Interpreting the molecular mechanisms of RBBP4/7 and their roles in human diseases (Review)

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Abstract. Histone chaperones serve a pivotal role in maintaining human physiological processes. They interact with histones in a stable manner, ensuring the accurate and efficient execution of DNA replication, repair and transcription. Retinoblastoma binding protein (RBBP)4 and RBBP7 represent a crucial pair of histone chaperones, which not only govern the molecular behavior of histones H3 and H4, but also participate in the functions of several protein complexes, such as polycomb repressive complex 2 and nucleosome remodeling and deacetylase, thereby regulating the cell cycle, histone modifications, DNA damage and cell fate. A strong association has been indicated between RBBP4/7 and some major human diseases, such as cancer, age-related memory loss and infectious diseases. The present review assesses the molecular mechanisms of RBBP4/7 in regulating cellular biological processes, and focuses on the variations in RBBP4/7 expression and their potential mechanisms in various human diseases, thus providing new insights for their diagnosis and treatment.

Contents

1. Introduction

Histone chaperones serve a pivotal role in histone metabolism, facilitating histone binding to DNA during processes such as DNA replication and repair (1). Originally, Laskey *et al* (2)

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Abbreviations: RBBP, RB binding protein; NuRD, nucleosome remodeling and deacetylase; PRC2, polycomb repressive complex 2; RB, retinoblastoma protein; CAF-1, chromatin assembly factor 1; HAT1, histone acetyltransferase 1; CENP-A, centromere protein A; HDAC, histone deacetylase; CDK, cyclin-dependent kinase; FOXM1, forkhead box M1; MTA1, metastasis associated 1; SUZ12, SUZ12 polycomb repressive complex 2 subunit; EED, embryonic ectoderm development; EZH, enhancer of zeste homolog; BRCA1, breast cancer type 1 susceptibility protein; GBM, glioblastoma; TMZ, temozolomide; FOG-2, friend of GATA protein 2; LC, lung cancer; NSCLC, non-small cell LC; CBX3, chromobox homolog 3; LUAD, lung adenocarcinoma; MPM, malignant pleural mesothelioma; NB, neuroblastoma; OCN, osteocalcin; AD, Alzheimer's disease; AML, acute myeloid leukemia; MM, multiple myeloma; CML, chronic myeloid leukemia; CRC, colorectal cancer; PPD, protopanaxadiol; GC, gastric cancer; SSeCKS, Src-suppressed C-kinase substrate; HCC, hepatocellular carcinoma; SALL4, Sal-like protein 4; EGCG, epigallocatechin gallate; MDR, multidrug resistance; ESCC, esophageal squamous cell carcinoma; EMT, epithelial-mesenchymal transition; EC, esophageal cancer; TC, thyroid cancer; NF-κB, nuclear factor κB; PMOP, postmenopausal osteoporosis; ESR1, estrogen receptor 1; BC, breast cancer; TNBC, triple-negative BC; BCL11A, BCL11 transcription factor A; HPV, human papillomavirus; ALA-PDT, 5-aminole-vulinic acid photodynamic therapy; SP1, specificity protein 1; BKVN, BK virus-associated nephropathy; RCC, renal cell carcinoma; OSCC, oral squamous cell carcinoma; OPSCC, oropharyngeal squamous cell carcinoma; PPI, protein-protein interaction

Key words: RBBP4, RBBP7, biological function, human diseases, mechanism

revealed that nucleophosmin in *Xenopus* eggs can bind histones and promote nucleosome formation independently of ATP. These two properties remain the only shared, and thus defining, characteristics of histone chaperones. Currently, histone chaperones are deemed to aid histone transfer but remain separate from the final histone-DNA complex (3). Extensive research has been conducted on the relationship between histone chaperones and human diseases (3-5). Their abnormal expression patterns, not only in tumors, but also in cardiovascular diseases, autoimmune disorders and neurodegenerative diseases, highlight their prognostic value in various human diseases. Given their role in chromatin dynamics and disease contexts, they present potential therapeutic targets and diagnostic markers in various human diseases.

Retinoblastoma binding protein (RBBP)4 and RBBP7 are recognized as histone chaperones, both of which belong to the WD40 family (6). The WD40 domain is a distinct protein motif that typically adopts a β-propeller architecture, mediating protein-protein interactions (PPIs). RBBP4/7 typically exist in complexes, such as the nucleosome remodeling and deacetylase (NuRD) complex (7) and polycomb repressive complex 2 (PRC2) (8), to regulate chromatin remodeling and gene expression through the interactions of their WD40 repeats with the H4 α1 helix and H3 tail (9,10). Dysregulation of RBBP4/7 may disrupt the normal chromatin remodeling process, resulting in altered gene expression patterns that contribute to the initiation and progression of cancer and other human diseases (11). Notably, alterations in the expression levels of RBBP4/7 have been observed in different types of human disease, such as esophageal squamous cell carcinoma (ESCC) and colorectal cancer (CRC). These changes are closely related to clinicopathological features (12-15).

The present review summarizes the pivotal role of RBBP4/7 in regulating cell fate, assessing their expression, functions, clinical features and associated mechanisms in human diseases.

2. Molecular structure of RBBP4 and RBBP7

RBBP4, also known as RbAp48 or NURF55, is integral to multiple chromatin-modifying and remodeling complexes. It was originally discovered as a binding partner of the tumor suppressor retinoblastoma protein (RB) in yeast (16), and subsequently revealed to cofractionate with histone deacetylase (HDAC)1 (17). Located on chromosome 1p35.1, the *RBBP4* gene encodes a 425-amino acid protein ubiquitously present across human tissues (18). The molecular structure of the RBBP4 protein is shown in Fig. 1A.

RBBP7, alternatively known as RbAp46, is a nuclear protein ubiquitously expressed across various cell types. Located on chromosome 3p25.1, the *RBBP7* gene encodes a 425-amino acid protein that is universally expressed in human tissues (18). RBBP4 and RBBP7 are 92% identical (9); however, they differ in certain amino acid sequences, which may lead to subtle structural variations, especially in domains that interact with other proteins. The molecular structure of RBBP7 is displayed in Fig. 1B. Structurally, both RBBP4 and RBBP7 possess a seven-bladed WD40 repeat domain, indicating that RBBP4 and RBBP7 can serve multiple roles in chromatin remodeling, histone modification and transcriptional regulation (19). Notably, both RBBP4 and RBBP7 are integral subunits of the NuRD complex (7), the switch-independent 3A complex (20) and PRC2 (8). Additionally, RBBP4 has been identified as a subunit of the chromatin assembly factor 1 (CAF-1) complex (21) and a core component of the MuvB complex (22), while RBBP7 is known to be an essential component of the histone acetyltransferase 1 (HAT1) complex (23). As part of these multisubunit protein complexes, RBBP4 and RBBP7 are believed to function as chromatin adapters, mediating direct interactions with histone H3/H4 (24).

3. The biological functions of RBBP4/7

The functions of RBBP4/7 in the cell cycle. RBBP4/7 have a pivotal role in cell cycle regulation, with their absence leading to dysregulation of cell cycle genes and cycle arrest (25). Specifically, RBBP4 deficiency results in S phase defects and inhibits mitotic exit (M to G_1 transition) (26), whereas RBBP7 deficiency causes G_2/M phase arrest in 293 cells (27). In addition, RBBP4/7 (LIN-53) are crucial for centromere protein A (CENP-A) localization to centromeres (28). It has also been suggested that the Cullin-4 (CUL4) RING ligase (CRL4) complex containing RBBP7 might regulate mitosis by promoting ubiquitin-dependent loading of newly synthesized CENP-A during the G_1 phase (29).

RBBP4/7 are members of the RB family (30). Studies conducted in yeast and cultured cells have shown that RBBP4 appears to function as a tumor suppressor along with RB, leading to inhibition of cell cycle progression and cell growth (16,18). Nevertheless, Schultz-Rogers *et al* (31) indicated that RBBP4 is essential for the cell cycle progression of neural progenitor cells and the initiation of G_0, irrespective of the involvement of RB. The E2F family plays a key role in cell cycle regulation, and all RB family members interact with typical E2F proteins to form transcriptional inhibition complexes (32). RB primarily inhibits E2F transcription factor 1, whereas RBBP4 can be directed to RB via HDAC1 (33). In the G_1 phase, RBBP4/7 and RB inhibit E2F target gene activation, preventing entry into S phase. Cyclin D-cyclin-dependent kinase (CDK)4/6 can monophosphorylate RB, whereas cyclin E-CDK1/2 are involved in poly-phosphorylation or hyper-phosphorylation of RB (34). Once hyperphosphorylated, RBBP4/7 and RB dissociate from E2F, activating target genes and recruiting chromatin remodelers (35) (Fig. 2A).

In addition, RBBP4 is a core component of the MuvB complex, collaboratively working with LIN9, LIN37, LIN52 and LIN54 to regulate the cell cycle (22). During the G_0/G_1 phase, the RBBP4-containing MuvB complex associates with p130/E2F4/DP1 to form the dimerization partner, RB-like, E2F and MuvB (DREAM) complex (36), which inhibits expression of cell cycle regulatory genes, maintaining the cell in a quiescent state. Within the DREAM complex, RBBP4 directly binds to LIN9 and LIN37 within the complex, playing a pivotal role in its assembly process (22). Additionally, RBBP4 collaborates with p130, E2F4 and DP1 to inhibit the transcriptional activity of E2F target genes (36). As the cell cycle progresses, phosphorylation by CDK leads to the disassembly of the DREAM complex, releasing p130/E2F4/DP1 from MuvB. Subsequently, the MuvB complex, inclusive of RBBP4, interacts with activated transcription factors B-MYB

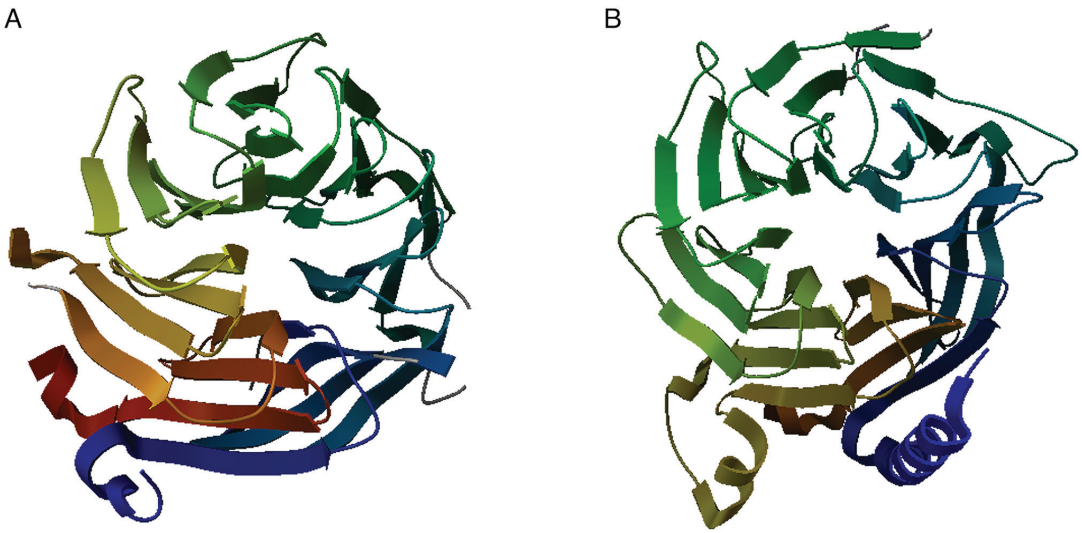

Figure 1. Crystal structure of histone-binding protein RBBP4/7. (A) Crystal Structure of RBBP4 (PDB ID: 3GFC). (B) crystal structure of the Apo form of human RBBP7 (PDB ID: 7M3X). RBBP, RB binding protein; PDB, Protein Data Bank.

(also known as MYB proto-oncogene like 2) and forkhead box M1 (FOXM1), culminating in the formation of the activated MYB-MuvB-FOXM1 complex. This complex further regulates the expression of cell cycle genes, especially during the G_2 phase and mitosis (37) (Fig. 2B). Thus, RBBP4, through its positioning and recruitment roles in the MuvB complex, serves a critical role in the regulation of various stages of cell cycle gene expression. Notably, the DREAM complex collaborates with RB during quiescence to suppress cell cycle gene expression (38,39). Furthermore, in response to the p53 tumor suppressor and genotoxic stress, the involvement of RBBP4 within the DREAM complex and its collaboration with RB becomes evident. Specifically, the DREAM complex and RB utilize the p53-p21 pathway to induce p21 and consequently arrest the cell cycle (39,40). The dual association of RBBP4 with the RB family and the DREAM complex indicates that it has a crucial role in maintaining cell cycle arrest.

Finally, RBBP4/7 serve as components of chromatin-remodeling complexes, such as NuRD and PRC2, further modulating the cell cycle via nucleosome acetylation and methylation regulation (8,41).

In summary, RBBP4/7, as components of the RB family or MuvB complex, have a pivotal role in cell cycle regulation. Their association with chromatin remodeling further influences cell cycle progression. While the role of RBBP4/7 in the cell cycle is evident, the specifics of their mechanism require further exploration.

The multifaceted role of RBBP4/7 in chromatin remodeling. Chromatin remodeling is a critical process that governs the accessibility of DNA to various cellular machineries, influencing gene transcription, replication and repair (42). RBBP4/7 can affect histone conformation by directly binding to histone H4 and H3 (43).

The NuRD complex, comprising several subunits, including the HDAC complex, chromodomain helicase DNA binding protein 3/4 ATPase, methyl-CpG binding domain protein 2/3, RBBP4/7, metastasis associated 1/2/3 (MTA1/2/3) and GATA zinc finger domain containing 2A/B, is a multifunctional entity with nucleosome remodeling and deacetylase activities (44). These activities enable the NuRD complex to alter chromatin structure, thereby regulating gene expression. Mu *et al* (45) suggested that RBBP4 may contribute to controlling the acetylation (ac) of lysine 27 on histone H3 (H3K27ac) levels at enhancer elements by promoting the deacetylase activity of the HDAC complex, effectively removing acetyl groups from H3K27 (Fig. 3A). RBBP4/7 also have regulatory chromatin remodeling effects independent of NuRD complexes. RBBP4 promotes H3K27ac by maintaining p300 levels (46), and together with RBBP7, mediates H4K5ac and H4K12ac to enable CENP-A deposition into centromeres (47). A network including SIN3 transcription regulator family member A-HDSAC3-RBBP4-H4 recognizes and deacetylates histones during chromatin assembly (48). RBBP4 also controls histone deacetylation at H3K4, H4K8, H4K12 and H4K16 during meiosis I (49). Additionally, RBBP4/7 collaborate with HAT1 in the site-specific *de novo* acetylation of histone H4 (50), facilitating its nuclear delivery and folding (51), which may be crucial in chromatin assembly and gene expression regulation.

PRC2, consisting of core subunits SUZ12 polycomb repressive complex 2 subunit (SUZ12), embryonic ectoderm development (EED), RBBP4/7 and enhancer of zeste homolog (EZH)2 or EZH1, is the sole confirmed methyltransferase responsible for the mono-, di- and trimethylation of H3K27, generating the H3K27me3 mark (52). RBBP4/7 interact with various molecules to facilitate PRC2 recruitment and activity modulation. Studies have shown that RBBP4 can recruit SUZ12 to PRC2 target sites, and methylate H3K27 or H1K26 with the histone lysine N-methyltransferase EZH2 (45,53). Simultaneously, EED can interact with the H3K27me3 mark, thereby activating the methyltransferase activity of EZH2 and influencing the overall activity of PRC2. Consequently, this process promotes the 'spreading' of H3K27me3 (54) (Fig. 3B). Notably, the absence of the SUZ12-RBBP4 complex influences H3K27me3 (55). Therefore, as pivotal constituents of PRC2, RBBP4/7 emerge as determinants of site-specific H3K27me3 and other histone methylations across the genome.

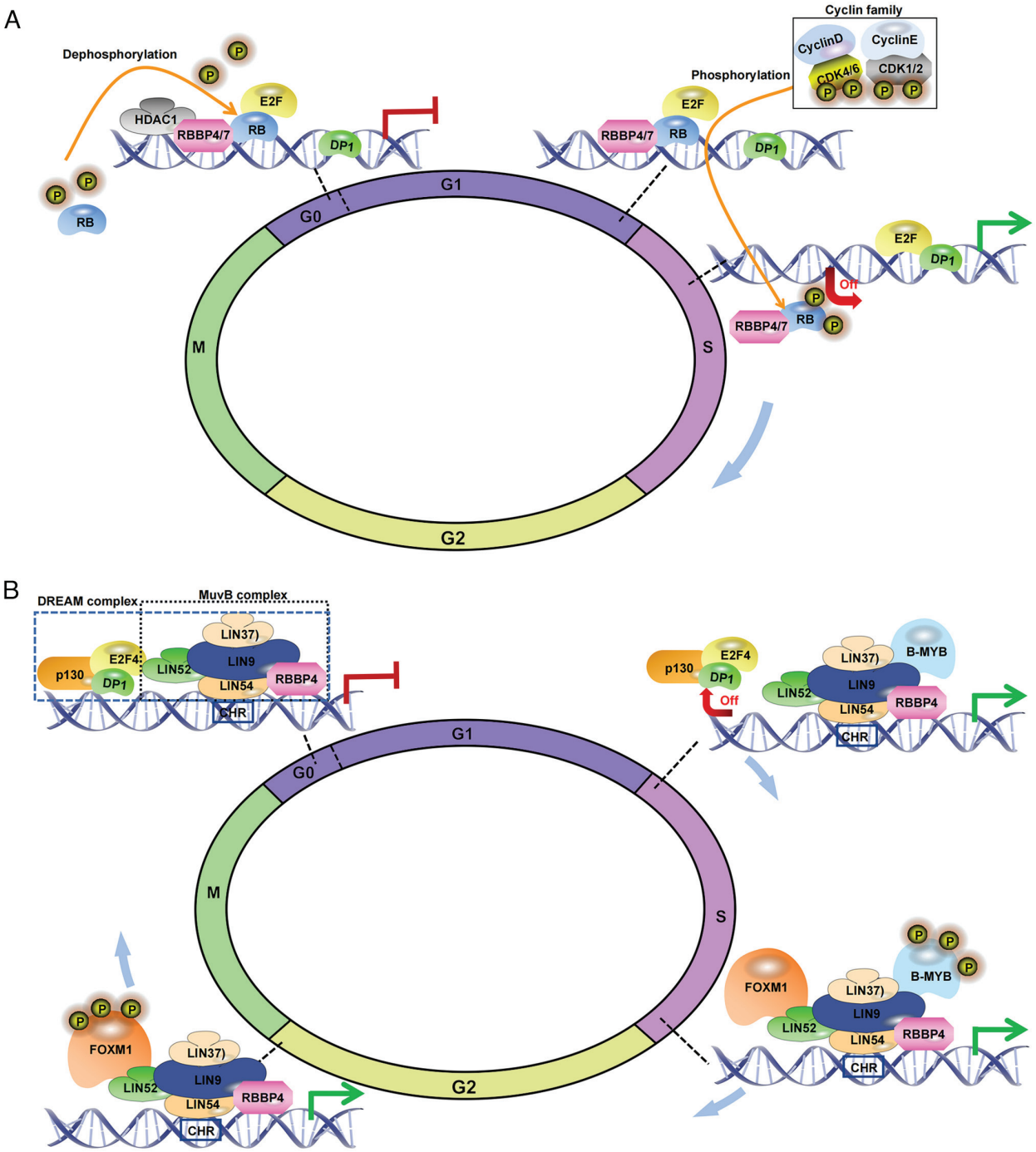

Figure 2. Molecular mechanism underlying how RBBP4/7 affects the cell cycle. (A) Involvement of RBBP4/7 in cell cycle regulation via RB interaction: Guided by HDAC1, RBBP4/7 is oriented to interact with RB. During the G_0/G_1 phase of the cell cycle, RB restrains the expression of genes regulated by transcription factors of the E2F family via binding to them, thus the dephosphorylated RB prevents cell entry into S phase. As the cell prepares to transition from the G_1 phase to the S phase, RB is phosphorylated by CDKs, and cyclins D/E. This phosphorylation leads to the disassociation of RB together with RBBP4 from E2F and gene promotors. Through dephosphorylation, RB regains its activity, binds to E2F once again, and inhibits excessive progression of the cell cycle. (B) During the G_0/G_1 phase, the MuvB complex, composed of LIN9, LIN37, LIN52, LIN54 and RBBP4, forms the DREAM complex through association with the RB-like protein p130, E2F4 and DP1 under quiescent conditions. This complex suppresses the expression of cell cycle regulatory genes during the G_0 phase. RBBP4, through its interactions with complex members, modulates the localization of the MuvB complex and suppresses the transcription of specific genes. When transitioning to the S phase, the p130/E2F4/DP1 module dissociates from the DREAM complex, resulting in the loss of suppression. Subsequently, the MuvB complex, with RBBP4 as the core complex, cooperates with B-MYB to form the MMB complex, activating the expression of genes required for the S/G_2 phase. FOXM1 is then recruited to MMB, forming the MMB-FOXM1 complex during the transition of S/G_2. B-MYB undergoes phosphorylation during the late S phase, leading to its dissociation from the MMB-FOXM1 complex as the cell cycle advances, while MuvB and FOXM1 persist in the DNA until mitosis. RBBP, RB binding protein.

RBBP4/7 also exhibit methyltransferase activity independent of PRC2. Kitange *et al* (56) showed that *RBBP4* knockdown can enhance the levels of H3K9 trimethylation. RBBP4/7 interact with SUV39H1 to specifically methylate lysine 9 on histone H3, leading to heterochromatin silencing or RB transcriptional repression (57). Furthermore, RBBP7

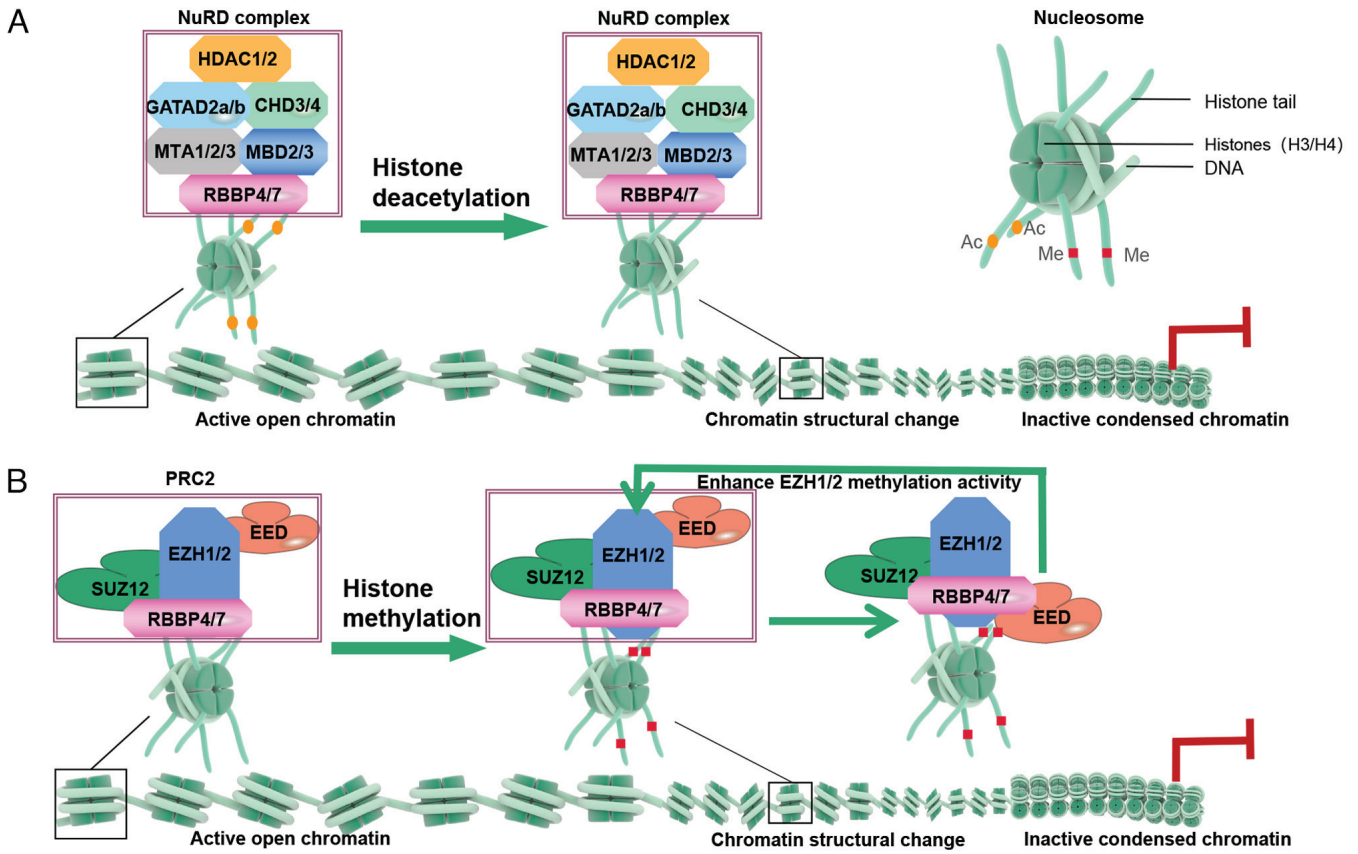

Figure 3. Mechanism of RBBP4/7 in chromatin remodeling. (A) Deacetylation: RBBP4/7 interacts with the tails of histones H3 and H4, promoting the deacetylase activity of the HDAC complex, resulting in the removal of acetyl groups from H3/H4. This leads to chromatin compaction, preventing gene promoter transcription and inhibiting gene expression. (B) Methylation: In PRC2, RBBP4 recruits SUZ12 to PRC2 target sites. The EZH2 subunit serves as the methyltransferase active center, performing primary, secondary and tertiary methylation on the 27th lysine of histone H3, resulting in H3K27me3 formation. EED binds to the H3K27me3 mark and further enhances the methyltransferase activity of EZH2. PRC2-mediated methylation induces chromatin compaction, limiting the binding of transcription factors and RNA polymerases, thus enabling gene silencing. RBBP, RB binding protein.

inhibits DNA methyltransferase 1, affecting DNA methylation and limiting transcription factor access to promoters (58).

In summary, RBBP4/7 serve an important role in regulating histone deacetylation and methylation, which are key processes in chromatin remodeling and the regulation of gene expression. The precise mechanisms underlying these regulatory activities of RBBP4/7 both inside and outside the aforementioned complexes remain an area of ongoing research and exploration.

The role of RBBP4/7 in the DNA damage response. RBBP4/7 have been identified as crucial components of several protein complexes involved in DNA repair, making them essential players in maintaining genome integrity.

The NuRD complex governs gene expression and DNA damage repair by modulating nucleosome RNA polymerase accessibility at transcription factor binding sites, enhancers and promoters (59). RBBP4/7, as subunits of the NuRD complex, mediate the interaction of NuRD with histone tails and transcription factors (59). Yang *et al* (60) showed that breast cancer (BC) anti-estrogen resistance 1 and RBBP4 can form a complex, be recruited to chromatin, and jointly occupy the promoter regions of some DNA repair genes, and promote DNA damage repair. Similarly, RBBP4/7 specifically interact with the C-terminal domain of BC type 1 susceptibility protein (BRCA1) and inhibit its transactivation activity (61). The association between BRCA1 and RBBP7 is disrupted in cells treated with DNA-damaging agents (62). Therefore, the interaction between RBBP4/7 and BRCA1 might be the key to regulating DNA damage repair.

Li *et al* (63) demonstrated that RBBP4 disruption results in heightened DNA damage and apoptosis in glioblastoma (GBM) cells post-temozolomide (TMZ) and radiotherapy. Additionally, in MCF10AT3B cells, which are neoplastigenic breast epithelial cells derived from a model of human proliferative breast disease, high levels of RBBP7 might induce the growth arrest- and DNA damage-induced (GADD) gene, *GADD45* (64). Consequently, aberrant expression of RBBP4/7 has implications for the DNA damage repair response.

In summary, RBBP4/7 serve a pivotal role in DNA damage repair and gene regulation, particularly in collaboration with BRCA1. Their interaction with BRCA1 facilitates DNA repair, and aberrant expression may affect this response, leading to the accumulation of DNA damage, as cell cycle progression and increased carcinogenic risk (Fig. 4). The complexity of these interactions warrants further investigation.

The role of RBBP4/7 in cell development, differentiation, maturation and senescence. In mouse oocytes, RBBP4 is crucial for bipolar spindle formation, and its deficiency can lead to mitotic

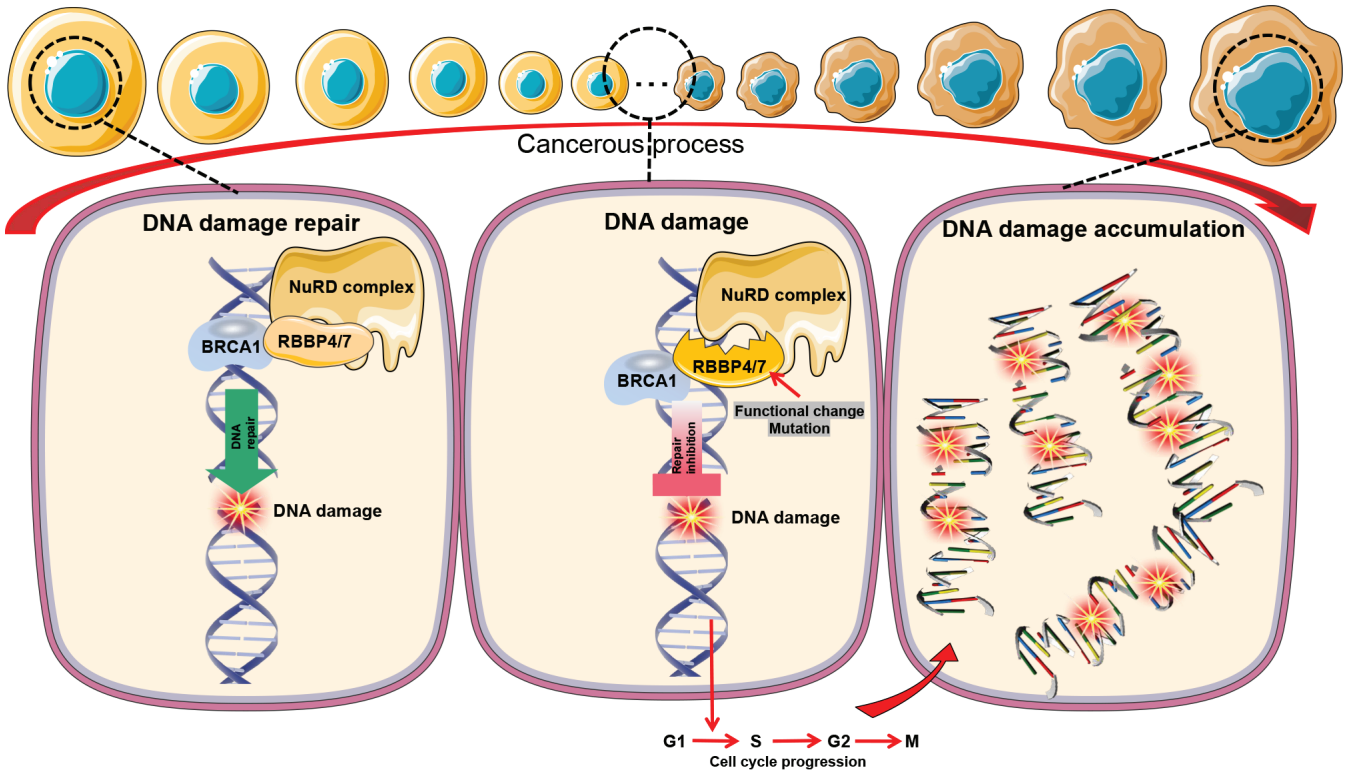

Figure 4. RBBP4/7 participate in the DNA damage response. As a subunit of the NuRD complex, RBBP4/7 facilitate DNA repair, especially in collaboration with BRCA1 at chromatin promoter regions. Disruption of RBBP4/7 can lead to accumulated DNA damage during the cell cycle, potentially giving rise to cancer cells. RBBP, RB binding protein.

abnormalities (49), suggesting its importance in cell division, a fundamental process of cell growth. RBBP7 is strongly expressed in the kidneys and brain from embryonic day 9.5 (65), regulating Kisspeptin-1 expression to participate in reproductive development (66). Giri *et al* (67) revealed that RBBP7 can be suppressed in relation to Ras-associated cell proliferation through stabilization by small ubiquitin like modifier 1.

RBBP4 is indispensable in heterochromatin assembly and serves as a crucial barrier in inducing cell fate transition from pluripotency to totipotency. Ping *et al* (68) demonstrated that the deletion of RBBP4 enhances the transition of mouse embryonic stem cells to trophectoderm cells. In the NuRD complex, RBBP4/7 and MTA interact with friend of GATA protein 2 (FOG-2) and are involved in FOG-2-mediated inhibition of GATA binding protein 4 activity, preventing the aberrant cell differentiation that leads to cardiac malformations (69). Moreover, the RBBP4 homolog DjRbAp48 in planarians (*Dugesia japonica*) regulates stem cell differentiation (70). In addition, notable discoveries have been made in the study of RBBP7. RBBP7 is involved in regulating histone acetylation and the expression of cyclin D3 in post-implantation trophoblast matrix cells (71), and it interacts with the pregnancy-induced non-coding RNA, inhibiting the differentiation of alveolar cells during pregnancy (72). Xin *et al* (73) showed that RBBP4/7 may be indirectly involved in the differentiation process of bone marrow cells by affecting the expression of the long noncoding RNA HOTAIRM1. Finally, in kidney development, *RBBP7*, as a target gene of the transcription factor Wilms tumor 1, exhibits decreased expression, reflecting podocyte dedifferentiation (74). These data suggested that RBBP4/7 may have a key role in cell differentiation processes.

During cell growth, RBBP4 influences cell morphology and cytoskeleton organization by enhancing K-Ras activity and mitogen-activated protein kinase signaling (75). Gasca *et al* (76) proposed that RBBP7 is involved in the maturation of oocytes. Likewise, RBBP7 also contributes to histone deacetylation during oocyte maturation (77). By contrast, Guan *et al* (78) showed that RBBP7 has strong growth inhibitory activity in the developing kidney and gonads. In summary, RBBP4/7 play diverse roles in cell maturation, influencing cell morphology, oocyte maturation and organ growth.

In aging human fibroblasts, a decrease in RBBP4 expression leads to chromatin defects (79). Concurrently, Hunt *et al* (80) demonstrated that ubiquitin protein ligase E3 component N-recognin 4 deficiency prevents skeletal muscle cell aging and atrophy by reducing the ubiquitination and degradation of the HAT1/RBBP4/RBBP7 histone-binding complex. Additionally, decreased RBBP4 expression in the aging hippocampus is associated with memory loss (81). Tsujii *et al* (82) further illustrated that *RBBP4* knockdown might inhibit nuclear transport and induce cellular aging. Furthermore, RBBP7 has been reported to be consistently upregulated in the lobules of degenerated mammary glands and to be associated with hormone induction (83). Collectively, RBBP4/7 are closely associated with cellular senescence, affecting chromatin defects, skeletal muscle cell aging and memory loss.

In summary, RBBP4/7 exhibit diverse functions throughout cell growth and development, impacting essential cellular

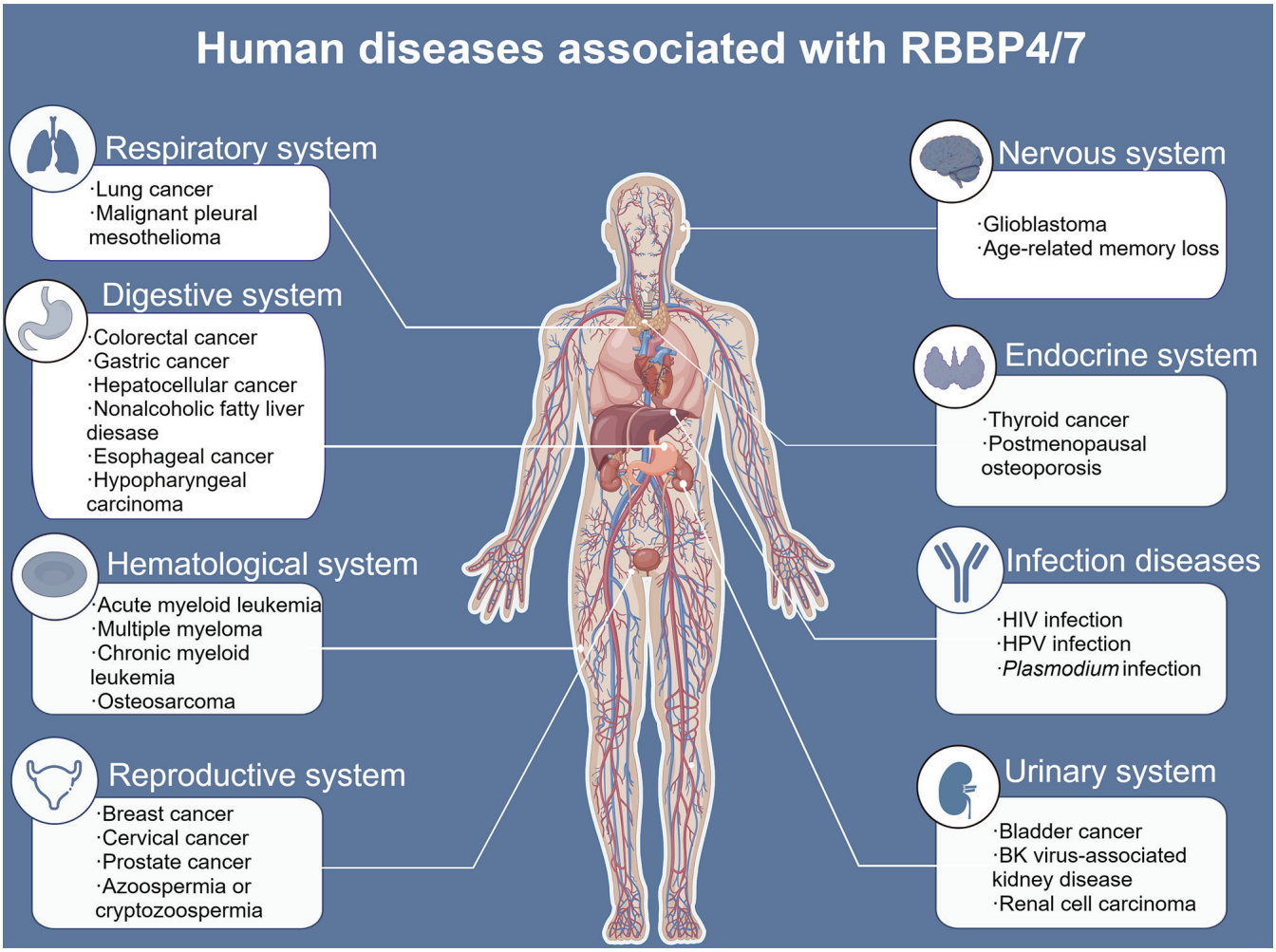

Figure 5. Human diseases associated with RBBP4/7. The diseases associated with RBBP4/7 are distributed across multiple systems, including the respiratory system, nervous system, digestive system, endocrine system, hematological system, reproductive system and urinary system. RBBP4/7 are also associated with infectious diseases. RBBP, RB binding protein.

processes and providing valuable insights into cellular differentiation, aging and chromatin regulation.

4. Expression and function of RBBP4/7 in diseases

Aberrant expression of RBBP4/7 has been observed in several diseases. The present review summarizes the various diseases regulated by RBBP4/7 (Fig. 5), the clinical characteristics of RBBP4 and RBBP7 in human diseases (Tables I and II), and their roles and mechanisms in disease development (Tables III and IV).

Respiratory system

Lung cancer (LC). RBBP4 is associated with genetic susceptibility to LC (84). Elevated RBBP4 expression in non-small cell LC (NSCLC) tissues amplifies cell proliferation and invasion, and is concomitantly linked to an adverse clinical outcome (13,84). RBBP4 is also increased in cisplatin-resistant NSCLC, affecting drug resistance (85), and is associated with enhanced DNA damage sensitivity and repair pathway activity (86). Additionally, in lung adenocarcinoma (LUAD) cells, RBBP4 interacts with chromobox homolog 3, which is found to be upregulated in current smokers with LUAD, thereby promoting LUAD progression (87). Thus, RBBP4 could be a potential biomarker or therapeutic target for LUAD recurrence and prognosis post-platinum treatment.

Research has revealed that the expression levels of RBBP7 in NSCLC are higher than those in normal lung tissues, and this elevated expression is associated with distant metastasis, poor prognosis and tumor immune response in NSCLC, serving as a predictor for the recurrence of early-stage NSCLC (88-90).

Despite these significant findings, the understanding of the functions of RBBP4/7 in LC is limited and more in-depth research is needed to develop new treatment strategies.

Malignant pleural mesothelioma (MPM). MPM has an average survival of 1 year post-diagnosis, urgently necessitating improved treatment methods (91). Vavougios *et al* (92) showed that RBBP4/7 interact with Parkinson disease protein 7 and are upregulated in an array of 18 different sarcoma types. However, the mechanism by which RBBP4/7 functions in MPM remains unknown.

Nervous system

GBM and other brain tumors. RBBP4 plays an indispensable role in the disease development of GBM (93), with its mRNA expression universally upregulated in GBM tissues

Table I. Expression of RB binding protein 4 in human diseases and relative clinical significance.

First author, year	Disease type	Expression	Samples	Clinical characteristics	(Refs.)
Gao M, 2023	NSCLC	Upregulated	LUAD: 54 adjacent normal, 497 tumor tissues; LUSC: 49 adjacent normal, 502 tumor tissues	Poor prognosis	(84)
Cao X, 2021	NSCLC	Upregulated	/	/	(13)
Hao D, 2023	NSCLC	Upregulated	54 NSCLC tissues and 54 adjacent normal tissues	/	(85)
Wang N, 2021	NSCLC	/	mRNA expression profiles of 43 patients with NSCLC	Poor prognosis, tumor recurrence	(86)
Vavougios GD, 2015	MPM	Upregulated	40 MPM tissues and 9 control tissues (5 pleura tissues and 4 lung tissues)	/	(92)
Shou J, 2021	GBM	Upregulated	33 GBM tissues and adjacent normal tissues	/	(94)
Li J, 2023	GBM	Upregulated	/	Poor prognosis	(63)
Li D, 2018	NB	Upregulated	Tissues from 42 primary cases of NB	Poor prognosis, tumor stage, survival rate	(97)
Pavlopoulos E, 2013	Age-related memory loss	Downregulated	Entorhinal cortex and DG of 10 healthy human brains, mouse DG tissues	Memory loss	(81)
Kosmidis S, 2018	Discriminative	Downregulated	Mouse DG tissues memory deficits	Discriminative memory, spatial memory	(100)
Khateb A, 2021	AML	Upregulated	/	Overall survival, tumor development	(106)
Casas S, 2003	AML	Upregulated	Bone marrow aspirate of 15 patients with AML and 5 healthy individuals	/	(107)
Sakhinia E, 2005	AML	Upregulated	Bone marrow aspirate of 26 patients with AML, 12 patients with AML in remission and 9 individuals with morphologically normal bone marrow	AML remission	(108)
Sakhinia E, 2005	ALL	Upregulated	Bone marrow aspirate of 5 patients with ALL and 9 individuals with morphologically normal bone marrow	/	(108)
Li YD, 2019	CRC	Upregulated	Colon cancer tissues, para-colon cancer tissues and haptic metastatic cancer tissues from 80 patients with CRC	Haptic metastases, poor prognosis	(117)
Ding L, 2019	GC	Upregulated	142 GC tissues and adjacent normal tissues	/	(120)
Song H, 2004	HCC	Upregulated	Tissue from a patient with primary HCC	/	(124)
Zhi S, 2022	NAFLD	Downregulated	Liver tissues of patients with NAFLD	/	(130)
Chen L, 2022	ESCC	Upregulated	ESCC tissues and corresponding normal tissues from 111 patients	/	(131)
Pacifico F, 2007	TC	Upregulated	/	/	(135)

Table I. Continued.

First author, year	Disease type	Expression	Samples	Clinical characteristics	(Refs.)
Guo Q, 2020	BC	Upregulated	240 BC tumor tissues	Overall survival, lymph node metastasis, tumor development	(141)
Gong X, 2020	BC	Upregulated	/	/	(142)
Zheng Z, 2022	TNBC	Upregulated	/	/	(144)
Barreiro-Alonso A, 2021	PCa	Upregulated	494 prostate adenocarcinoma tissues	Progression-free survival	(160)
Lohavanichbutr P, 2009	OSCC	Upregulated	124 OSCC patient tissues and 45 normal tissues	Radiosensitivity, chemosensitivity	(174)
Wurlitzer M, 2020	HPV-positive OPSCC	Upregulated	8 HPV-positive and 9 HPV-negative oropharyngeal tumor tissues	/	(175)

NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MPM, malignant pleural mesothelioma; GBM, glioblastoma; NB, neuroblastoma; DG, dentate gyrus; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; ESCC, esophageal squamous cell carcinoma; TC, thyroid cancer; BC, breast cancer; TNBC, triple-negative BC; PCa, prostate cancer; OSCC, oral squamous cell carcinoma; HPV, human papillomavirus; OPSCC, oropharyngeal squamous cell carcinoma; / indicates data not specified or applicable in the sources.

where it acts as an oncogene to promote GBM malignancy, countering the tumor-suppressive effects of microRNA (miR)-885-5p (94). In GBM cells, the RBBP4/p300 complex governs pro-survival genes and influences the responsiveness to TMZ (95). This suggests that disrupting RBBP4 or p300 might enhance sensitivity to TMZ. In addition, RBBP4 increases TMZ resistance by regulating the expression of the MRN complex (MRE11 homolog, RAD50 double-strand break repair protein, and nibrin), thereby reducing sensitivity to radiotherapy and TMZ (63). Therefore, RBBP4 potentially enhances cancer progression or drug resistance through DNA repair and might be considered a new therapeutic target for future GBM treatment.

RBBP4 is required during brain development, and RBBP4 is upregulated in RB1-mutated embryonic brain tumors, serving as a potential target for inducing apoptosis in RB1-mutated brain cancer cells (96). Additionally, in neuroblastoma, RBBP4 is upregulated and is associated with poor patient prognosis (97).

By contrast, limited research has been conducted on the involvement of RBBP7 in GBM. Notably, Crea *et al* (98) explored the Oncomine database and observed an upregulation of RBBP7 in anaplastic astrocytoma and anaplastic oligodendroglioma.

Age-related memory loss. Loss of RBBP4 is key to age-related memory decline. Its expression in human and mouse brains declines with age, affecting memory formation (81). Another study demonstrated that RBBP4 regulates the expression of brain-derived neurotrophic factor and G protein-coupled receptor 158, key components of the mouse hippocampal osteocalcin (OCN) signaling pathway (99). Inhibition of RBBP4 disrupts the cognitive benefits of OCN and leads to discriminative memory deficits (100). Furthermore, certain genetic variants in a cAMP element binding protein-dependent histone acetylation pathway, associated with RBBP4, influence memory performance in cognitively healthy elderly individuals (101). Therefore, RBBP4 could serve as a potential therapeutic target for age-related memory loss.

Current research has explored RBBP4/7 as therapeutic targets to address age-related memory loss. The functional role of RBBP4 in Alzheimer's disease (AD) might be influenced by the instability of the RBBP4-FOG1 complex (102). Huang *et al* (103) identified three traditional Chinese medicine compounds (bittersweet alkaloid ii, eicosanedioic acid and perivine), which could enhance the stability of the RBBP4-FOG1 complex, offering potential therapeutic benefits for AD. However, another study showed that RBBP4/7 did not contribute to the neuroprotective effects of green tea polyphenols (104). Thus, the mechanism of RBBP4/7 as a target for age-related memory loss requires further investigation.

Dave *et al* (105) discovered that *RBBP7* mRNA expression is diminished in AD cases, with significant negative correlations with the Consortium to Establish a Registry for AD and Braak stage. Moreover, this previous study revealed that high RBBP7 expression mitigates tau acetylation and phosphorylation, thereby preventing tau pathologies (105).

In summary, RBBP4/7 play crucial roles in age-related memory deficits, and present promising therapeutic targets for future interventions in cognitive aging and associated diseases.

Hematological (blood and bone marrow) system diseases

Acute myeloid leukemia (AML). In AML, elevated RBBP4 expression is linked to poorer survival and disease progression (106-108). Moreover, AML primary blasts with lower levels of ring finger protein 5/RBBP4 have demonstrated increased sensitivity to the HDAC inhibitor FK228. These findings suggest that the abundance of RBBP4 may serve as valuable marker to stratify patients with AML who might benefit from treatment with HDAC inhibitors (106). However,

Table II. Expression of RB binding protein 7 in human diseases and relative clinical significance.

First author, year	Disease type	Expression	Samples	Clinical characteristics	(Refs.)
Wang CL, 2009	NSCLC	Upregulated	154 lung cancer tissues and adjacent normal tissues	Distant metastasis	(90)
Wang H, 2022	LUAD	Upregulated	334 LUAD samples and 59 adjacent normal lung samples, and 23 cancer tissues and adjacent normal tissues from patients with LUAD	Relapse-free survival, poor prognosis, TNM stage	(89)
Zhu H, 2022	LUAD	/	/	Poor prognosis	(88)
Vavougios GD, 2015	MPM	Upregulated	40 MPM tissues and 9 control tissues (5 pleura tissues and 4 lung tissues)	/	(92)
Crea F, 2010	Anaplastic astrocytoma	Upregulated	/	/	(98)
Crea F, 2010	Anaplastic oligodendroglioma	Upregulated	/	/	(98)
Dave N, 2021	AD	Downregulated	89 AD brain tissues and 98 normal brain tissues	CERAD (neuritic plaque density), Braak stage, brain weight	(105)
Hu SY, 2005	AL	Upregulated	Bone marrow cells from 98 patients with AL, 5 patients with relapsing AL, 8 patients with CR-AL and 32 healthy individuals	/	(113)
Hu SY, 2005	CML-BC	Upregulated	Bone marrow cells from 13 patients with CML-CP, patients with CML-BC and 32 healthy individuals	Tumor progression	(113)
Yu N, 2018	ESCC	Upregulated	126 ESCC tissues, 72 of which had adjacent non-neoplastic tissues	Poor differentiation, lymph node invasion and progression, pathological TNM stage, poor prognosis, overall survival	(14)
Wang R, 2022	EC	Upregulated	182 EC tissues and 286 normal tissues	Overall survival, relapse-free survival, tumor stage	(133)
Thakur A, 2007	BC	Upregulated	20 breast cancer and adjacent benign or normal breast tissue	/	(150)
Ebata A, 2012	pDCIS	Upregulated	53 pDCIS and 27 IDC tissues	/	(151)
Barreiro-Alonso A, 2021	PCa	Upregulated	494 prostate adenocarcinoma tissues	Progression-free survival	(160)
Riera-Escamilla A, 2022	Azoospermia	/	X-linked protein-coding genes in 2,354 men with idiopathic NOA/ cryptozoospermia	Spermatogenesis	(163)
Yeh HH, 2015	Bladder cancer	Upregulated	Tissues from 4 patients with clinical bladder cancer	/	(166)
Wang Y, 2022	BKVN	Upregulated	/	Immune cell infiltration, graft rejection, diagnosis	(167)

Table II. Continued.

First author, year	Disease type	Expression	Samples	Clinical characteristics	(Refs.)
Wurlitzer M, 2020	HPV-positive OPSCC	Upregulated	8 HPV-positive and 9 HPV-negative oropharyngeal tumor tissues	/	(175)

NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; TNM, tumor-node-metastasis; MPM, malignant pleural mesothelioma; AD, Alzheimer's disease; CERAD, Consortium to Establish a Registry for AD; AL, acute leukemia; BM, bone marrow; CR-AL, complete remission acute leukemia; CML-CP, chronic myeloid leukemia in chronic phase; CML-BC, chronic myeloid leukemia in blast crisis; ESCC, esophageal squamous cell carcinoma; EC, esophageal cancer; BC, breast cancer; pDCIS, pure ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; PCa, prostate cancer; NOA, non-obstructive azoospermia; BKVN, BK virus-associated nephropathy; HPV, human papillomavirus; OPSCC, oropharyngeal squamous cell carcinoma; / indicates data not specified or applicable in the sources.

to the best of our knowledge, there is no currently research indicating an association between RBBP7 and AML.

Multiple myeloma (MM). Gao *et al* (109) showed that *RBBP4* is a core gene in MM, and its dysregulation is evident in the epigenetic modifications of MM. Thus, RBBP4 emerges as a potential focal point in MM research, providing promising avenues to understand the pathogenesis of MM and develop more effective therapeutic strategies. However, to the best of our knowledge, no studies have revealed a role for RBBP7 in MM.

Chronic myeloid leukemia (CML). CML is a malignant hematological disorder. It has been shown that *BMI1* (encoding B lymphoma Mo-MLV insertion region 1 homolog) transcript levels are significantly increased in CML cells, and the expression of RBBP4 is decreased after *BMI1* silencing (110). In addition, RBBP7 in K562 leukemic cells inhibits growth by inducing *IGFBP7* expression (111). These findings revealed that RBBP4/7 might serve an important role in the biological process of CML. However, the expression levels of RBBP7 were significantly elevated in patients with acute leukemia and CML in blast crisis compared with healthy donors and those with CML in chronic phase, indicating that it might be involved in the occurrence of leukemia (112,113). In addition, RBBP7 overexpression slows growth in the U937 leukemia cell line (114).

Osteosarcoma. Osteosarcoma originates from primitive mesenchymal cells in the bone, rarely in soft tissue, and if untreated, can lead to local and often metastatic progression (115). Zhang *et al* (116) showed that the inducible expression of RBBP7 can activate the c-Jun N-terminal kinase signaling pathway, and trigger apoptosis in Saos-2 osteosarcoma cells, while also strongly suppressing the formation of tumor grafts in nude mice and significantly reducing the growth of established osteosarcoma xenografts.

Digestive system

CRC. RBBP4 has been identified as a key factor in CRC, with studies showing its upregulation in colon cancer tissues, and linking increased RBBP4 expression to poor prognosis and liver metastasis (117). Reducing RBBP4 levels can hinder the growth and migration, and increase the apoptosis of HCT116 and SW620 colon cancer cells, and also suppress the Wnt/β-catenin pathway (12). Concurrently, knocking down *RBBP4* also inhibits H3K27ac acetylation and *HSPB8* gene transcription (118). Another study demonstrated that RBBP4 is a key target of protopanaxadiol (PPD), a major ginseng metabolite (119), suggesting its potential as a new diagnostic and therapeutic target for CRC.

RBBP7 has been reported to form a trimeric complex with long non-coding RNA FIT and p53, enhancing p53-mediated FAS gene transcription, which promotes CRC cell apoptosis (15). This suggests the apoptosis-inducing role of RBBP7 in CRC, which differs from the role of RBBP4. However, the precise expression and mechanism of RBBP7 in CRC warrant further investigation.

Gastric cancer (GC). Ding *et al* (120) revealed that the expression of RBBP4 is increased in GC tissues, and knocking down *RBBP4* can significantly inhibit GC cell proliferation, migration and invasion, and promote cell apoptosis. Radiation can also increase RBBP4 expression in AGS GC cells, leading to G_2 phase arrest. Moreover, RBBP4 enhances the radiosensitivity of these cells by inhibiting the PI3K/Akt pathway (121). These results underscore the potential of RBBP4 as a promising target for future gene therapy interventions in the treatment of GC.

Currently, research on the role of RBBP7 in GC is limited. Src-suppressed C-kinase substrate (SSeCKS), a crucial substrate for protein kinase C, is significantly downregulated in GC (122). Liu *et al* (123) demonstrated that the re-expression of SSeCKS induces RBBP7, suggesting a potential connection. However, the specific function and significance of RBBP7 in GC remains to be further determined.

Hepatocellular carcinoma (HCC). It has been shown that RBBP4 is highly expressed in liver tumor tissues, and is associated with clinical severity and disease prognosis (124). In HCC cells, Liu *et al* (125) identified that RBBP4 interacts with the N-terminal peptide of Sal-like protein 4 (SALL4), contributing to the silencing of tumor suppressor genes, such as *PTEN*. Furthermore, a potent SALL4 peptide antagonist (FFW) targeting RBBP4 significantly inhibits HCC cell growth. These studies have shown that RBBP4 plays a role in promoting HCC, which is expected to be a potential target for future HCC treatment.

By contrast, Li *et al* (126) observed a decrease in RBBP4 expression in HCC tissues; it was revealed that *RBBP4* knockdown may enhance the self-renewal and tumorigenic potential

Table III. The functions and mechanisms of RB binding protein 4 in diseases.

First author, year	Disease type	Cell lines	Role	Functions	Upstream regulators	Target/interacting genes	(Refs.)
Cao X, 2021	NSCLC	A549, HC827	Oncogene	Promotes cell proliferation, invasion and migration	hsa_circ_0102231, miR-145	/	(13)
Hao D, 2023	NSCLC	A549, H1299	Oncogene	Promotes cell proliferation, migration, invasion, glycolysis and drug resistance	circ_0110498, miR-1287-5p	/	(85)
Jin X, 2022	LUAD	A549, H1299	Oncogene	/	/	CBX3, ARHGAP24	(87)
Shou J, 2021	GBM	U87, U251	Oncogene	Promotes cell proliferation, viability and adhesion, inhibits cell apoptosis	HOXA-AS2, miR-885-5p	/	(94)
Mladek AC, 2022	GBM	U251	Oncogene	TMZ resistance	/	p300, c-MYC, RAD51	(95)
Kitange GJ, 2016	GBM	GBM12, GBM22	Oncogene	Promotes tumor growth in orthotopic xenografts and TMZ resistance	/	p300, CBP, RAD51, MGMT	(56)
Li J, 2023	GBM	U87MG, T98G, U118, U251	Oncogene	Reduces sensitivity to RT and TMZ, promotes DNA damage repair	/	MRE11, RAD50, NBS1, ELF-1	(63)
Li D, 2018	NB	BE (2)-C, IMR32, SH-SY5Y	Oncogene	Promotes cell growth and invasion	/	ARMC12	(97)
Kosmidis S, 2018	Age-related memory loss	/	/	Maintains normal brain function	/	GPR158, BDNF	(100)
Khateb A, 2021	AML	MOLM-13, U937	Oncogene	Promote cell growth	RNF5	ANXA1, NCF1, CDKN1A	(106)
Hu SY, 2006	CML	K562	Tumor suppressor	Inhibits cell growth, arrests cell cycle	/	IGFBP-rP1	(111)
Zhu X, 2023	CRC	HT29, HCT116, LOVO, SW620, RKO	Oncogene	Promotes cell proliferation and invasion	circAGO2, miR-1-3p	HSPB8	(118)
Li YD, 2020	CRC	SW620, HT29, LoVo, SW480, HCT-116	Oncogene	Promotes cell proliferation, migration and invasion, inhibits cell apoptosis	/	Wnt/β-catenin	(12)
Zhuo FF, 2022	CRC	HCT116	Oncogene	Promotes cell proliferation and migration	/	/	(119)
Ding L, 2019	GC	BGC-823, AGS	Oncogene	Promotes cell growth and reduces apoptosis	circ-DONSON	SOX4	(120)
Jin X, 2018	GC	AGS	Tumor suppressor	Promotes apoptosis, inhibits cell proliferation, enhances radiosensitivity and cell cycle arrest	/	PI3K/Akt	(121)
Song H, 2004	HCC	L02, Bel-7404, HepG2, Bel-7402 and HuH7	/	/	/	/	(124)

Table III. Continued.

First author, year	Disease type	Cell lines	Role	Functions	Upstream regulators	Target/interacting genes	(Refs.)
Li L, 2015	HCC	$EPCAM^+$ and $EPCAM^-$ HCCLM3	Oncogene	Promotes cell proliferation, self-renewal, chemotherapy resistance and tumorigenesis	miR-429	E2F1, OCT4	(126)
Zhi S, 2022	NAFLD	Mouse AML12 hepatocytes	Reduces hepatic steatosis	Regulates lipid metabolism and reduces lipid accumulation in liver cells	/	Cpt1α, Acox1	(130)
Chen L, 2022	ESCC	Kyse150, Kyse170, Eca109, TE1	Oncogene	Promotes EMT transition	KTN1-AS1	HDAC1	(131)
Bai X, 2015	Hypopharyngeal carcinoma	FaDu	Tumor suppressor	Inhibits cell proliferation, colony formation and tumor formation. Promotes apoptosis and regulates tumor suppressors	/	p53, RB, Bax, caspase-3, caspase-8, caspase-9	(132)
Pacifico F, 2007	TC	FRO	Oncogene	Promotes cell proliferation and cell cycle arrest	NF-κB	/	(135)
Yang C, 2019	PMOP	/	/	Regulates mitochondrial function	/	ESR1	(138)
Ishimaru N, 2006; Ishimaru N, 2008	Autoimmune exocrine disease	/	/	Promotes exocrine cell apoptosis	/	p53	(139, 140)
Gong X, 2020	BC	MCF-7, MDA-MB-231	Oncogene	Promotes cell proliferation, migration and invasion, inhibits cell apoptosis	/	LCPAT1, MFAP2	(142)
Creekmore AL, 2008	BC	MCF-7	/	Regulates the expression of estrogen-responsive genes and estrogen signaling	/	ERα	(143)
Zheng Z, 2022	TNBC	/	Oncogene	Promotes cell proliferation, invasion and migration, and regulates EMT activity	/	/	(144)
Moody RR, 2018	TNBC	/	Oncogene	Promotes tumorigenesis	/	BCL11A	(145)
Kong L, 2007	Cervical cancer	Caski, H8	Tumor suppressor	Inhibits cell proliferation and colony formation, promotes cell senescence and prevents tumor formation	/	RB, p53, caspase-3, caspase-8, E6, E7, CCND1, c-MYC	(153)
Wu S, 2017	Cervical cancer	SiHa, HeLa	Tumor suppressor	Promotes cell apoptosis and inhibits cell proliferation	/	HPV E6/E7, RB, p53, caspase-3	(155)
Zhong J, 2015	Cervical cancer	MS751	Oncogene	Promotes cell migration and invasion, inhibits EMT	/	SNAIL, TWIST	(156)
Zheng L, 2013	Cervical cancer	SiHa, Caski, HeLa	Tumor suppressor	Promotes apoptosis, inhibits cell proliferation and enhances radiosensitivity	/	/	(157)
Cai L, 2014	PCa	LNCaP	Tumor suppressor	Promotes apoptosis and inhibits cell proliferation	/	EAF2	(159)

Table III. Continued.

First author, year	Disease type	Cell lines	Role	Functions	Upstream regulators	Target/interacting genes	(Refs.)
Wang J, 2016	HIV infection	293T, TZM-bl, CEM-ss	Antiviral	Inhibits the expression of HIV-1	/	/	(169)
Wang J, 2019	HIV infection	HIV-1 infected T cells, J-lat	Antiviral	Suppresses transcription and remodels chromatin	/	NR2F1, HDAC1/2	(170)
Biswas S, 2018	HIV infection	HIV-2-infected MDMs	/	/	/	/	(171)
Xu W, 2020	HIV infection	293T	antiviral	Inhibits the activity of LTR, affect the nuclear translocation of p65	/	P65, NF-κB pathway	(172)

NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; GBM, glioblastoma; TNM, tumor-node-metastasis; TMZ, temozolomide; RT, radiotherapy; NB, neuroblastoma; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; ESCC, esophageal squamous cell carcinoma; TC, thyroid cancer; BC, breast cancer; PMOP, postmenopausal osteoporosis; TNBC, triple-negative BC; EMT, epithelial-mesenchymal transition; HPV, human papillomavirus; PCa, prostate cancer; LTR, long terminal repeat; / indicates data not specified or applicable in the sources.

of epithelial cell adhesion molecule-positive liver tumor-initiating cells, suggesting that RBBP4 serves as a downstream target of miR-429. Furthermore, epigallocatechin gallate (EGCG) can reverse multidrug resistance (MDR) in HCC, and RBBP4 has been reported to be significantly upregulated after EGCG treatment (127), suggesting that RBBP4 could be a potential anti-MDR target in HCC.

Nonalcoholic fatty liver disease. Hepatic steatosis, crucial in nonalcoholic steatohepatitis development, elevates the risk of cirrhosis and HCC (128). Within the NuRF complex, the subunit RBBP4 assumes a role in the regulation of lipid droplet size by transcriptionally suppressing target genes (129). Zhi *et al* (130) suggested that RBBP4 exerts a favorable influence on liver cell steatosis by promoting the expression of genes associated with fatty acid β-oxidation. These findings illustrate a protective role of RBBP4 in the context of hepatic steatosis.

Esophageal cancer (EC) and hypopharyngeal carcinoma. Research has shown that RBBP4 is upregulated in ESCC and promotes the epithelial-mesenchymal transition (EMT) process (131). By contrast, Bai *et al* (132) demonstrated that in hypopharyngeal carcinoma, a distinct squamous cell carcinoma impacting the upper aerodigestive tract, *RBBP4* overexpression curtails proliferation, colony formation and tumorigenesis in the FaDu hypopharyngeal carcinoma cell line. The role of RBBP4 in hypopharyngeal carcinoma growth appears linked to its modulation of tumor suppressors. This contrasting role of RBBP4, from facilitating tumor progression in ESCC to inhibiting growth in hypopharyngeal carcinoma, demonstrates its functional variability across different types of cancer, highlighting its potential complexity as a therapeutic target.

Yu *et al* (14) observed that higher RBBP7 expression in ESCC tissues is correlated with poor differentiation, advanced lymph node involvement, higher tumor-node-metastasis stage, reduced survival, and increased cell invasion and migration. Mechanistically, hypoxia can induce high expression of RBBP7, which in turn upregulates CDK4 expression and promotes tumor progression (133). Furthermore, RBBP7 is upregulated in EC. As a target of miR-384, *RBBP7* mRNA levels are elevated by circ_0006168 through its interaction with miR-384. This, in turn, promotes cell proliferation, migration, invasion and glycolysis in EC (134).

Collectively, RBBP4/7 are crucial in EC progression and prognosis, with their complex molecular interactions making them promising for future therapeutic and diagnostic developments in esophageal oncology.

Endocrine system

Thyroid cancer (TC). Pacifico *et al* (135) detected increased RBBP4 expression in primary human TC via immunohistochemical analysis, particularly in undifferentiated TC samples and cell lines. In addition, *RBBP4* knockdown was shown to reduce FRO anaplastic thyroid carcinoma cell colony formation, suggesting RBBP4 as a target of nuclear factor (NF)-κB and a potential therapeutic target for NF-κB-dependent TC. Therefore, RBBP4 might be a potential target for TC therapy, particularly for NF-κB-dependent cases.

Postmenopausal osteoporosis (PMOP) and other estrogen-influenced conditions. PMOP represents a significant

Table IV. The functions and mechanisms of RB binding protein 7 in diseases.

First author, year	Disease type	Cell lines	Roles	Functions	Upstream regulators	Target/interacting genes	(Refs.)
Wang CL, 2009	NSCLC	CL1-0, CL1-5	Oncogene	Promotes cell migration	/	/	(90)
Dave N, 2021	AD	HT-22	/	Inhibits cell death	/	tau, p300	(105)
Duan WM, 2004	/	U937	Tumor suppressor	Inhibits leukemic tumor growth	/	/	(114)
Zhang TF, 2003	Osteosarcoma	Saos-2	Tumor suppressor	Promotes apoptosis and inhibits the growth of tumor grafts	/	JNK	(116)
Guo L, 2023	CRC	/	Tumor suppressor	Promotes apoptosis	/	p53, FAS, FIT	(15)
Yu N, 2018	ESCC	TE1, KYSE30, KYSE150, Eca109	Oncogene	Promotes cell invasion and migration	/	/	(14)
Wang R, 2022	EC	Eca109, KYSE450	Oncogene	Promotes cell viability and proliferation	HIF1α	CDK4	(133)
Xie ZF, 2020	EC	ECA-109, KYSE-510c	Oncogene	Promotes cell proliferation, migration, invasion and glycolysis	circ_0006168, miR-384	S6K/S6,	(134)
Creekmore AL, 2008	BC	MCF-7	/	Regulates the expression of estrogen-responsive genes and estrogen signaling	/	ERα	(143)
Moody RR, 2018	TNBC	/	Oncogene	Promotes tumorigenesis	/	BCL11A	(145)
Zhang TF, 2003	BC	MCF-7, MDA-MB-231, MDA-MB-43	Tumor suppressor	Inhibits tumor formation	/	/	(146)
Zhang TF, 2007	BC	MCF10AT3B	Tumor suppressor	Inhibits tumor formation and cell proliferation	/	β-catenin	(147)
Li Gc, 2003	BC	MCF10AT3B	Tumor suppressor	Promotes apoptosis and inhibits cell growth	/	JNK	(64)
Li GC, 2006	BC	MCF10AT3B	Oncogene	Promotes cell migration, invasion and EMT	/	N-cadherin, E-cadherin, α/β/γ-catenin	(149)
Fu J, 2011	BC	MDA-MB-435	Oncogene	Promotes cell migration, invasion and EMT	/	E-cadherin, TWIST	(148)
Li HJ, 2016	Cervical cancer	HeLa, SiHa	Tumor suppressor	Inhibits cell invasion and EMT	NKX6.1	Vimentin, N-cadherin	(158)
Cai L, 2014	PCa	LNCaP	Tumor suppressor	Promotes apoptosis and inhibits cell proliferation	/	EAF2	(159)
Wang J, 2020	PCa	DU145	Tumor suppressor	Inhibits cell migration and EMT	/	HNF1B	(161)
Yeh HH, 2015	Bladder cancer	T24, NIH3T3	Oncogene	Promotes cell invasion and tumor metastasis	Ras	RECK, MMP-9, HDAC1, Sp1	(166)

NSCLC, non-small cell lung cancer; AD, Alzheimer's disease; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; EC, esophageal cancer; BC, breast cancer; TNBC, triple-negative BC; EMT, epithelial-mesenchymal transition; PCa, prostate cancer; / indicates data not specified or applicable in the sources.

global public health concern. RBBP4 expression is elevated in estrogen-deficient rats and patients with PMOP, decreasing after treatment with Liuwei Dihuang pills (136,137). Moreover, RBBP4 has been reported to be upregulated in the blood of patients with PMOP, suggesting that it could serve as a potential diagnostic biomarker of PMOP (138). The interaction between RBBP4 and estrogen receptor 1 (ESR1) is believed to serve a crucial role in the pathogenesis of PMOP (138). In summary, RBBP4 serves as a potential biomarker for PMOP diagnosis and its interaction with ESR1 suggests a fundamental mechanism in PMOP pathogenesis.

Additionally, estrogen deficiency-induced overexpression of RBBP4 triggers p53-mediated apoptosis in exocrine cells, implying a link to autoimmune exocrine disorders in postmenopausal women (139,140). Therefore, RBBP4 represents a novel immunotherapeutic target for preventing the development of sex-based autoimmune exocrine disorders.

Reproductive system

BC. RBBP4 is highly expressed in BC and is associated with poorer overall survival and a greater likelihood of lymph node metastasis (141). Knockdown of *RBBP4* inhibits the proliferation, migration and invasion of BC cells, while affecting the transcription of tumor-related genes, such as microfibril-associated protein 2, which is activated via the interaction between RBBP4 and the long noncoding RNA *LCPAT1* (142). Another study showed that RBBP4/7 interact with DNA-bound estrogen receptor α to alter the expression of estrogen-responsive genes in MCF-7 cells (143). Thus, RBBP4 is implicated in BC progression, in which it influences survival, metastasis and estrogen-responsive gene expression.

RBBP4 expression has also been shown to be significantly elevated in triple-negative BC (TNBC) cells and tissues; and its knockdown markedly inhibits TNBC cell proliferation, invasion and migration, and concurrently downregulates EMT regulatory activities (144). In addition, Moody *et al* (145) demonstrated that BCL11 transcription factor A (BCL11A), which possesses the ability to promote BC progression, can interact with RBBP4/7; therefore, targeting RBBP4-BCL11A binding may have therapeutic potential.

The role of RBBP7 in BC appears complex and contradictory. Zhang *et al* (146) observed decreased expression levels of RBBP7 in BC cell lines, and its dysregulation was shown to contribute to BC tumorigenesis. Further research has revealed that RBBP7 is related to estrogen regulation and may affect the early development of BC (64,147). As a component of the Mi2/NuRD complex, RBBP7 regulates TWIST-mediated repression of E-cadherin expression and inhibits BC cell metastasis (148). By contrast, Li and Wang (149) found that recombinant RBBP7 induces EMT and enhances mammary epithelial cell migration. Thus, the mechanism of RBBP7 in BC progression and metastasis requires further investigation.

Notably, in contrast to the observation of Zhang *et al* (146) of decreased RBBP7 expression in BC, Thakur *et al* (150) showed that RBBP7 expression was upregulated in 79% of BC cases and its expression was positively correlated with malignancy. RBBP7 may also be involved in the pathogenesis of estrogen receptor-positive pure ductal carcinoma *in situ* (151). In addition, Mieczkowska *et al* (152) found that RBBP7 was downregulated in parental G-2 cells from the WAP-T transgenic breast cancer line after surviving traditional cytotoxic combination therapy, suggesting that RBBP7 might be considered a potential therapeutic target for BC in the future.

In summary, both RBBP4 and RBBP7 have demonstrated significant roles in the progression, metastasis and therapeutic potentialities of BC; however, their precise mechanisms and interactions in various BC subtypes warrant deeper exploration.

Cervical cancer. Kong *et al* (153) observed that RBBP4 overexpression inhibits cervical cancer growth and affects human papillomavirus (HPV)16 transformation by regulating tumor suppressors and oncogenes. Notably, 5-aminole-vulinic acid photodynamic therapy (ALA-PDT), an effective treatment for HPV-related conditions, has been reported to elevate RBBP4 expression in HPV16 immortalized cervical epithelial H8 cells (154). A subsequent decrease in RBBP4 can mitigate the inhibitory effects of ALA-PDT-induced cell proliferation and apoptosis in cervical cancer cells (155). These studies demonstrated that RBBP4 may function as a tumor suppressor in cervical cancer and could serve as a promising therapeutic target for future cervical cancer intervention.

However, studies have also indicated that RBBP4 promotes cervical cancer, influencing EMT and radiotherapy outcomes (156,157). This implicates RBBP4 as a prospective target to boost radiotherapeutic outcomes in patients with cervical cancer. In addition, RBBP7 can be recruited by NK6 homeobox 1, thereby inhibiting the invasive ability of cervical cancer cells (158).

In conclusion, RBBP4/7 have complex roles in cervical cancer and may be potential therapeutic targets. However, the role of RBBP4 in cervical cancer remains controversial, and its mechanism requires further study.

Prostate cancer. Cai *et al* (159) showed that there is a physical interaction between the tumor suppressor gene *EAF2* (encoding ELL associated factor 2) and RBBP4/7, where their overexpression induces cell death in LNCaP prostate cancer cells. High RBBP4/7 expression in prostate adenocarcinoma is also linked to shorter progression-free survival, with RBBP7 interacting with high mobility group box 1 to regulate RNA processing (160). Furthermore, overexpression of *RBBP7* suppresses SLUG1/EMT in DU145 cells and exerts tumor suppressive functions in presence of hepatocyte nuclear factor 1β (161). Thus, RBBP4/7 are pivotal in prostate cancer progression and potential therapeutic targets.

Azoospermia or cryptozoospermia. Male infertility, affecting ~7% of men in the general population, is often due to factors such as azoospermia or cryptozoospermia (162). The X chromosome is vital for male reproductive health. Riera-Escamilla *et al* (163) linked *RBBP7* mutations to early spermatogenic failure in an analysis of 2,354 men with azoospermia/cryptozoospermia, revealing that these mutations were more prevalent in this infertile group compared with in control individuals with normozoospermia. RBBP7 forms the CRL4B-RBBP7 complex with CUL4B (encoded by another mutated gene found in infertile men), which contributes to the degradation of HUWE1 and is associated with non-obstructive azoospermia (164). In conclusion, RBBP7 has a central role in male infertility, highlighting the importance of genetic factors in reproductive health.

Urinary system

Bladder cancer. Bladder cancer, affecting >440,000 individuals annually worldwide (165), shows high RBBP7 expression in specimens. Mechanistically, RBBP7 can bind to HDAC1 and specificity protein 1 (SP1), and then bind to the *RECK* (encoding reversion inducing cysteine rich protein with kazal motifs) promoter at the SP1 site, thereby inhibiting the expression of *RECK*, which in turn leads to matrix metalloproteinase-9 activation and metastasis, thereby participating in Ras-induced experimental lung metastasis (166). Therefore, RBBP7 could be used as a therapeutic target for Ras-related cancer; however, to the best of our knowledge, there are currently no studies on RBBP4 in bladder cancer.

BK virus-associated kidney disease. Wang *et al* (167) demonstrated that RBBP7 is highly enriched in BK virus-associated nephropathy (BKVN) tissues and is associated with alterations in various immune cells, such as CD8 naïve cells, induced regulatory T cells, neutrophils and $CD8^+$ T cells. Furthermore, RBBP7 serves as a molecular biomarker for the precise diagnosis of BKVN, effectively distinguishing transplant rejection responses. Thus, targeting RBBP7 as a diagnostic tool may offer novel therapeutic and prognostic opportunities for BKVN in transplant recipients.

Renal cell carcinoma (RCC). Kim *et al* (168) showed that RBBP7 is highly expressed in the chromaffin subtype of RCC, but not in traditional RCC. Therefore, RBBP7 could be used as a candidate biomarker in RCC, and its existence and expression patterns might be related to the pathological characteristics of RCC subtypes, providing a novel direction for the diagnosis and treatment of RCC.

Infectious diseases

HIV infection. Wang *et al* (169) reported increased RBBP4 expression following HIV-1 infection in cell culture models, with *RBBP4* knockdown enhancing HIV infection and viral production. RBBP4 suppresses HIV-1 transcriptionally by binding to its long terminal repeats, recruiting nuclear receptor subfamily 2 F group member 1 and HDAC1/2, leading to H3 deacetylation and replication control (170). Similarly, Biswas *et al* (171) observed elevated RBBP4 levels in HIV-2-infected monocyte-derived macrophages, and Xu *et al* (172) reported that thieno[3,4-d] pyrimidine treatment in infected cells increases RBBP4 levels and activates the NF-κB pathway, suppressing HIV-1. Collectively, these findings demonstrate a critical role for RBBP4 in the regulation of HIV infection and suggest its potential as a therapeutic target for HIV management.

HPV infection. Oral squamous cell carcinoma (OSCC) and oropharyngeal squamous cell carcinoma (OPSCC) constitute a major global public health burden, and there is an association between infection with high-risk types of HPV and OSCC risk (173). Lohavanichbutr *et al* (174) identified differential expression of RBBP4 in HPV-positive vs. HPV-negative oropharyngeal cancer. Wurlitzer *et al* (175) performed a mass spectrometric comparison of eight HPV-positive and nine HPV-negative OPSCC cases, and found that RBBP4/7 was expressed at higher levels in HPV-positive OPSCC.

In cervical cancer, a major HPV-related cancer, RBBP4 mediates the transforming activity of HPV16 (153) and is upregulated by ALA-PDT in HPV16 immortalized cervical cells (154). These findings indicated that RBBP4 plays a key role in HPV infection; however, the specific mechanism still needs further exploration. Moreover, current research on the role of RBBP7 in HPV infection is insufficient.

Plasmodium infection. Kaushik *et al* (176) discovered that the homologs of RBBP4/7 in *Plasmodium falciparum* (PfRBBP4/7, PF3D7_0110700) retain the β-helical conformation and binding interfaces, exhibit significant interspecies differences, and show stage-specific expression in the asexual blood stages of the parasite, increasing from the ring stage to the schizont stage, and localizing in the nucleus. Furthermore, PfRBBP4/7 have been shown to interact with histone H4, suggesting their role in chromatin assembly and remodeling pathways in *P. falciparum*. As CAF-1 family members, they show structural and functional consistency. PfRBBP4, central in malaria biology with 108 PPIs, emerges as a potential antimalarial drug target (177). Thus, the function of PfRBBP4/7 in *P. falciparum* illustrates their potential as targets to develop novel antimalarial interventions.

5. RBBP4/7 as potential targets for human disease treatment

In the realm of targeted therapy research focused on RBBP4/7, these proteins have demonstrated significant potential in the treatment of various diseases, particularly in modulating therapeutic outcomes. For example, increased expression of RBBP4 has been linked to mitigating lead-induced neuronal apoptosis, suggesting a potential role in alleviating lead poisoning and related neurological disorders (178). Additionally, the interaction of RBBP4 with the efficacy of multiple drugs has been extensively studied, including its role in enhancing the sensitivity of GBM cells to TMZ (56,95), suppression of LC cell malignancy via ropivacaine by downregulating RBBP4 (179), and the identification of the circ-0110498/miR-1287-5p/RBBP4 axis as a novel target for overcoming cisplatin resistance in NSCLC (85). RBBP4 is also considered a potential target for treating CRC with PPD (119). In therapeutic contexts, RBBP4 expression is significantly increased in cervical cancer cell lines treated with ALA-PDT (155), and upregulation of RBBP4 has been found to induce radiosensitivity in BC, melanoma and TNBC (180). Conversely, reduced levels of RBBP7 may be associated with survival rates and chemoresistance phenotypes in basal-like BC (152).

PPIs play a pivotal role in cellular functions, and modulating PPIs offers a novel therapeutic avenue. It has been reported that blocking the interaction between BCL11A and RBBP4 reduces the cancer stem cell population in TNBC (145). Furthermore, compounds, such as bittersweet alkaloid II, may aid in AD treatment by stabilizing the RBBP4-FOG1 complex (103). Additionally, peptides designed by Hart *et al* targeting the RBBP4/MTA1 interaction interface show potential as future therapeutic strategies for disrupting epigenetic regulation mechanisms in various types of cancer (181). Despite the potential of small molecules or peptides targeting RBBP4/7, challenges such as low oral bioavailability and poor *in vivo* stability remain, necessitating further research to overcome these obstacles.

Emerging research has consistently linked elevated RBBP4/7 expression to poorer prognosis across various cancer types (Table V), underscoring their pivotal role in

Table V. Prognostic significance of RBBP4/7 in cancer.

A, RBBP4

First author, year	Disease type	Omics type	Samples or sample sources	Analysis methods	Prognostic relevance	(Refs.)
Gao M, 2023	NSCLC	Transcriptomics	LUAD: 54 adjacent normal, 497 tumor samples; LUSC: 49 adjacent normal, 502 tumor samples	KM-plotter	Poor prognosis: Reduced OS	(84)
Wang N, 2021	LUAD	Transcriptomics	KM website	KM-plotter	Poor prognosis: Reduced OS	(86)
Jia W, 2023	LUAD	Transcriptomics	Patients with LUAD from the KM-plotter database	KM-plotter	Poor prognosis: Reduced OS, FP and PPS	(179)
Li J, 2023	GBM	Transcriptomics	Samples from patients withMGMT-negative GBM in TCGA database	KM-plotter	Poor prognosis: Reduced OS and PFS	(63)
Li D, 2018	NB	Transcriptomics, proteomics	Tissues from 42 primary cases of NB, GSE14340 and GSE16476 datasets	Log-rank test	Poor prognosis: Poor differentiation, reduced survival probability	(97)
Khateb A, 2021	AML	Transcriptomics	GEPIA and TCGA	Log-rank test	Poor prognosis: Reduced OS	(106)
Li YD, 2019	CRC	Proteomics	Tumor tissues of 80 patients with CRC	KM-plotter, log-rank test	Poor prognosis: Reduced OS	(117)
Guo Q, 2020	BC	Proteomics	240 BC tumor tissues	KM-plotter, log-rank test	Poor prognosis: Reduced OS	(141)
Barreiro-Alonso A, 2021	PCa	Transcriptomics	494 prostate adenocarcinoma tissues	Log-rank test	Poor prognosis: Reduced PFS	(160)

B, RBBP7

First author, year	Disease type	Omics type	Samples or sample sources	Analysis methods	Prognostic relevance	(Refs.)
Wang H, 2022	LUAD	Transcriptomics	Samples of patients with early-stage LUAD from different cohorts (TCGA, GSE30219, GSE31210, GSE37745, GSE50081)	KM-plotter, log-rank test, meta-analysis	Poor prognosis: Reduced RFS	(89)
Zhu H, 2022	LUAD	Transcriptomics	/	LASSO regression, forest plots	Poor prognosis	(88)
Yu N, 2018	EC	Transcriptomics, proteomics	126 ESCC tissues, 182 patients with EC from TCGA database	KM-plotter, log-rank test	Poor prognosis: Reduced OS and DFS	(14)
Wang R, 2022	EC	Transcriptomics	Patients with EC in GEPIA database and TCGA database	KM-plotter	Poor prognosis: Reduced OS and DFS	(133)
Barreiro-Alonso A, 2021	PCa	Transcriptomics	494 prostate adenocarcinoma tissues	Log-rank test	Poor prognosis: Reduced PFS	(160)

RBBP, RB binding protein; NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; KM, Kaplan-Meier; OS, overall survival; FP, first progression; PPS, post-progression survival; GBM, glioblastoma; MGMT, O-6-methylguanine-DNA methyltransferase; TCGA: The Cancer Genome Atlas; PFS, progression-free survival; NB, neuroblastoma; AML, acute myeloid leukemia; GEPIA: Gene Expression Profiling Interactive Analysis; CRC, colorectal cancer; BC, breast cancer; PCa, prostate cancer; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; DFS, disease-free survival; LASSO, least absolute shrinkage and selection operator; / indicates data not specified or applicable in the sources.

disease therapy. Despite the evident potential of RBBP4/7 in treating various diseases, the success of targeted strategies remains elusive, possibly due to the complex biological roles of RBBP4/7 and their involvement in multiple protein complexes. Future research should investigate the mechanisms of RBBP4/7 to develop targeted and effective treatment approaches. This includes a deeper understanding of the specific roles of RBBP4/7 in different cell types and disease states, identifying the molecular networks interacting with RBBP4/7, studying their expression and functional variations across diseases, and validating therapeutic interventions targeting RBBP4/7 in preclinical and clinical studies. Through these efforts, the scientific groundwork may be laid for novel treatment methods based on RBBP4/7, offering more personalized and effective therapeutic options for patients.

6. Conclusion and future perspectives

RBBP4/7 are conserved proteins ubiquitously present in various organisms, which function in chromatin modification and gene regulation across species. However, their specific structure, expression patterns and molecular mechanisms may differ depending on the organism. For example, in *P. falciparum*, *Drosophila*, zebrafish and *Saccharomyces cerevisiae*, the structure of RBBP4 might resemble that in humans; however, there could be unique structural domains or adjustments (18,80,96,176). Moreover, in these organisms, RBBP4/7 primarily function during developmental and reproductive stages. By contrast, in humans, RBBP4/7 are expressed across diverse cells and tissues, and are associated with cell cycle regulation and gene transcription.

As histone chaperones, RBBP4/7 regulate various cellular processes and are implicated in a variety of human diseases, thus the future of RBBP4/7 research is promising. However, the expression patterns of RBBP4/7 exhibit significant variability in certain tumor types. This variability is attributed to the diverse roles of RBBP4/7 within multiple functional complexes, whose impact on tumorigenesis is intricately linked to the specific actions of these complexes, which vary with the cellular context and tumor type. In addition, research into gene mutations and DNA methylation abnormalities of RBBP4/7 in diseases remains limited, with mutations in RBBP7 identified only in cases of early spermatogenic failure (163). This underscores an important area for further investigation. Further studies of the complex molecular functions of RBBP4/7 may improve the understanding of cellular processes and disease pathways, leading to the development of innovative therapies for a variety of human diseases and cancers. Furthermore, exploring RBBP4/7 as potential biomarkers could improve diagnostic accuracy, enabling early detection and personalized medicine approaches.

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Competing interests

The authors declare that they have no competing interests.

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