tumour cells such as GBM and accelerating malignant progression [161, 162]. Further studies have demonstrated that the expression of CBX3 in PCa cells is positively regulated by PSMC4, which directly interacts with CBX3 to enhance its transcriptional activation. This interaction upregulates EGFR expression, promotes PAM signalling pathway activation, and induces EMT, thereby accelerating the malignant proliferation, migration, and invasion of PCa cells and contributing to poor patient prognosis [103]. It has long been established that PAM inhibitors could enhance the chemotherapy sensitivity of PCa patients to sunitinib [163]. Consequently, CBX3 small-molecule inhibitors might exhibit effects similar to PAM inhibitors by targeting the inhibition of PAM signalling pathway activation and potentially reducing chemotherapy resistance in PCa patients. However, the efficacy of such an approach requires further investigation. Hypoxia is a hallmark feature of PC, and hypoxia-inducing factor HIF plays a critical role in regulating various processes in PC cells, including proliferation, metastasis, immunosuppression [164], and angiogenesis [165]. Post-translational modifications of insulin receptor substrate 1 (IRS1) could activate the mTORC1 signalling pathway through the progressive phosphorylation of multiple serine residues [166]. Studies have confirmed that HIF-1α is upregulated in hypoxic PC cells, facilitating its binding to the promoter region of the oncogenic factor CBX8 and upregulating CBX8 expression at the transcriptional level. CBX8 recognizes H3K27me3 marks on downstream target genes in PC but does not function as a transcriptional repressor. Instead, it exerts transcriptional activation independently of the canonical PRC1-dependent pathway. By modulating H3K27me3 levels in the IRS1 promoter region, CBX8 enhances the transcriptional activity of IRS1, leading to the overactivation of the downstream PI3K/AKT signalling pathway and promoting the malignant proliferation of PC cells [7].

In UBC, CBX7 functions as a tumour suppressor by transcriptionally silencing the expression of downstream target genes through the classical PRC1-dependent pathway. This silencing inhibits the activation of the PI3K-AKT signalling pathway, thereby delaying the malignant progression of tumours.

H3K27me3 is widely recognized as the most significant histone modification within the CBX7 promoter region. Research has demonstrated that EZH2, the predominant histone-lysine N-methyltransferase [167], could hyperactivate the CBX7 promoter region by elevating H3K27me3 levels, thereby downregulating CBX7 expression in UBC cells. Additionally, fibroblast growth factor receptor 3 (FGFR3) has been identified as one of the most frequently mutated targets in UBC [168], with its aberrant activation linked to higher tumour grade and advanced tumour stage in UBC [169]. FGFR3 contributes to the activation of the PI3K-AKT signalling pathway by enhancing EGFR phosphorylation, which subsequently promotes resistance of UBC cells to cisplatin therapy [170]. Further studies have confirmed that CBX7 in UBC recognizes H3K27me3, catalysed by PRC2, within the downstream FGFR3 promoter region. This recognition facilitates the recruitment of PRC1 to the FGFR3 promoter, promoting H2AK119ub and resulting in chromatin structure abnormalities. Consequently, FGFR3 expression is downregulated through the classical PRC1-dependent transcriptional pathway. This process reduces the activation of the PI3K-AKT signalling pathway, inhibits the proliferation of UBC cells, and enhances tumour cell sensitivity to cisplatin therapy, thereby delaying the malignant progression of UBC tumours [115]. Additionally, researchers observed that downregulation or overexpression of CBX7 and p-AKT in UBC 5637 and T24 cell lines altered p-AKT expression levels. However, CBX7 overexpression did not affect p-AKT expression in UMUC-3 cells [119]. These findings suggest that the CBX7-AKT signalling pathway might exhibit cell line-dependent behaviour.

CBX 4/6/7 regulates NF-κB signalling pathway

The nuclear factor NF-κB is a key component of the transcription factor family, mediating both classical and non-classical NF-κB signalling pathways [171, 172]. The classical NF-κB signalling pathway is rapidly and transiently activated in a phosphorylation-dependent manner by the IκB kinase complex (IKK) in response to stimuli such as inflammation, immune responses, cell proliferation, differentiation, and survival [173, 174]. In contrast, the non-classical NF-κB signalling pathway exhibits more specialized biological functions and is activated by a limited number of receptors within the tumour necrosis factor (TNF) superfamily. NIK (NF-κB-inducing kinase) serves as the central kinase in this pathway [171, 175], which mainly regulates the development of immune cells in multiple layers [176]. In tumour cells, activation of the classical NF-κB signalling pathway is more prevalent.

This pathway accelerates malignant progression by modulating the tumour inflammatory microenvironment, upregulating pro-inflammatory factors, promoting tumour angiogenesis, and recruiting inflammatory cells to amplify the inflammatory response [174]. Recent studies have revealed that epigenetic regulatory factors CBX4/6/7 could transcriptionally regulate the activation of the NF-κB signalling pathway in tumour cells, thereby either promoting or inhibiting tumour progression (Fig. 4B).

Current studies have not yet established that the transcriptional regulatory mechanism of the oncogenic factor CBX4 is involved in modulating the activation of the NF-κB signalling pathway in NSCLC or OS cells. In contrast, CBX6 has been shown to exert transcriptional activation independently of the classical PRC1-dependent pathway (although the specific mechanism remains unclear). This activation upregulates the expression of downstream target genes, promotes the activation of the NF-κB signalling pathway in HCC, and functions as a carcinogenic factor. Although CBX7 functions as an oncogenic factor in GC, it also exhibits transcriptional inhibitory activity and promotes the activation of the NF-κB signalling pathway in GC. However, the specific regulatory mechanisms underlying these dual roles remain unclear.

Research has demonstrated that CBX4 is significantly overexpressed in NSCLC cells through the positive regulation of the long non-coding RNA small nucleolar RNA host gene 5 (SNHG5). CBX4 upregulates the expression of p-NF-κB-p65 protein, promotes the activation of the NF-κB signalling pathway, and functions as an oncogenic factor by enhancing the proliferation, migration, and invasion of NSCLC cells while inhibiting apoptosis [108]. Casein kinase-1α (CK1α) is a multifunctional protein that regulates multiple signalling pathways [177] and could act as either an oncogenic or tumour suppressor factor in different types of tumours [178, 179]. In OS, CK1α functions as a tumour-suppressor gene, whereas CBX4 acts as an oncogenic factor [109]. Activation of the TNFα signalling pathway in OS downregulates CK1α expression and reduces the binding of CK1α to T437, the primary phosphorylation site required for CBX4 degradation. Inhibition of the carboxyl terminus of HSC70-interacting protein (CHIP) disrupts CBX4 ubiquitination and phosphorylation-mediated degradation, leading to the upregulation of CBX4 expression and enhancing its oncogenic functions. This results in the promotion of NF-κB signalling pathway activation, accelerating the malignant proliferation and metastasis of OS [109]. Dysregulation of the S100A9 gene in human granulocytes and macrophages could induce neutrophil adhesion to fibronectin, contributing to the development of malignant tumours [180]. Additionally, S100A9 mediates the activation of NF-κB and MAPK signalling pathways, promoting tumour cell proliferation [181]. Independent of the classical PRC1-dependent transcriptional inhibition, CBX6 could activate the expression of the downstream target gene S100A9 through alternative pathways. This activation increases the phosphorylation of ERK1/2, MAPK-p38, NF-κB-p50, and NF-κB-p65 proteins in HCC cells, thereby promoting the activation of NF-κB and MAPK signalling pathways. As a result, CBX6 functions as an oncogenic factor, accelerating the malignant proliferation of HCC cells [111]. CBX7 and miR-21 play crucial roles in promoting the self-renewal and stem cell-like properties of CSCs, acting as oncogenic factors [182]. The CBX7-AKT-NF-κB-miR-21 axis has been identified as a key regulator in determining the phenotype of gastric cancer stem cells (GCSCs). CBX7 inhibits the expression of tumour suppressors P16INK4A and PTEN in GC cells, leading to the upregulation of p-AKT and overactivation of the PI3K/AKT signalling pathway. This enhances the transcriptional activity of the downstream NF-κB signalling pathway, promoting its activation and upregulating miR-21 expression. Consequently, this increases the expression of stem cell markers OCT-4 and CD44, fostering GCSC phenotypes such as tumour sphere formation, migration, invasion, and chemotherapy resistance. These mechanisms enhance GCSC-like properties and accelerate the malignant progression of GC [116].

CBX6 and CBX7 could suppress the activation of the NF-κB signalling pathway in BC and ccRCC cells by silencing the expression of downstream target genes through the classical PRC1-dependent transcriptional pathway, thereby functioning as tumour suppressors. CBX7 could transcribe and activate the expression of downstream target genes in PC cells independently of the classical PRC1-dependent pathway, resulting in the activation of the NF-κB signalling pathway, which allows CBX7 to function as a tumour suppressor.

Studies have demonstrated that bone marrow stromal cell antigen-2 (BST2), functioning as an oncogene, plays a significant role in processes such as proliferation, migration, invasion, and chemotherapy resistance in BC, nasopharyngeal carcinoma, and other tumour cells [183, 184]. Additionally, BST2 promotes the activation of the NF-κB signalling pathway, leading to the production of pro-inflammatory factors and contributing to the malignant progression of tumours [185]. In BC cells, EZH2, a catalytic subunit of PRC2, binds to the CBX6 promoter region. It catalyses the generation of H3K27me3 in CBX6 chromatin in a PRC2-dependent manner, thereby negatively regulating CBX6 expression [112]. CBX6, in turn, recognizes the enrichment of H3K27me3 in the BST2 promoter

region of BC cells and recruits PRC1 to the BST2 promoter. This upregulates the level of H2AK119ub1, causing chromatin structure abnormalities and exerting transcriptional inhibition through the classical PRC1-dependent pathway. As a result, CBX6 downregulates BST2 expression, reducing the activation of the NF-κB signalling pathway, inducing tumour cell cycle arrest, and inhibiting the malignant proliferation and metastasis of BC [112]. Furthermore, TNF-mediated activation of the NF-κB signalling pathway plays a critical role in the growth of ccRCC tumours [186]. CBX7 serves as a substrate for the E3 ubiquitin ligase RNF26 in ccRCC cells, leading to its degradation and resulting in low expression. However, the tumour suppressor CBX7 does not directly regulate the activation of TNF or its downstream NF-κB signalling pathway in ccRCC. Instead, CBX7 recruits PRC1 to the promoter of the ETS proto-oncogene 1 (ETS1) by recognizing the enrichment of H3K27me3 on the ETS1 promoter. This recruitment catalyses H2AK119ub1, causing chromatin structure abnormalities and downregulating ETS1 expression at the transcriptional level through the classical PRC1-dependent pathway. Consequently, CBX7 indirectly inhibits the activation of TNF and its downstream NF-κB signalling pathway, thereby reducing the proliferative capacity of ccRCC cells. Additionally, this mechanism reduces the expression of interleukin-6 (IL6), a drug resistance factor downstream of the TNF signalling pathway. As a result, CBX7 enhances the sensitivity of tumour cells to tyrosine kinase inhibitor (TKI) treatment and delays the malignant progression of ccRCC [117]. Extensive studies have demonstrated that the activation of the classical NF-κB signalling pathway could be regulated by the PI3K/AKT signalling pathway, which is mediated by the tumour suppressor gene PTEN. AKT could directly and rapidly phosphorylate and degrade IκB, leading to the phosphorylation and nuclear accumulation of NF-κB proteins, thereby triggering the activation of the downstream NF-κB signalling pathway [187]. Research has shown that in PC cells, CBX7 does not transcriptionally inhibit the expression of downstream target genes through the classical PRC1-dependent pathway. Instead, CBX7 recruits the transcriptional coactivator p300 acetyltransferase to bind to the PTEN promoter region. This interaction catalyses the acetylation of histone H3, transcriptionally activating the expression of the downstream target gene PTEN. Consequently, the expression of p-AKT and NF-κB p65 proteins is reduced, inhibiting the activation of the PI3K/AKT pathway and its downstream NF-κB signalling pathway. Through this mechanism, CBX7 functions as a tumour suppressor, inhibiting the proliferation, migration, invasion, and other malignant progression of PC cells [8].

CBX 3/7 regulates TGF-β signalling pathway

Transforming growth factor-β (TGF-β) is a multifunctional cytokine that orchestrates a signalling pathway, stimulating a diverse array of cellular responses and playing a pivotal role in numerous physiological and pathological processes. The TGF-β signalling pathway could be activated through both integrin-dependent and integrin-independent mechanisms, mediated by TGF-β receptor I/II (TβRI, TβRII), which are two types of enzyme-linked receptors on the cell surface. This pathway bifurcates into the SMAD-dependent canonical TGF-β signalling pathway and several SMAD-independent TGF-β signalling pathways [188]. The SMAD-independent pathways have the capacity to activate other critical signalling cascades, including PI3K/AKT [189], MAPK [190], and NF-κB [191]. Dysregulation of the TGF-β signalling pathway is instrumental in modulating the TME, cell apoptosis, metastasis, EMT, immune evasion, and treatment sensitivity in tumours [188]. Emerging research has identified that the epigenetic regulatory factors CBX3/7 could transcriptionally modulate the activation of the TGF-β signalling pathway in tumour cells, exerting either tumour-promoting or tumour-suppressing effects (Fig. 5A).

CBX3, functioning as a transcriptional repressor within the HP1 family of proteins, downregulates the expression of downstream target genes. This repression facilitates the activation of the TGF-β signalling pathway in PC cells, thereby acting as an oncogenic factor.

Smoking-induced mutations in the SMAD4 gene are recognized as one of the key drivers in the development of PC, leading to the overactivation of the TGF-β signalling pathway in PC cells [192, 193]. SMAD-specific E3 ubiquitin protein ligase 2 (SMURF2) has been demonstrated to ubiquitinate and degrade components of the TGF-β signalling pathway, including SMAD1, SMAD2, SMAD4, and TGF-β receptor 1 (TGF-βR1). This process inhibits the activation of the TGF-β signalling pathway and attenuates its tumourigenic effects [193]. Recent studies have revealed that the smoking-related oncogenic driver protein Y-box-binding protein 1 (YBX1) could bind to the promoter region of CBX3 in PC cells, transcriptionally upregulating CBX3 expression and synergistically acting as a cancer-promoting factor. CBX3, in turn, recognizes and binds to the H3K9me3 mark in the promoter region of SMURF2 in PC cells. This interaction promotes the demethylation of adjacent H3K9 residues, forms repressive H3K9me3 marks, induces heterochromatin formation, and compacts the chromatin structure, thereby transcriptionally repressing SMURF2 expression.

Consequently, the ubiquitination-mediated degradation of TGF-βR1, a key receptor in the SMURF2-dependent TGF-β signalling pathway, is reduced. This reduction promotes the activation of the TGF-β signalling pathway and accelerates the malignant proliferation of tumour cells [9].

CBX7 has been shown to function as a tumour suppressor in CCA cells by modulating the activation of the TGF-β/PI3K/AKT signalling pathway. However, the precise mechanisms underlying CBX7's transcriptional regulation and its critical role in this process remain poorly understood and require further investigation.

It has been established that CBX7 could upregulate the expression of the EMT-related protein E-cadherin, playing a pivotal role in suppressing EMT and the advanced progression of tumour cells [194]. Dysregulation of the TGF-β signalling pathway and its downstream PI3K/AKT cascade have been implicated in the malignant progression of various tumour types [8, 195]. Studies have revealed that CBX7 downregulates the expression of key proteins associated with the TGF-β signalling pathway, including integrin ITGβ3 and transforming growth factor-β1 (TGFβ1), as well as components of the PI3K/AKT pathway, such as PI3K, AKT, and p-AKT, in CCA cells By inhibiting the activation of the TGF-β signalling pathway and its downstream PI3K/AKT cascade, CBX7 reduces the expression of the EMT-related protein vimentin while increasing E-cadherin levels. This effectively suppresses EMT, promotes tumour cell apoptosis, and delays malignant progression, thereby functioning as a tumour suppressor [118].

CBX 2/7/8 regulates MAPK signalling pathway

The MAPK signalling pathway is highly conserved throughout biological evolution and is primarily mediated by three subfamilies: extracellular signal-regulated kinases (ERK MAPK, Ras/Raf1/MEK/ERK), MAPK14 (p38 MAPK), and stress-activated protein kinase or c-Jun N-terminal kinase (SAPK or JNK) [196]. Among these, the ERK-associated signalling pathway is regarded as the classical MAPK signalling pathway. The Ras-Raf-ERK signalling pathway plays a critical role in growth factor-mediated cell proliferation, differentiation, malignant transformation, and apoptosis across various cell types, making it one of the most prominent kinase cascades in tumour cell biology [197]. The JNK family is primarily involved in cellular stress responses to changes in radiation, osmotic pressure, and temperature. Additionally, the p38 MAPK signalling pathway mediates inflammatory responses, apoptosis, and other cellular processes

(See figure on next page.)

Fig. 5 Details of CBX members regulate TGF-β, Notch, HFI-1, P53/P21, E2F1/BIRC5, Rho GTPase, PRDM1/c-FOS signalling pathways in tumours and mechanism. (**A**) CBX3 could exert the transcriptional inhibition of HP1 family proteins, downregulating the expression of downstream target genes, promoting the activation of TGF-β signalling pathway in PC cells, and play the role of carcinogenic factor. CBX7 could play a role as a cancer suppressor in CCA cells by regulating the activation of TGF-β/PI3K/AKT signalling pathway, but the important role of CBX7 transcriptional regulation mechanism is still unclear. CBX4 could inhibit the expression of downstream target genes through classical PRC1-dependent pathway transcription, promote the activation of Notch signalling pathway in BC cells, and play a role as a carcinogenic factor. However, CBX8 inhibits the expression of downstream target genes through non-classical PRC1-independent pathway transcription, promotes the activation of Notch signalling pathway in BC cells, and plays a role as a carcinogenic factor. (**B**) CBX4, independent of the classical PRC1-dependent pathway, exerts SUMO E3 ligase activity to enhance the transcriptional activity of downstream target genes, overactivates HIF-1α signalling pathway in HCC cells, and acts as a carcinogenic factor. However, whether CBX4 promotes the activation of HIF-1α signalling pathway in OS cells through the same pathway remains to be further explored. CBX3 could play a role as a carcinogenic factor by exerting transcriptional inhibition mediated by HP1 family proteins, silencing the expression of downstream target genes, inhibiting the activation of P53/P21 signalling pathway in TSCC and CRC. However, the transcriptional regulatory mechanisms of CBX3 and CBX8 in regulating P53/P21 signalling pathway activation in ESCC, UBC, and HCC remain unclear. CBX7 could interact with HDAC2 independently of the classical PRC1-dependent pathway in thyroid cancer, lung cancer and brain glioma cells, regulate histone acetylation in the promoter region of downstream target genes, transcriptively activate or silence the expression of downstream target genes, and reduce migration, invasion and activation of cell cycle-related signalling pathways, acting as a cancer suppressor. The low expression of CBX5 in EGFR-mutated LUAD cells could inhibit the expression of E2F1, weaken the transcriptional activation of E2F1, downregulate the expression of anti-apoptotic gene BIRC5, inhibit the activation of anti-apoptotic signalling pathway of E2F1/BIRC5, induce apoptosis, and enhance the sensitivity of patients to EGFRi treatment. Exert tumour-suppressive effect. At the same time, the combination of epigenetic regulatory factor-related small-molecule inhibitors BETi and EGFRi could restore the expression of CBX5 and re-improve the sensitivity of LUAD resistant patients with EGFR mutation to EGFRi treatment. (**C**) CBX3 could downregulate the expression of downstream target genes through the transcriptional inhibition mediated by HP1, promote the activation of Rho GTPase signalling pathway in LUAD cells, and play a role in tumour promotion. CBX8 could also transcriptionally inhibit the transcriptional activity of downstream target genes, promote the activation of Rho GTPase signalling pathway in GBM, BC and lung cancer, and play a tumour-promoting role. However, more evidence is needed to confirm whether CBX8 exerts transcriptional inhibition through the classical PRC1-dependent pathway. CBX8 could act as a methylation reader in UBC, identify H3K27me3 catalysed by PRC2 in the downstream target gene PRDM1 promoter region, recruit non-classical PRC1-BCOR complex to bind to PRDM1 promoter and promote H2AK119ub1. Then, the expression of PRDM1 is inhibited by non-classical PRCI-independent transcriptional pathway, so as to upregulate the expression of c-FOS, promote the activation of PRDM1/c-FOS signalling pathway, induce EMT, and promote the malignant proliferation and metastasis of UBC cells.

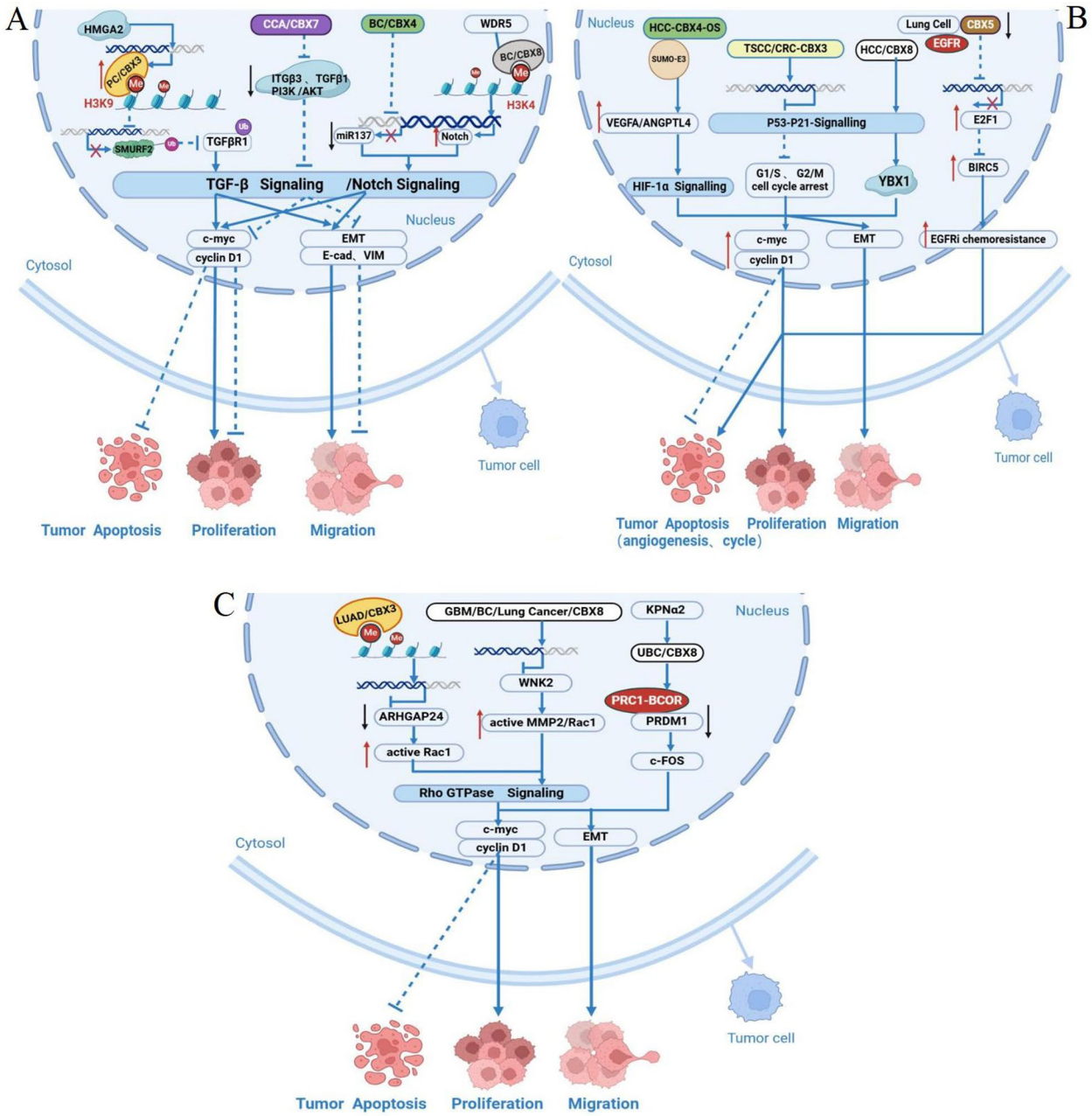

Fig. 5 (See legend on previous page.)

[198, 199]. Dysregulation or mutations in the MAPK signalling pathways at the genetic, transcriptional, and post-translational levels could contribute to the development of various tumours [200]. Existing evidence indicates that the abnormal regulation of the MAPK signalling pathway in tumour cells is influenced by the transcriptional activity of epigenetic regulatory factors CBX2/7/8 (Fig. 3B).

Current studies have confirmed that CBX2 could inhibit the expression of downstream target genes through the classical PRC1-dependent pathway, thereby promoting the activation of the MAPK signalling pathway in AML and functioning as an oncogenic factor. In contrast, CBX8, while recognizing H3K27me3 in HCC cells, transcriptionally activates the expression of downstream target genes through mechanisms independent of the classical PRC1-dependent pathway. This activation promotes the MAPK signalling pathway and contributes to its role as a carcinogenic factor.

CBX2 functions as a methylation reader in AML, recognizing and binding to the negative regulatory

transcription factor RASGRP2 of the KRAS/P38MAPK signalling pathway and the AP-1 promoter region marked by H3K27me3, which is catalysed by PRC2. CBX2 recruits PRC1 to these sites, facilitating the generation of H2AK119ub1 [10]. Through the classical PRC1-dependent transcriptional pathway, CBX2 inhibits the expression of RASGRP2 and AP-1, downregulates key mediators of the P38MAPK signalling pathway such as KRAS and IL-1β, and reduces the expression of MAPK phosphatases DUSP5 and DUSP10. This leads to decreased phosphorylation-dependent degradation of ERK and P38, thereby promoting the activation of the KRAS/P38MAPK signalling pathway. As a result, CBX2 acts as an oncogenic factor, driving malignant progression, including the proliferation of AML cells [10]. Additionally, researchers have found that CBX2 inhibits the activation of caspase-8 in AML cells, downregulates the expression of the apoptosis-related gene TNF-α, and blocks the activation of the TNF-α signalling pathway, then inhibiting tumour cell apoptosis, further contributing to AML progression [10]. Bone morphogenetic protein 4 (BMP4)-mediated signalling could bind to type I and type II serine/threonine kinase receptors, subsequently activating both SMAD-dependent and SMAD-independent pathways. This activation regulates the expression of numerous genes involved in cellular functions. Multiple lines of evidence suggest that the tumourigenic effects of BMP4 are primarily mediated through the SMAD-independent pathway [201]. CBX8 has been identified as a key driver in the development of HCC cells. However, unlike its classical role in PRC1-dependent transcriptional repression, CBX8 employs alternative mechanisms to exert transcriptional activation. Specifically, CBX8 inhibits the presence of H3K27me3 at the promoter region of the BMP4 gene, although it does not directly bind to the BMP4 promoter. This inhibition enhances BMP4 transcription, upregulates BMP4 expression, and increases the levels of p-Smad1/5/8, p-ERK1/2, and p-JNK proteins. Consequently, CBX8 promotes the activation of both SMAD-dependent and MAPK signalling pathways mediated by BMP4. This activation downregulates the expression of the EMT-related protein E-cadherin while upregulating the expression of EMT-related proteins such as N-cadherin, vimentin, Snail, and Slug, thereby inducing EMT. These changes collectively drive the malignant proliferation and metastasis of HCC [125].

CBX7 could silence the expression of downstream target genes through the classical PRC1-dependent transcriptional pathway, thereby inhibiting the activation of the MAPK signalling pathway in UBC and functioning as a tumour suppressor. However, it remains unclear whether the transcriptional regulatory mechanisms of CBX7 are involved in modulating the activation of the ERK/MAPK signalling pathway in NSCLC cells.

Aldo–keto reductase family 1, member B10 (AKR1B10), is highly expressed in various cancer cells, including BC and LUAD, where it activates the ERK signalling pathway and promotes tumour progression, leading to poor patient prognosis [202, 203]. Existing research has demonstrated that CBX7 functions as a methylation reader in UBC cells. It recognizes H3K27me3, a modification catalysed by PRC2, and recruits PRC1 to the P1 and P2 promoters of its downstream target, AKR1B10. This recruitment catalyses H2AK119ub1, resulting in chromatin structural abnormalities. Consequently, the expression of AKR1B10 is suppressed through the classical PRC1-dependent transcriptional pathway. This suppression leads to the downregulation of p-ERK protein expression, inhibition of the ERK signalling pathway, upregulation of the EMT-related protein E-cadherin, and downregulation of EMT-related proteins such as N-cadherin, vimentin, and matrix metalloproteinases (MMP2 and MMP9). These changes inhibit EMT and delay the malignant progression of UBC cells, including proliferation, migration, and invasion, thereby improving patient prognosis [119]. Furthermore, researchers observed that the knockdown of AKR1B10 only partially reversed the tumour-promoting effects induced by CBX7 knockdown, suggesting that CBX7 inhibits UBC progression through additional mechanisms beyond AKR1B10 regulation. This implies that the ERK signalling pathway might not be the sole pathway through which CBX7 exerts its inhibitory effects in UBC. Activation of the ERK/MAPK signalling pathway has been well-documented to play a critical role in the growth, migration, and invasion of NSCLC cells [204]. Additionally, studies have shown that the expression of the tumour suppressor gene CBX7 is significantly reduced in NSCLC cells. CBX7 could inhibit the activation of the ERK/MAPK signalling pathway by upregulating the expression of phosphorylated proteins associated with this pathway, such as p-ERK1/2 and p-p38, thereby exerting its tumour-suppressive function and delaying the malignant progression of NSCLC [120].

CBX 4/8 regulates Notch signalling pathway

The Notch signalling pathway, which is highly conserved throughout evolution, plays a critical role in regulating numerous physiological and pathological processes. In mammals, the Notch signalling pathway primarily comprises ligands that bind to the extracellular domains of Notch receptors (Jagged1, Jagged2, Dll1, Dll3, and Dll4), Notch receptors (Notch1-4), and RBP-J-dependent classical downstream effectors (Hes family proteins) and independent non-classical downstream effectors such as ικκB, NF-κB, and PI3K/AKT [205, 206]. The activation

of the Notch signalling pathway could be modulated through various mechanisms, including epigenetic modifications, AKT, RUNX1, SIRT6, and DEC1 signalling pathways, among others. Dysregulation of the Notch signalling pathway is frequently observed in various cancers and is implicated in multiple malignant processes [207, 208], where it could function either as a tumour suppressor or an oncogenic factor. Notably, studies have demonstrated that the Notch signalling pathway in tumour cells could be overactivated by epigenetic regulators such as CBX4 and CBX8, thereby promoting oncogenic behaviour (Fig. 5A).

Research has demonstrated that CBX4 suppresses the expression of downstream target genes via the classical PRC1-dependent transcriptional pathway, facilitating the activation of the Notch signalling pathway in BC cells and thereby acting as an oncogenic factor. In contrast, CBX8 inhibits the expression of downstream target genes through a non-classical PRC1-independent transcriptional pathway, similarly promoting the activation of the Notch signalling pathway in BC cells and functioning as an oncogenic factor.

It has been documented that miR137 functions as a tumour suppressor gene within various tumours, exerting influence over numerous cellular processes including tumour cell proliferation, migration, invasion, and resistance to chemotherapy. The expression of miR137 is diminished through the inhibition of promoter hypermethylation [209]. In BC cells, CBX4 serves as a methylation reader, capable of identifying H3K27me3, a mark catalysed by PRC2 within the promoter region of the suppressive gene miR137. This recognition facilitates the recruitment of PRC1 to the miR137 promoter, enhances H2AK119ub1, and results in aberrations of the chromatin structure. The transcriptional activity of miR137 is suppressed through a mechanism dependent on classical PRC1, which in turn upregulates the expression of Notch signalling pathway-associated proteins Notch1, Hey2, and Jag1. This cascade promotes the activation of the Notch1 signalling pathway, thereby accelerating the malignant proliferation and metastasis of BC cells [77]. WD repeat domain 5 (Wdr5) serves as the core subunit of the MLL1-4 histone methyltransferase complex and is a pivotal component of the H3K4 methyltransferase (HMT) complex, which is responsible for catalysing H3K4me1/3 [210]. Research findings indicate that the expression of the oncogenic factor CBX8 is reduced following the depletion of H3K27me3 in BC cells treated with EZH1/2 inhibitors. However, inhibiting the expression of Ring1b did not alter the tumour-promoting effects of CBX8, nor did it diminish the expression of genes associated with the Notch signalling pathway. It has been established that CBX8 is solely involved in the formation of PRC1 in BC cells and does not regulate the activation of the Notch signalling pathway through classical PRC1-dependent transcriptional repression [11]. Intriguingly, researchers discovered that CBX8 in BC cells could interact with a novel non-classical PRC1 complex involving Wdr5. This interaction facilitates the enrichment of H3K4me3 on the Notch3 receptor promoter via a non-classical PRC1-independent pathway, thereby acting as a transcriptional activator. This mechanism upregulates the expression of the downstream target gene Notch3 and leads to the overactivation of the Notch signalling pathway, ultimately promoting the malignant progression of BC cells [11].

CBX4 regulates HIF-1α signalling pathway

Hypoxia-inducible factor 1 (HIF-1), composed of the oxygen-sensitive HIF-1α subunit and the constitutively expressed HIF-1β subunit, is widely recognized as a pivotal transcription factor in cellular responses to acute hypoxia [211]. The activity of HIF-1α is modulated through various post-translational modifications, including hydroxylation, acetylation, ubiquitination, and phosphorylation, under hypoxic conditions. Additionally, under normoxic conditions, its activity is influenced by growth factor signalling pathways such as the PAM signalling pathway, the mouse double minute 2 homolog (Mdm2) signalling pathway, and the heat shock protein 90 (Hsp90) pathway [212]. Tissue hypoxia, along with alterations in certain oncogenes (ERBB2) and tumour suppressor genes (VHL and PTEN), contributes to the overexpression of HIF-1α in tumour cells. By interacting with cofactors, HIF-1α facilitates the activation of signalling pathways such as Notch and NF-κB, which synergistically promote tumour cell proliferation, angiogenesis, and chemotherapy resistance, while also inhibiting malignant processes [213, 214]. Recent studies have revealed that the activation of the HIF-1α signalling pathway in tumour cells could be regulated by the epigenetic factor CBX4, which plays a positive regulatory role in this process (Fig. 5B).

It has been discovered that CBX4, operating independently of the classical PRC1-dependent pathway, exhibits SUMO E3 ligase activity, which enhances the transcriptional activity of downstream target genes. This mechanism leads to the overactivation of the HIF-1α signalling pathway in HCC cells, thereby CBX4 functioning as an oncogenic factor. However, whether CBX4 promotes the activation of the HIF-1α signalling pathway in OS cells through a similar mechanism warrants further investigation.

Research has demonstrated that CBX4 possesses both PcG protein activity and SUMO E3 ligase activity [215]. In HCC cells, CBX4 exerts its SUMO E3 ligase activity

via its N-terminal domain and two SUMO interaction motifs (SIM1/2), directly interacting with HIF-1α to enhance Small Ubiquitin-like Modifier (SUMO) modification at lysine residues K391 and K477. This modification promotes HIF-1α trans-activation, increasing its transcriptional activity and leading to the overactivation of the HIF-1α signalling pathway. Consequently, this upregulates the expression of vascular endothelial growth factor (VEGFA), facilitating hypoxia-induced angiogenesis in HCC and accelerating tumour malignancy [12]. Furthermore, the activation of the HIF-1α signalling pathway has been implicated in the growth and metastasis of OS, closely associated with tumour progression and patient prognosis [216]. Although CBX4 is also significantly overexpressed in OS cells and functions as an oncogenic factor, current studies have only established that CBX4 upregulates HIF-1α expression and promotes HIF-1α signalling pathway activation under normoxic conditions. This leads to increased mRNA and protein levels of HIF-1α downstream target genes, such as VEGFA and ANGPTL4, thereby enhancing OS cell proliferation, migration, invasion, angiogenesis, and inhibiting apoptosis [110].

CBX 3/8 regulates P53/P21 cell cycle-related signalling pathway

The transcription factors $P21^{CDKN1A}$/$P16^{INK4a}$/P53 are tumour-suppressor genes that play critical roles in tumour development. $P21^{CDKN1A}$, one of the most important cyclin-dependent kinase inhibitors (CKIs), specifically binds to cyclin-dependent kinases (CDKs) and inhibits the activity of various cyclin-CDK complexes, including cyclin D-CDK4 and cyclin E-CDK2 [217]. P53 exerts its tumour-suppressive functions by inducing the expression of $P21^{CDKN1A}$ and pro-apoptotic Bcl-2 family members such as Puma and Noxa. This leads to the inhibition of transcription of numerous cell cycle-related genes, downregulation of various cell cycle regulators, and mediation of cell cycle arrest in response to acute DNA damage, thereby effectively suppressing tumour progression [218, 219]. Emerging evidence suggests that epigenetic regulatory factors, such as CBX3 and CBX8, could modulate the activation of cell cycle-related signalling pathways (P53/P21 signalling pathway) in tumours. These factors could either promote or inhibit tumourigenesis, depending on the context (Fig. 5B).

Current studies have only established that CBX3 functions as an oncogenic factor by mediating transcriptional repression through HP1 family proteins, leading to the silencing of downstream target genes and the inhibition of the P53/P21 signalling pathway in TSCC and CRC. However, the transcriptional regulatory mechanisms by which CBX3 and CBX8 modulate the activation of the P53/P21 signalling pathway in ESCC, UBC, and HCC remain poorly understood.

Studies have demonstrated that CBX3 could inhibit the activation of the P53-P21 signalling pathway in ESCC, thereby preventing cell cycle arrest. This inhibition upregulates the expression of CSC markers such as CD133, Nanog, Oct4, and Sox2, enhancing the stem cell-like properties of ESCC cells, promoting tumour cell self-renewal, and ultimately functioning as an oncogenic factor [104]. In both TSCC and CRC, CBX3 recognizes and catalyses the enrichment of H3K9me2/3 in the promoter region of its downstream target gene, P21. It recruits the H3K9 methyltransferase SUV39H1 to methylate adjacent H3K9 residues, forming repressive H3K9me3 marks. This process leads to the recruitment of heterochromatin-associated proteins, inducing heterochromatin formation and chromatin compaction. As a result, the expression of the tumour suppressor P21 is downregulated, inhibiting the activation of the P21 pathway and preventing cell cycle arrest at the G1/S phase. Concurrently, the upregulation of CDK6 expression promotes the malignant proliferation of tumour cells [105]. In UBC, CBX8 has been shown to suppress the activation of the P53 signalling pathway, upregulate the expression of cell cycle-related proteins CDC2 and CyclinB1, prevent G2/M cell cycle arrest, and promote tumour malignancy [126]. YBX1, a multifunctional transcription and translation regulator, plays a critical role in modulating protein expression, and its aberrant activation is associated with various malignant phenotypes in tumour cells [220]. Notably, transcriptional repression of CBX8 has not been observed in HCC cells. Instead, CBX8 interacts with YBX1 to regulate cell cycle-related signalling pathways in a YBX1-dependent manner. This interaction upregulates cyclinD1 expression, inhibits cell cycle arrest, and ultimately drives the proliferation of HCC cells [127].

CBX7 has been demonstrated to interact with HDAC2 through a mechanism independent of the classical PRC1-dependent pathway in thyroid cancer, lung cancer, and brain glioma cells. This interaction enables CBX7 to modulate histone acetylation in the promoter regions of downstream target genes, thereby transcriptionally activating or repressing their expression. As a result, CBX7 suppresses cell migration, invasion, and the activation of cell cycle-related signalling pathways, functioning as a tumour suppressor in these cancer types.

HDAC2 is recognized for its role in inhibiting complex formation and suppressing the expression of E-cadherin, thereby contributing to tumour progression [221]. In thyroid cancer, CBX7 has been shown to counteract the activity of HDAC2 in the promoter region of the E-cadherin gene. This inhibition leads to increased acetylation of histone H3 and H4 lysine residues, resulting in the

transcriptional activation of E-cadherin expression. Consequently, CBX7 suppresses signalling pathways associated with cell migration and invasion, prevents EMT, and inhibits the migration and invasion of tumour cells. These actions delay the progression of thyroid cancer and underscore CBX7's role as a tumour suppressor. Histone modifications such as H3K4me and H3K36me are generally linked to transcriptionally active chromatin, whereas H3K9me, H3K27me, and H4K20me are typically associated with gene silencing [121]. Furthermore, studies have revealed that CBX7 could upregulate the expression of H3K4me while downregulating H3K9me and H4K20me. This modulation enhances transcriptional activation and amplifies the transcriptional activity of E-cadherin, further reinforcing its tumour-suppressive functions [222]. The CCNE1 gene plays a critical role in the G1/S phase transition of the mammalian cell cycle, and its promoter region contains an E-box that serves as a binding site for CBX7. The activity of CCNE1 is negatively regulated by chromatin regulation and remodelling proteins, such as HDAC and PcG proteins [223, 224]. Notably, CCNE1 is frequently overexpressed in lung cancer, where it functions as an oncogenic driver [225]. The HMGA protein enhances E2F activity by displacing HDAC from E2F-responsive promoters, including that of CCNE1 [226]. In lung cancer cells, CBX7 interacts with HDAC2 and binds to the promoter region of CCNE1. This interaction increases histone H4 acetylation, counteracts the transcriptional activation of CCNE1 by HMGA1b, and exerts transcriptional repression on CCNE1. Consequently, CBX7 negatively regulates CCNE1 expression while upregulating the expression of tumour suppressor proteins P16, P21, and P53. This activation of the P53/P21 cell cycle-related signalling pathway leads to reduced expression of cyclin-related proteins, such as cyclin A and cyclin E, induces G1/S phase cell cycle arrest, and inhibits the malignant proliferation of tumour cells. Through these mechanisms, CBX7 functions as a tumour suppressor in lung cancer [122]. In GBM, CBX7 similarly interacts with HDAC2 and binds to the promoter region of CCNE1. This interaction enhances the acetylation of histone H3 and H20 lysine residues, leading to the transcriptional repression of CCNE1 activity, thus upregulating the expression of P16, and promotes the activation of the P16-related cell cycle signalling pathway. As a result, the expression of cell cycle-related proteins, such as cyclin E and CDK2, is reduced, inducing G1/S phase arrest in GBM cells and inhibiting tumour growth [123].

CBX 3/8 regulates Rho GTPase signalling pathway

Rho GTPases, members of the Ras superfamily of small G proteins, play pivotal roles in regulating diverse cellular processes, including cytoskeletal dynamics. Prominent members of this family include RhoA, Rac1, and Cdc42 [227]. The Rho GTPase signalling pathway is intricately controlled by feedback mechanisms involving upstream regulators (cytokines, extracellular matrix), as well as downstream effectors like RHO-associated protein kinases (ROCK1 and ROCK2). Activation of this pathway is mediated by guanine nucleotide exchange factors (GEFs), while inhibition is achieved through GTPase-activating proteins (GAPs) and guanine nucleotide dissociation inhibitors (GDIs) [228]. Additionally, the activity and function of Rho GTPases are modulated by post-translational modifications, including lipid modification, phosphorylation, ubiquitination, sumoylation, and transcriptional regulation [227]. Aberrant activation of the Rho GTPase signalling pathway is a common feature in various cancers, where it drives tumour cell proliferation, migration, invasion, and the formation of the TME [228]. Recent studies have revealed that the activation of the Rho GTPase signalling pathway in tumour cells is influenced by epigenetic regulators, specifically CBX3 and CBX8 (Fig. 5C).

CBX3 has been shown to downregulate the expression of downstream target genes through HP1-mediated transcriptional repression, thereby promoting the activation of the Rho GTPase signalling pathway in LUAD cells and contributing to its tumour-promoting role. Similarly, CBX8 has been found to transcriptionally repress the activity of downstream target genes, facilitating the activation of the Rho GTPase signalling pathway in GBM, BC, and lung cancer, where it also acts as a tumour-promoting factor. However, further evidence is required to determine whether CBX8 exerts its transcriptional repression through the classical PRC1-dependent pathway.

The GTPase-activating protein ARHGAP24 serves as a negative regulator of the Rho GTPase signalling pathway [229]. Research has demonstrated that CBX3 functions as a methylation reader in smoke-induced LUAD. Specifically, CBX3 recognizes H3K9me3 in the promoter region of ARHGAP24 and recruits SUV39H1 to methylate adjacent H3K9 residues. This process forms repressive H3K9me3 marks, which recruit a variety of proteins to establish and stabilize heterochromatin. As a result, the chromatin structure becomes more condensed, leading to the transcriptional repression of ARHGAP24. The downregulation of ARHGAP24 increases the activity of Rac1, promotes the activation of the Rho GTPase signalling pathway, and accelerates the malignant proliferation and metastasis of tumour cells. Additionally, studies have revealed that CBX3 interacts with several proteins, including RBBP4, TRIM28, and TRIM24, to cooperatively regulate the expression of ARHGAP24. However, the precise mechanisms underlying these interactions

and their collective impact on ARHGAP24 expression remain to be fully elucidated [106, 230]. MMP2 and Rac1 are critical players in the malignant metastasis of tumour cells. MMP2 facilitates extracellular matrix (ECM) degradation, thereby enhancing tumour invasion [231], while Rac1 mediates the Rho GTPase signalling pathway to regulate tumour cell migration and invasion [232]. WNK2, a member of the WNK protein kinase family, acts as a tumour suppressor by negatively regulating the expression of MMP2 and Rac1 [233, 234]. Research has shown that CBX8 expression is upregulated in GBM, BC, and lung cancer, where it primarily influences tumour cell migration and invasion. Notably, the impact of CBX8 on migration and invasion is more pronounced in GBM and BC cells compared to lung cancer, and its effect on tumour cell invasion is stronger than its effect on migration. In GBM, BC, and lung cancer, CBX8 directly interacts with the promoter region of WNK2, transcriptionally repressing its expression. This repression leads to increased activity of MMP2 and Rac1, promoting ECM degradation and activation of the Rac1-mediated Rho GTPase signalling pathway. These changes induce EMT, thereby accelerating the malignant metastasis of tumour cells [128].

CBX 8 regulates PRDM1/c-FOS signalling pathway

c-Fos, encoded by the FOS gene, is a crucial member of the activator protein 1 (AP-1) family of proto-oncogenes. It plays a significant role in regulating cell proliferation, migration, and invasion [235]. PR domain zinc finger protein 1 (PRDM1), a member of the PR/SET domain (PRDM) family, regulates downstream gene expression through epigenetic mechanisms and mediates the activation of multiple signalling pathways involved in tumourigenesis and metastasis [236]. It has been established that PRDM1 negatively regulates the expression of c-FOS in urothelial UBC cells [237]. Recent studies have revealed that CBX8 is highly expressed in UBC cells, where it exerts transcriptional repression through a non-classical PRC1-independent pathway. This repression downregulates the expression of downstream target genes, promotes the activation of the PRDM1/c-FOS signalling pathway, and contributes to its role as an oncogenic factor (Fig. 5C).

Previous studies have demonstrated that CBX8 could interact with the non-classical PRC1-BCOR (BCL6 corepressor, BCOR) complex to transcriptionally repress the B cell differentiation gene PRDM1 through a non-classical PRC1-independent pathway, thereby promoting the development of lymphoma [23]. Building on this, Fanchang Zeng et al. revealed that CBX8 is significantly overexpressed in UBC, where it employs a similar mechanism of transcriptional repression to drive tumour progression [238]. In UBC, CBX8 functions as a methylation reader by recognizing H3K27me3, a mark catalysed by PRC2, in the promoter region of the downstream target gene PRDM1. CBX8 recruits the non-classical PRC1-BCOR complex to the PRDM1 promoter, facilitating the deposition of H2AK119ub1. This epigenetic modification leads to the transcriptional repression of PRDM1 through a non-classical PRC1-independent pathway. Consequently, the expression of c-FOS is upregulated, activating the PRDM1/c-FOS signalling pathway. This activation induces EMT and promotes the malignant proliferation and metastasis of UBC cells [129]. In addition, the nuclear transport receptor Karyopherin alpha 2 (KPNα2) is known to facilitate the translocation of numerous proteins involved in tumourigenesis, actively contributing to the malignant progression of various cancers [129]. Researchers have further discovered that KPNα2 assists in the nuclear shuttling of CBX8 in UBC cells. By positively regulating the expression and nuclear localization of CBX8, KPNα2 collaborates with CBX8 to promote tumour progression.

CBX 5 regulates E2F1/BIRC5 signalling pathway

The anti-apoptotic gene BIRC5, commonly referred to as survivin and a constituent of the inhibitor of apoptosis (IAP) protein family, is modulated by the E2 promoter binding factor 1 (E2F1), which is part of the E2F transcription factor family, within tumour cells. The transcriptional activation and subsequent overexpression of E2F1 [239] have the capacity to override anti-apoptotic checkpoints, facilitate cellular mitosis [240, 241], modulate tumour cell apoptosis and cell cycle arrest, and expedite the malignant evolution of tumours. The EGFR is capable of activating the PI3K/AKT and MEK-ERK anti-apoptotic signalling cascades, thereby enhancing the expression of anti-apoptotic genes, suppressing tumour cell apoptosis, and diminishing the responsiveness of tumour patients to EGFRi, which are tyrosine kinase inhibitors targeting EGFR [242]. Furthermore, epigenetic regulatory mechanisms have been implicated in playing a pivotal role in conferring resistance to EGFRi across a spectrum of tumours, including NSCLC [243]. Current studies have demonstrated that the downregulation of CBX5 in LUAD cells with EGFR mutations results in the transcriptional silencing of downstream target genes. This suppression inhibits the activation of the E2F1/BIRC5 anti-apoptotic signalling pathway, thereby establishing CBX5 as a tumour suppressor. Such activity enhances patient sensitivity to chemotherapy resistance and improves patient prognosis. However, whether CBX5 exerts transcriptional inhibition through the HP1 family protein pathway remains to be further validated experimentally (Fig. 5B).

Suresh Bugide et al. were the first to demonstrate that the loss of CBX5 expression is a critical driver of EGFRi resistance in LUAD patients with EGFR mutations. In EGFR-mutated LUAD cells, the downregulation of CBX5 inhibits the expression of E2F1, attenuates its transcriptional activation, and reduces the expression of the anti-apoptotic gene BIRC5. This suppression inhibits the activation of the E2F1/BIRC5 anti-apoptotic signalling pathway, promotes apoptosis, and enhances patient sensitivity to EGFRi treatment, thereby exerting a tumour-suppressive effect [82]. Simultaneously, the combination of the epigenetic regulatory factor-related small-molecule inhibitor BETi and EGFRi has been shown to restore CBX5 expression, thereby re-sensitizing EGFR-mutated LUAD patients with resistance to EGFRi treatment. This finding underscores the critical role of CBX5 in mediating EGFRi resistance in EGFR-mutated LUAD patients and highlights its potential as a novel therapeutic target for overcoming resistance in these patients [82]. Furthermore, researchers have discovered that CBX5 could modulate the expression of genes involved in oxidative phosphorylation, mitochondrial dysfunction, sirtuin signalling, and GADD45 pathways. This suggests that CBX5 regulates drug resistance in tumour cells through a multifaceted mechanism, with the E2F1/BIRC5 signalling pathway being only one of several potential pathways involved.

New strategies for tumour therapy targeting CBXs

A substantial body of research has demonstrated that CBXs are closely associated with the enhancement of CSC characteristics, including self-renewal, malignant proliferation, migration, invasion, and chemotherapy resistance in tumour cells. Additionally, CBXs have been shown to mediate tumour patient sensitivity to radiotherapy [244] and chemotherapy [245, 246]. Consequently, CBXs represent a promising potential target for cancer treatment. Given the structural and functional complexity of CBXs, as well as the ongoing advancements in research, the development of CBX-targeting inhibitors is currently being pursued from multiple perspectives: (i) Developed for the common structure of CBX methylation reader function: the methyllysine recognition chromatin domain CHD. For instance, the selective CBX2 chromatin domain probe SW2_152F could specifically inhibit CBX2 chromatin binding in cells and block the neuroendocrine differentiation of prostate cancer cell lines in response to androgen deprivation [247]. The CBX7 CHD inhibitor MS37452 competes for binding to H3K27me3 by interacting with key residues in the methyllysine binding pocket of CBX7 CHD, thereby displacing CBX7 binding to INK4A/ARF loci in prostate cancer cells. This inhibition suppresses the transcription of the target gene p16/CDKN2A, mediated by the polycomb repressive complex [248]. The CBX8 CHD-selective and cell-permeable inhibitor SW2_110A specifically blocks CBX8 binding to chromatin in AML cells, attenuates CBX8-mediated transcriptional activation of MLL-AF9 target genes, and consequently inhibits the proliferation of tumour cells driven by MLL-AF9 translocation [249]. In addition to the selective chemical probes mentioned above, peptide-based inhibitors targeting the methyllysine reader function of CBX homologs have also been developed. Examples include CBX6/8-active peptide mimetic inhibitors [250], PSL [251], and UNC3866/4976/7040 [252–254]. (ii) CBXs have been shown to be regulated by post-translational modifications such as ubiquitination, SUMOylation, and phosphorylation [255–257], offering novel avenues for the development of CBXs inhibitors. For instance, the histone deacetylase inhibitor SAHA not only modulates global acetylation levels but also suppresses CSC properties and self-renewal in AML by promoting CBX2 polyubiquitination and subsequent proteasome-dependent degradation mediated by SUMO2/3 [258]. (iii) Additional studies have demonstrated that the anti-cancer effects of certain natural compounds are mediated through the inhibition of CBXs. For example, resveratrol has been found to downregulate CBX7 expression, attenuate AKT signalling pathway activation, enhance p16 signalling pathway activity, and thereby delay the proliferation of oral squamous cell carcinoma cells while inducing apoptosis [259].

The advancement of inhibitors targeting existing CBX proteins primarily revolves around the engagement of the CBX-associated chromodomain CHD, which impedes the methyllysine reading function of PcG proteins CBX2/4/6/7/8, potentially leading to the dissociation of the PRC1. In contrast, the exploration of inhibitors aimed at the HP1 family proteins CBX1/3/5 remains nebulous. These CBX inhibitors might function autonomously as tumour suppressants or might be synergistically employed with BMI1 inhibitors, taxanes, or cisplatin-based chemotherapeutic agents to amplify therapeutic outcomes [260]. Nonetheless, the progression and clinical deployment of small-molecule inhibitors related to CBXs are fraught with significant hurdles: (i) The cellular permeability of extant CBX inhibitors is constrained, hindering the accessibility to their sites of action. (ii) A potential disparity exists between the biochemical selectivity within tumour cells and the off-target effects of the drugs. Certain small-molecule inhibitors of CBXs do not exclusively target unique CBX members [252], which might augment anti-neoplastic efficacy but could concurrently escalate drug toxicity. Consequently, it is imperative for researchers to judiciously evaluate

whether the therapeutic impact of a CBX inhibitor targeting a singular member of the CBX family is optimal, and whether the observed phenotypic outcomes are genuinely attributable to the intended molecular target. (iii) The small-molecule inhibitors of CBXs developed thus far are confined to cellular applications, with a paucity of xenotransplantation studies, thereby necessitating an extended timeframe before their potential clinical application could be realized.

Conclusion and perspective

The regulatory mechanisms by which CBX proteins mediate various signalling pathways in tumour cells are highly intricate and remain incompletely understood. Both CBX1 and CBX3/5 belong to the HP1 family, which exhibit dual roles in transcriptional repression and activation. However, existing studies have demonstrated that these proteins exert distinct transcriptional regulatory effects in different tumour cells, influencing tumourigenesis and progression through diverse mechanisms. CBX1 has been shown to transcriptionally activate the expression of downstream HMGA2, promoting the activation of the Wnt/β-catenin signalling pathway in HCC cells, thereby acting as a tumour-promoting factor [96]. In contrast, CBX3 could function as either a transcriptional repressor or activator, modulating the transcriptional activity of downstream target genes. It regulates the activation of signalling pathways such as Wnt/β-catenin [101], PI3K/AKT [102, 103], Rho GTPase [106], and P53/P21 [104, 105] in HCC, CRC, ccRCC, and other tumours, playing a role as an oncogenic factor. On the other hand, low expression of CBX5 in EGFR-mutated LUAD cells has been found to transcriptionally silence downstream target genes, inhibit the activation of the E2F1/BIRC5 anti-apoptotic signalling pathway [82], and function as a tumour suppressor, thereby enhancing chemotherapy sensitivity. The PcG family proteins CBX2/4/6/7/8 have been demonstrated to exhibit dual transcriptional regulatory functions. They could transcriptionally silence downstream target gene expression through the classical PRC1-dependent pathway or activate downstream target gene expression via non-classical PRC1-independent mechanisms, such as the formation of non-classical PRC1 complexes (BCOR, Wdr5), SUMO E3 ligase activity, and other pathways. These proteins regulate the activation of multiple signalling pathways, including Wnt/β-catenin [5, 97, 107, 113, 114, 124], Hippo [6, 81, 98], HIF-1α [12, 110], PI3K/AKT [7, 99, 100, 115], NF-κB [8, 108, 109, 111, 112, 116, 117], Notch [11, 77], MAPK [10, 119, 120, 125], TGF-/PI3K/AKT [118], P53/P21 [121–123, 126, 127], and Rho GTPase [128], in various cancer types such as GC, HCC, BC, GBM and other cells. CBX2/4/6/8 generally promotes the malignant progression of tumours, whereas CBX7 has been shown to inhibit tumour progression. However, CBX7 exhibits dual roles as both a tumour suppressor and an oncogenic factor. It could promote tumour progression by regulating the activation of the NF-κB signalling pathway in GC cells and the MAPK signalling pathway in OC cells. The activation and inhibition of signalling pathways are influenced by a multitude of factors, and these pathways often interact with one another, forming intricate regulatory networks. Consequently, the involvement of CBX family members in the initiation and progression of different tumours is likely mediated through more than one signalling pathway. Additionally, the underlying regulatory mechanisms might be influenced by other oncogenic factors, adding layers of complexity to their roles in tumour biology.

In addition, the expression levels of CBXs in different tumours do not always align with their biological roles in tumourigenesis and progression. Current research on CBXs also faces several limitations. For instance, some studies have only identified the expression patterns of CBXs in tumours through bioinformatic analysis without fully elucidating the relationship between CBX expression and tumour development or the specific mechanisms underlying their actions. Furthermore, certain studies suggest that the same tumour cells could be regulated by multiple CBXs, and there might be interactions among these CBXs, although no conclusive evidence has been provided to date. Another challenge is the inconsistency in findings regarding CBX expression in the same type of tumour across different studies. This discrepancy might arise from factors such as sample heterogeneity, differences in data sources, or variations in research methodologies. These inconsistencies highlight that our current understanding of the expression patterns, biological functions, and underlying mechanisms of CBXs in tumours remains incomplete, warranting further exploration. The pursuit of understanding the causes and treatments of cancer is fraught with challenges, yet it is also ripe with opportunities and hope. In this review, we aim to summarize the regulatory roles and mechanisms of CBXs, epigenetic regulatory factors, in tumour cell signalling pathways. By doing so, we hope to provide insights that will aid researchers in further elucidating the mechanisms driving tumour progression and identifying effective therapeutic targets. Although numerous studies have demonstrated that CBXs could serve as valuable biomarkers for tumour diagnosis and prognosis prediction, as well as potential therapeutic targets, it is regrettable that the development of CBX-related small-molecule drugs has not yet transitioned to clinical application. Therefore, it remains imperative to further clarify the tumour-promoting or tumour-suppressing mechanisms of CBXs across a broader range of tumour types.

Such efforts will facilitate the discovery of more precise therapeutic targets and advance the frontier of cancer treatment.

Abbreviations

H3AC	Acetylation of histone 3
AP-1	Activating protein 1
AML	Acute myelocytic leukaemia
AKR1B10	Aldo-keto reductase family 1, member B10
BCOR	BCL6 corepressor
BST2	Bone marrow stromal cell antigen-2
BMP4	Bone morphogenetic protein4
BC	Breast cancer
CSCs	Cancer stem cells
cPRC1	Canonical PRC1
CK1α	Casein kinase-1α
CCA	Cervical carcinoma
ChIP	Chromatin immunoprecipitation
CD	Chromatin domain
CSD	Chromatin shadow domain
CBX	Chromobox
ccRCC	Clear cell renal cell carcinoma
CRC	Colorectal cancer
Sce	Sex Combs Extra
CTGF	Connective tissue growth factor
CDK	Cyclin-dependent kinase
CKI	Cyclin-dependent kinase inhibitors
HDAC	Deacetylation of histone deacetylase
DLBCL	Diffuse large B cell lymphoma
EED	Embryonic ectoderm development
EGFR	Epidermal growth factor receptor
EMT	Epithelial–mesenchymal transition
EC	Oesophageal cancer
ESCC	Oesophageal squamous cell carcinoma
ETS1	ETS proto-oncogene 1
ECM	Extracellular matrix
EZH1/2	Enhancer of zeste homolog 1/2
FGFR3	Fibroblast growth factor receptor 3
GCSCs	Gastric cancer stem cells
GC	Gastric cancer
GBM	Glioblastoma
HNSCC	Head and neck squamous cell carcinoma
HCC	Hepatocellular carcinoma
HP1	Heterochromatin protein 1
HMGA2	High mobility group A2
H	Hinge domain
HAT	Histone acetyltransferase
HDAC2/3	Histone deacetylase 2/3
H2AK119ub	Mono-ubiquitination of histone H2A at lysine K119
H3K9me2/3	Methylated histone H3 at lysine K9
HIF-1	Hypoxia-inducible factor 1
ICIs	Immune checkpoint inhibitors
IKK	IκB kinase complex
KPNα 2	Karyopherin alpha 2
LUAD	Lung adenocarcinoma
H3K27me1/2/3	Methylation of histone H3 at lysine K27
Mdm2	Mouse bismeric 2 homology
ncPRC1	Non-canonical PRC1
miRNA/miR	Non-coding small Rnas
NSCLC	Non-small cell lung cancer
NCAPG	Non-structural maintenance of chromosomes (SMC) Condensin I complex subunit G
IRS1	Insulin receptor substrate 1
OC	Ovarian cancer
PAAD	Pancreatic adenocarcinoma
PC	Pancreatic cancer
PDE4B	Phosphodiesterase 4B
PAM	PI3K/AKT/mTOR
Pc	Polycomb
PcG	Polycomb group
PCGF2/4	Polycomb group RING finger proteins 2/4
Ph	Polyhomeotic
PHC1/2/3	Polyhomeoproteins
Psc	Posterior sex combs
PTMs	Post-translational modifications
PCa	Prostate carcinoma
PSMC4	Proteasome 26S subunit ATPase 4
PPIs	Protein–protein interactions
RBAP46/48	Retinoblastoma protein-associated proteins 46/48
SCML1/2 or SCMH1	SCM proteins
Scm	Sex comb on midleg
SKCM	Skin cutaneous melanoma
SMURF2	SMAD-specific E3 ubiquitin protein ligase 2
SNHG5	Small nucleolar RNA host gene 5
SUMO	Small ubiquitin-like modifier
SIM1/2	SUMO interaction moxa 1/2
SUZ12	Suppressor of zeste 12
TβRI, TβRII	TGF-β receptor I /II
TSCC	Tongue squamous cell carcinoma
TGF-β	Transforming growth factor-β
TGFβ1	Transforming growth factor-β1
TME	Tumour microenvironment
TNF	Tumour necrosis factor
TKI	Tyrosine kinase inhibitors
UBC	Urinary bladder cancer
VEGFA	Vascular endothelial growth factor
Wdr5	WD repeat domain 5
WTIP	WT1-interacting proteins
YBX1	Y-box-binding protein 1
YAP	Yes-associated protein
PRDM1	PR domain zinc finger transcription factor 1

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Declarations

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