Essential role of bromodomain proteins in renal cell carcinoma (Review)

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Abstract. Histone alterations are a hallmark of kidney cancer. Histone acetylation modification mediated by bromodomain proteins (BRD) has been indicated to be related to a variety of cancer types and several targeted inhibitors have been proven to be promising modalities for cancer adjuvant therapy. As renal cell carcinoma (RCC) is not sensitive to radiotherapy or chemotherapy, the exploration of effective adjuvant therapies remains an important research direction for advanced RCC. At present, studies on bromodomain family proteins in RCC are limited and the roles of bromodomain family proteins in RCC have remained to be fully elucidated. The present review discussed the role of bromodomain family proteins in RCC, aiming to explore possible potential therapeutic targets of BRD-related drugs in this type of cancer.

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1. Introduction

According to the Global Cancer Statistics 2020, the number of new cases of renal cell carcinoma (RCC) has increased by ~100,000 over the past decade (1,2). Among cancers of the urinary system, RCC ranks third in terms of prevalence (3). Organ metastasis of advanced RCC is the main cause of a poor prognosis. Since RCC is not sensitive to conventional radiotherapy and chemotherapy (4), the search for specific biomarkers and individualized treatment options for RCC is an important direction.

Epigenetic alterations are among the hallmarks of cancer. Epigenetics has a critical role in RCC, including DNA methylation, chromatin remodeling and histone acetylation. The main function of the bromodomain proteins (BRD) is the acetylation modification of histones (5). The first BRD was discovered in 1992 (6). Although the BRD is highly conserved structurally, BRD family proteins may be divided into eight distinct subfamilies (I-VIII) based on their secondary structure (5,7). Research has indicated that targeting these BRDs may provide a novel strategy for the treatment of metastatic RCC. The present review summarizes the roles of existing BRD families in related pathways in renal cancer and discusses the efficacy of existing BRD inhibitors and their prospects for clinical application.

2. Acetylation of BRD

Histone modification in transcriptional regulation. In eukaryotic cells, DNA is packaged into chromatin in three processes: The binding of DNA to core histones, the formation of nucleosome core particles and chromosome core particles by core histones (H2A, H2B, H3 and H4) and junctional histones (H1) (8). The functions of histones are divided into the regulation of DNA transcription, DNA replication and DNA repair. Of these, core histones have a critical role in transcriptional regulation mainly through their post-translational modifications (PTMs) (9,10).

Histone modification was the first confirmed PTM. It was first hypothesized by Allfrey *et al* (11) that there was a 'switch' that regulates cellular gene expression. The subsequent discovery of histone acetyltransferase (HAT), histone

deacetylase (HDAC) and the mechanisms that control histone acetylation activity support the hypothesis put forth by Allfrey *et al* (11) on the role of histone acetylation in gene expression (12-14).

However, whether lysine acetylation controls histone activity and how it controls gene activation and repression remain to be fully elucidated. Until the discovery that BRD was the first chromatin 'reader', it was known to exist in the nucleus as an acetyl-lysine (Kac) binding domain and to be associated with numerous transcriptional proteins (6,15). Thus, histone acetylation was established as a fundamental mechanism for regulating gene transcription. However, BRD does not have a role in histone modification alone. Such 'large-scale engineering' may require multiple histone combination modifications or sequential initiation, with BRD acting on one or more histone tails to activate target genes and downstream functions (16,17). BRD-mediated lysine acetylation modifications are a major epigenetic modification in RCC tumor metabolism. BRDs are involved in histone modifications, transcription factor recruitment and transcriptional regulation, and DNA damage repair in RCC as chromatin remodeling factors (5). Furthermore, BRDs have unique structural properties (7).

Structure and function of BRD. BRD consists of 110 amino acids and includes four α helices (αZ, αA, αB and αC) with two distinct interhelical αZ-αA (ZA) and αB-αC (BC) loop regions. The two loops in turn produce a hydrophobic pocket that functions as a module for the recognition of the acetyl-lysine modification (Fig. 1) (15,18). Different BRDs have BRD modules with varying lengths of the ZA and BC loop regions and may contain other types of action modules (19).

BRDs also include other domains, which combine with BRD to perform specific functions (Fig. 2). Certain BRDs contain ATPase structures that enhance the ability to bind Kac, contribute to the assembly of its associated complex, facilitate the movement of the complex along chromatin and coordinate the function of multiple protein docking in chromatin remodeling (20). For instance, ATPase family AAA domain containing 2 (ATAD2) of the ATPase family is directly involved in DNA replication by being recruited to the DNA replication site (21). In addition, ATAD2 has been identified as a chromatin modifier that promotes melanoma (22). Although ATAD2 has not been extensively studied in RCC, studies have indicated an increased risk of developing RCC in patients with melanoma and vice versa. Both may have the same type of genomic mutation (23). Coactivators containing both HAT and BRD structural domains assist substrate recruitment by enabling the HAT-mediated acetylation of multiple lysine residues on histones and transcription factors, thereby promoting transcriptional activation (24). ATPase-containing structures of BRDs enhance the ability to bind Kac, contribute to the assembly of its associated complexes, facilitate the movement of the complexes along chromatin and coordinate multiple protein-protein functions in chromatin remodeling. Unlike other BRDs, BRD and extraterminal (BET) proteins have two tightly packed BRDs that specifically bind diacetylated lysine residues (25,26), promote chromatin opening, recruit transcription factors and coactivators to target gene promoters and enhancers, and activate the RNA polymerase II (Pol II) complex to promote transcriptional elongation (27). Similarly, tandem plant homeodomain (PHD) fingers with BRDs contribute to the assembly and activity of their associated complexes in nucleosomes and act on DNA replication in chromosome segregation (28,29). BRDs are widely involved in the transcription of cancer-related genes, and depending on the subtle differences in BRDs and various combinations of functional groups, highly selective inhibitors may be designed with potential clinical applications for the treatment of metastatic cancers (30).

Functions of BRDs in RCC. The development of RCC mainly includes the following biological behaviors: Angiogenesis, proliferation and immune regulation. In the pathogenesis of RCC, 3p deletion and von Hippel-Lindau (VHL) gene inactivation are the most frequently-occurring mutations (31,32). Their co-mutation has a decisive role in the initiation of RCC. Inactivation of VHL leads to the uncontrolled activation of hypoxia-inducible factor (HIF) target genes that regulate angiogenesis, glycolysis and apoptosis (4). The deletion of these tumor suppressor genes and the activation of oncogenes eventually lead to the development of RCC.

Different BRDs have different roles, which has led to the consideration of different BRDs in RCC (Table I). Angiogenesis is a typical feature of RCC and BRDs may be involved in RCC angiogenesis from different signaling pathways (33), and may even promote angiogenesis in RCC with a low HIF expression (34). Furthermore, the majority of the BRDs mainly function as oncogenic proteins, promoting the proliferation of RCC cells (35-41), and are associated with influencing the occurrence of renal cancer recurrence and metastasis (42). According to the 'braided river' model to interpret RCC (43), the gene mutation of RCC has an evolutionary process. Certain BRDs appear in RCC of more advanced stages and are more likely to cause distant metastasis (39,44,45). Finally, the formation of tumors is also inseparable from changes in immune regulation. The immune-killing effect on the tumor is the main error correction method of the human system. The killing of RCC may be achieved by upregulating IFNα expression (46) and by the induction of $CD4^+$ T-cells (47); polybromo 1 (PBRM1), as a protective factor, may enhance these effects. However, E1A binding protein P300 (EP300)/CREB binding protein (CBP) also leads to the depletion of peripheral lymphocytes (48), and the inhibition of peripheral inflammatory factors by BRD4 diminishes its killing effect on tumor cells (49). On the one hand, different or opposing roles between BRDs and mutations in BRDs are evolutionary in RCC. These generally increase the difficulty of RCC-specific biomarker research. On the other hand, differential mutations in RCC allow patients to select therapeutics with high specificity. In the following sections, the progress of BRDs in RCC is discussed after being classified according to their main roles.

3. Possible functions of oncogenic BRD and their inhibitors in RCC

EP300/CBP. EP300 and CBP, two homologous lysine acetyltransferases (Fig. 2), are homologous transcriptional adapters targeted to the E1A oncoprotein and have a core role in the transcriptional regulation of hypoxia-responsive

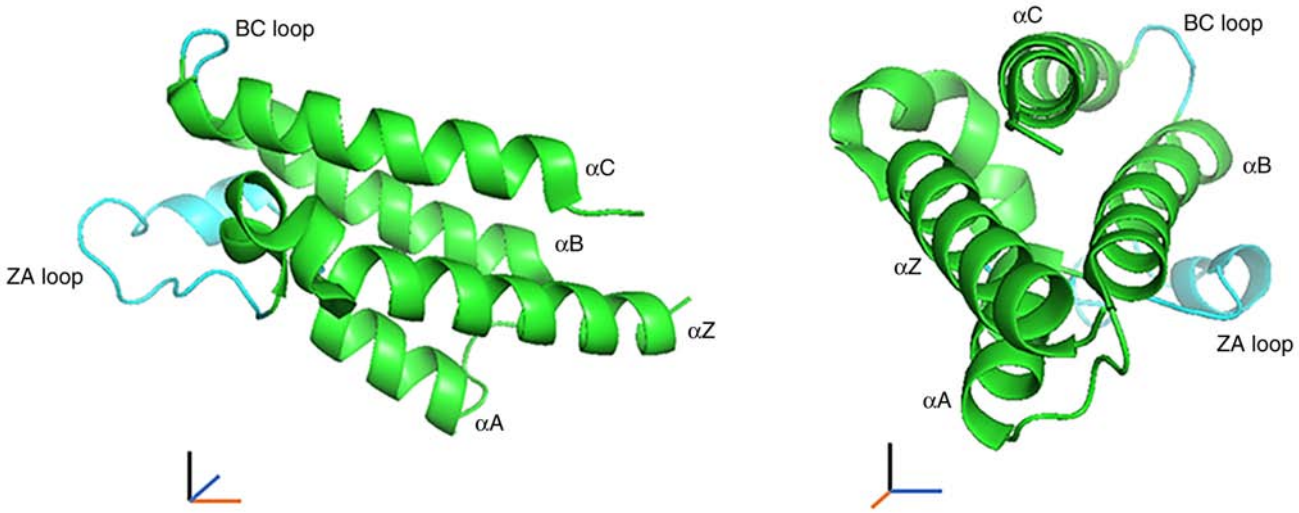

Figure 1. Structure of the first BRD module of BRD4 (PDB ID: 2dww). The four BRD α-helices (αZ, αA, αB and αC) are linked by flexible loop regions (AB, BC and ZA loops). Software used: Python 3.8 and pymol-2.4.0-cp38-cp38-win_amd64. BRD, bromodomain.

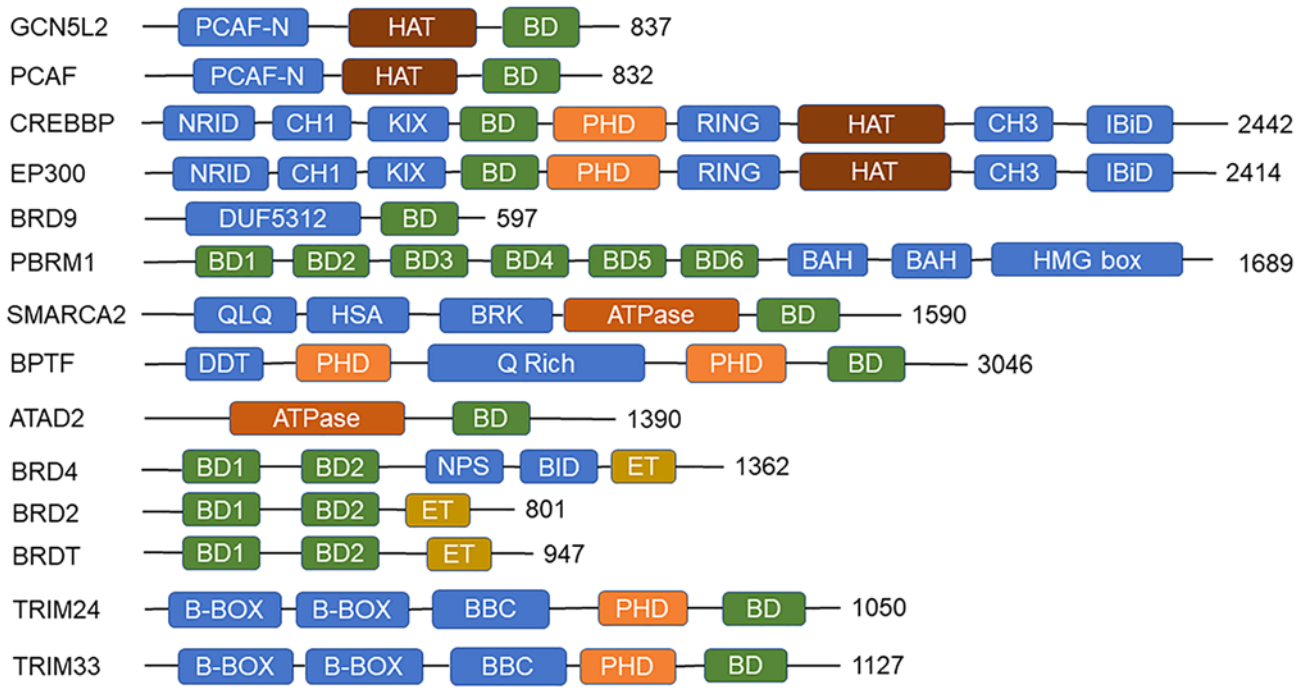

Figure 2. Domain of BRD. The name of the selected protein and the number of amino acids are provided at either end of the graphic presentation. Software used: BioRender (https://app.biorender.com/). GCN5L2, general control of amino acid synthesis protein 5-like 2; PCAF-N, PCAF N-terminal domain; HAT, acetyl transferase; BD, bromodomain; PCAF, P300/CBP-associated factor; EP300, E1A binding protein p300; NRID, nuclear receptor interaction domain; KIX, kinase-inducible domain of CREB-interacting domain; RING, really interesting new gene; PHD, plant homeodomain; CH1, cysteine-histidine-rich region 1; NRID, nuclear receptor interaction domain; CREBBP, CREB Binding protein; BRD9, bromodomain-containing protein 9; DUF3512, domain of unknown function; PBRM1, polybromo 1; BAH, bromo-adjacent homology; HMG, high-mobility group; SMARCA2, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2; QLQ, glutamine-leucine-glutamine domain; HSA, small helicase/SANT associated domain; BRK, brahma and kismet domain; BPTF, bromodomain PHD finger transcription factor; DDT, DNA-binding homeobox and different transcription factors domain; Q-rich, glutamine-rich domain; ATAD2, ATPase family AAA domain containing 2; ATPase, ATPase domain; BRD4, bromodomain-containing protein 4; NPS, N-terminal cluster of phosphorylation sites; BID, basic residue enriched interaction domain; ET, extra-terminal domain; BRD2, bromodomain-containing protein 2; BRDT, bromodomain testis associated; TRIM24, tripartite motif containing 24; B-Box, B-box-type zinc finger domain; BBC, B-box, C-terminal domain; TRIM33, tripartite motif-containing 33.

genes (50). EP300/CBP interacts with EP300/CBP-associated factor (PCAF) to function in the normal cell cycle. However, EP300/CBP is overexpressed in RCC, while PCAF is frequently demonstrated to be absent as a tumor suppressor gene (51).

EP300/CBP promotes cell growth and angiogenesis in RCC through acetylation modification. EP300/CBP functions as a co-transcription factor and forms a transcriptional complex with proteins such as HIF1α to recruit to the promoter of VEGF (52,53), and HIF-1α transcriptional activation or

Table I. BRDs in RCC.

Class	Gene name	Alias	Function	Role in RCC	(Refs.)
Histone acetyltransferase	GCN5L2	KAT2A, GCN5, PCAF-B	Histone acetyltransferase	Carcinogenic	(99)
	PCAF	KAT2B	Histone acetyltransferase	Cancer inhibition	(102)
	EP300	p300, KAT3B, MKHK2, RSTS2	Transcriptional coactivator	Carcinogenic	(35)
	CREBBP	CBP, KAT3A, MKHK1, RSTS1	Chromatin remodeling factor, transcriptional coactivator	Carcinogenic	(50)
Subunits of the SWI/SNF complex	BRD9	FLJ13441, LAVS3040, PRO9856, SMARCI2	Transcriptional regulator	Carcinogenic	(39)
	PBRM1	PB1, HPB1, BAF180, SMARCH1, RCC	Chromatin remodeling factor	Cancer inhibition	(90) (91)
	SMARCA (A/B)	BRM, HBRM, SNF2L2, BAF190, SNF2A, HSNF2a, NCBRS	Chromatin remodeling factor	Cancer inhibition	(95)
ISWI family of chromatin remodeling factors	BPTF	FAC1, FALZ, NURF301	Chromatin remodeling factor	Carcinogenic	(44)
ATPase family	ATAD2	ANCCA, CT137, PRO2000, MGC5254	Transcriptional coactivator	Carcinogenic	(38)
BET family proteins	BRD4	CAP, MCAP, HUNK1	Transcriptional regulator	Carcinogenic	(49)
	BRD2	FSH, RING3, KIAA9001, D6S113E, FSRG1, NAT, RNF3	Transcriptional regulator	Carcinogenic	(37)
	BRDT	BRD6, CT9, SPGF21	Transcriptional coactivator	Carcinogenic	(41)
TRIM family proteins	TRIM24	TIF1α, PTC6, RNF82, TIF1A	Transcriptional activator	Carcinogenic	(40)
	TRIM3 (A/B)	TIF1-γ, PTC7, RFG7, KIAA1113, TIF1G, FLJ11429, ECTO	E3 ubiquitin protein ligase, transcriptional inhibitor	Cancer inhibition	(103)

BRD, bromodomain protein; GCN5L2, general control of amino acid synthesis protein 5-like 2; PCAF, EP300/CBP-associated factor; CREBBP, CREB binding protein; PBRM1, polybromo 1; BPTF, BRD PHD finger transcription factor; ATAD2, ATPase family AAA domain containing 2; TRIM, tripartite motif-containing; EP300, E1A binding protein P300; SMARCA2, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 2; RCC, renal cell carcinoma.

transcriptional repression is dependent on EP300/CBP (54). Consistent with HIF1α, HIF2α induces EP300/CBP recruitment so that it not only binds specifically to the enhancer of HIF2α to promote HIF2α expression for RCC cell growth, but also promotes RCC angiogenesis by enhancing VEGF transcription (55). In addition, HIF1α and HIF2α induce the recruitment of EP300/CBP at the promoter of telomerase reverse transcriptase, promoting the immortalization and

transformation of renal cancer cells (56). Furthermore, EP300/CBP binding to H3AcK18 enhances RCC cell viability, adhesion and invasiveness (35).

EP300/CBP also promotes RCC progression by promoting macrophage infiltration through the RNA-binding motif protein 15 (RBM15)-C-X-C motif chemokine ligand 11 signaling axis (57). In addition, EP300/CBP upregulation is also associated with T-cell dysfunction. EP300/CBP reduces tumor-infiltrating lymphocytes by downregulating immune checkpoint gene expression via binding to serine and arginine-rich splicing factor 2 and cause immune escape of RCC cells (48).

EP300/CBP is structurally and functionally complex; however, it currently only has two related inhibitors in RCC. Inhibitors targeting the BRD binding of EP300/CBP include C646, which effectively inhibits EP300/CBP (57). HBS1, a high-affinity ligand of cysteine-histidine-rich region 1, functions as an antibody to HIF1α, but is able to block the binding of HIF1α to the CH300 structural domain of EP300/CBP without affecting normal cell function (58).

The BET family: BRD4, BRD2 and BRD testis associated (BRDT)

BRD4. BRD4 is highly expressed in RCC (36). BRD4 is a transcriptional and epigenetic regulator that has a crucial role in transcription (59,60). BRD4 has multiple substrate binding sites and a common kinase structural domain that phosphorylates Pol II, the proto-oncogene C-MYC and the transcription factors TATA-box binding protein associated factor 7 (a component of the TFIID complex, controls the first steps of transcription) and cyclin-dependent kinase (CDK)9. BRD4 is also a scaffolding protein that interacts with chromatin modifiers and transcription factors, including recruiting transcription factors and transcription elongation factor b (61).

Normally, BRD4 is inhibited by caspase-3, leading to the pyroptosis of RCC cells. When BRD4 is activated, it inhibits the production of the peripheral inflammatory factors, IL-1β and IL-18, by cells. This allows immune evasion of RCC from IL-1β and IL-18 (49), promotes RCC cell proliferation and epithelial-mesenchymal transition (EMT) and inhibits tumor killing by peripheral T-cells (62). Another study demonstrated that BRD4 acetylation modified the histones of B-cell lymphoma-2 (BCL2) and C-MYC to increase their expression (36). MYC is a heterogeneous gene fragment frequently activated in cancer, and targeting BRD4 may inhibit its expression (63). This suggests that BRD4 upregulation is closely related to RCC; the inhibition of BRD4 gene expression and the enhancement of peripheral inflammatory factors may become a novel treatment strategy for metastatic RCC.

BRD4-related drugs have been tested *in vivo* and *in vitro*. JQ1, a BET inhibitor, has been demonstrated to inhibit RCC (49). JQ1 not only acts on ordinary RCC (36), but also exerts a notable inhibitory effect on sunitinib-resistant RCC (64). There are other BET inhibitors, such as physachenolide C, which enhances T-cell-mediated tumor cell killing through the targeted inhibition of BRD4 (62). High selectivity is a prominent indicator of the inhibitory effect: BDF-1253 leads to a ~4-fold greater inhibition of BRD4 compared to the prototype, nitroxibenzylidine, and exhibits suitable selectivity for BET proteins over other BRDs or epigenetic modifiers (37). The effective blockade of BRD4 downstream gene expression by inhibiting BRD4 induces cell cycle arrest and apoptosis, impairs RCC cell viability and reduces RCC cell growth (36).

Pharmacological studies on kidney cancer cells have revealed that BRD4 and the PI3K/mTOR pathway complement each other to promote the proliferation of kidney cancer cells. VS-5584, a dual inhibitor of PI3K/mTOR, may effectively inhibit the proliferation and survival of RCC cells (65), but leads to increased BRD4 expression, resulting in enhanced tumor drug resistance. By contrast, the simultaneous inhibition of BRD4 and PI3K/mTOR significantly inhibits tumor cell survival and does not increase tumor drug resistance. Furthermore, the dual inhibitor of mTORC1/2 (Palomid 529) has been found to be more effective in BRD4-negative RCC cells than normal RCC cells (66), demonstrating that BRD4 and the PI3K/mTOR pathway have a complementary effect on each other. By contrast, SF2523 is a dual inhibitor of BRD4 and PI3K-AKT; SF2523 is more effective than the PI3K inhibitor and JQ1 in killing RCC cells (67). Furthermore, the BET inhibitor OTX015 exerts a therapeutic effect on cancer patients with deletion of BRCA1-associated protein 1 (BAP1), a ubiquitin carboxy-terminal hydrolase (68); patients with a BAP1 deletion in RCC tend to have poor prognosis (69).

The aforementioned inhibitors exert potent effects by inhibiting BRD4 or when BRD4 is inhibited (Fig. 3). The inhibition of BET family members has great therapeutic potential in the treatment of RCC. Currently, clinical resistance to BET inhibitors limits their application; however, synergistic antitumor effects have been observed when used in combination with other tumor suppressors (70). Therefore, the design of BET BRDs dual-target inhibitors and their combination is a reasonable strategy, which may be used to enhance the efficacy of cancer therapy and reduce drug resistance. However, extensive animal studies are still required to verify the efficacy and toxicology prior to clinical application.

BRD2. BRD2 may be a surrogate for BRD4 (37). JQ1, a BET inhibitor, is also partially selective for BRD2 and BRD3 (64). Researchers have found overexpression of both BRD2 and BRD4 BET family proteins in RCC. It has also been indicated that knockdown of BRD2 or BRD4 only moderately inhibits RCC cell proliferation. However, co-knockdown of BRD2 and BRD4 results in significant inhibition of BCL2 and C-MYC oncoprotein expression, thereby reducing the proliferation of RCC cells. This indicates the compensatory effect between members of the BET family (37).

BRDT. BRDT functions as a chromatin remodeling factor in recognizing acetylated histones and recruiting transcriptional complexes (71). It interacts with eukaryotic translation initiation factor 4E-binding protein 1 (eIF4EBP1) to promote C-MYC transcription and RCC progression. BRDT inhibitor PLX51107 exerts an inhibitory effect on RCC cells; however, eIF4EBP1 overexpression hinders its inhibitory effect (72). Therefore, dual inhibitors of both proteins or a combination of both inhibitors may be required for clinical application in RCC. The initiation of BET family proteins in RCC does not appear to proceed via a sole mechanism, i.e. not only in terms of the binding of BETs to other proteins, but also among BETs (64), which complement each other while interacting.

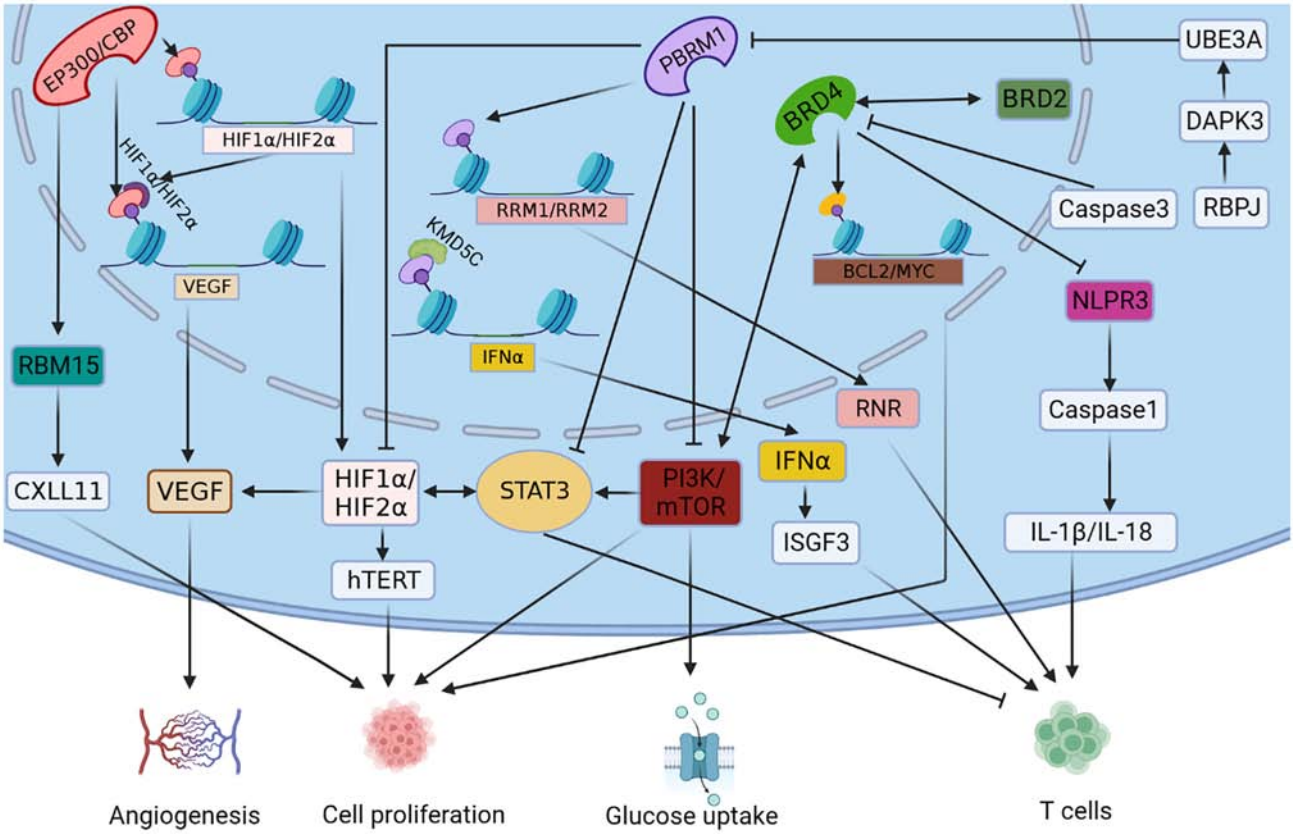

Figure 3. BRD regulate important carcinogenic factors through histone modification. The EP300/CBP complex promotes the expression of RBM15 and downstream CXCL11 and SRSF2 expression. Furthermore, EP300/CBP recruits STAT3 and promotes MYC expression. EP300/CBP binds to HIF1α and HIF2α and promotes angiogenesis. In PBRM1-inactivated RCC cells, the increase in HIF1α/HIF2α expression promotes tumor tissue angiogenesis. The inactivation of *PBRM1* also results in uninhibited STAT3 and PI3K pathways, promoting RCC development. In RCC, RBPJ promotes the production of DAPK3, which competes with PKA for the binding site of UBE3A, ultimately degrading PBRM1 and promoting RCC proliferation. BRD4/BRD2 promotes PI3K/mTOR pathways and the expression of BCL2 and MYC. It also inhibits T-cell infiltration in tumor tissues by inhibiting NLPR3. Software used: BioRender (https://app.biorender.com/). EP300, E1A binding protein P300; CBP, CREB binding protein; RBM15, RNA-binding motif protein 15; CXCL11, C-X-C motif chemokine ligand 11; SRSF2, serine and arginine-rich splicing factor 2; STAT3, signal transducer and activator of transcription 3; HIF, hypoxia-inducible factor; BRD, bromodomain protein; RCC, renal cell carcinoma; RBPJ, recombination signal binding protein for immunoglobulin kappa J region; DAPK3, death associated protein kinase 3; PKA, protein kinase A; UBE3A, ubiquitin protein ligase E3A; p21, one of the downstream target genes of p53; NLRP3, NOD-like receptor thermal protein domain associated protein 3.

Other oncogenic BRDs

BRD PHD finger transcription factor (BPTF). BPTF contains two PHD fingers and a BRD that regulates gene transcription by interacting with the MYC-associated zinc finger protein, ZF87/MAZ (73). BPTF is a subunit of the ISWI chromatin remodeling complex, NURF, and has a crucial role in chromatin remodeling as a transcription factor (74). The increased expression of BPTF causes glycolytic reprogramming and distant lung metastasis in RCC. Its inhibitor, AU1, is effective in inhibiting the metastatic potential of patient-derived cells, metastatic RCC-derived organoids, as well as *in situ* xenograft models of metastatic RCC, suggesting that BPTF may be applied as an initial therapeutic marker for metastatic RCC (44).

ATPase family AAA domain containing 2 (ATAD2). There are two isoforms of human ATAD2, ATAD2A and ATAD2B (75). However, the majority of published functional studies have been performed on ATAD2A (21,75,76). ATAD2 is an emerging oncoprotein, a potential biomarker and a potent cancer drug target. In RCC, ATAD2 has been found to be a novel gene that is associated with prognosis, and its high expression increases the risk of RCC progression (77). By knocking down and overexpressing ATAD2, it has been found that its overexpression promotes RCC progression (38).

BRD9. BRD9 is highly expressed in HIF2α-deficient RCC. SOX17 recruits BRD9 to upregulate genes in RCC pathogenesis, including VEGFR2 (34). There is a negative correlation between the expression of BRD9 and HIF2α, and the expression of related genes is upregulated by BRD9 to target the Notch1-Hes1 signaling pathway to promote the proliferation, migration and invasion of RCC cells (39). A previous study demonstrated that BRD9 inhibitor (I-BRD9, also known as GSK602) effectively inhibited tumor growth *in vitro* and *in vivo*. It also prolonged the survival of RCC mice compared to sunitinib (34). Due to HIF activation in RCC caused by VHL inactivation, targeting HIF2α and applying anti-angiogenic targeted drugs are considered mainstream therapeutic approaches for metastatic RCC (78). A lower expression of HIF2α in RCC was indicated to be associated with a lower survival rate and prognosis. Hence, the search for novel drug targets in HIF2α-deficient RCC may be promising. BRD9 is expected to be a valuable target for the treatment of HIF2α-deficient RCC.

4. Tumor suppressor BRD in RCC

PBRM1 regulates multiple biological processes of RCC. PBRM1 is frequently mutated in human tumors and PRBM1 comprises 1,689 amino acids. PBRM1 is characterized by a C-terminal high migration pattern, including two bromine-associated homologous structural domains and six bromine structural domains (79). These bromine structural domains combine with acetylated residues at the histone tail (80), and each bromine domain has a different affinity for the specific acetylated peptides on the histones and may coordinate with the exact pattern of acetylated lysine residues in the nucleosome (81,82). Previous studies suggested that RCC is characterized by partial loss of chromosome 3p, while *PBRM1* resides on 3p and has deletion mutations at a relatively high frequency, just second only to *VHL* in RCC, accounting for ~30-40% of RCC cases (79,80,83). As *PBRM1* is a tumor suppressor, the deletion mutation of *PBRM1* combined with *VHL* deletion produces stable tumor models (84,85).

RCC develops its mutations differently and at different time-points. In certain RCC cell lines, PBRM1 may remain present following the deletion of *VHL*. The deletion mutation or suppressed state of PBRM1 may be caused by other factors. For instance, recombination signal binding protein for immunoglobulin kappa J region (RBPJ) promotes death-associated protein kinase 3 binding to ubiquitin-protein ligase E3A (UBE3A), destabilizing PBRM1 in RCC cells and thereby reducing the protective effect of PBRM1 on normal renal tissue. UBE3A knockdown increased the sensitivity of CDK inhibitors, and RBPJ inhibitors modulate CDK4/6 inhibitor drug sensitivity to improve tumor suppression (86). By inhibiting PBRM1 upstream as described above, the presence of PBRM1 has been found to exert protective effects on normal kidney tissue, suggesting that it inhibits the action of common oncogenic factors in RRC. However, following the knockdown of PBRM1, it has been found that PBRM1 deletion did not allow for the inhibition of the HIF1/STAT3 signaling pathway in the kidney, and PBRM1 deletion attenuated the activity of the negative regulator of mTORC1, TSC1, facilitating mTORC1 activation and leading to advanced RCC (84,87). In addition, deletion of PBRM1 enhanced the hypoxic response, leading to increased induction of HIF1α and HIF2α, which promoted angiogenesis and cell proliferation in kidney cancer (88,89). The simultaneous knockdown of both PBRM1 and VHL genes in RCC cell lines also resulted in the activation of HIF and in the upregulation of PI3K signaling, promoting glucose uptake and adhesion in RCC cells (Fig. 3) (90,91).

PBRM1 deficiency is not only involved in angiogenesis following the induction of hypoxia, but also allows tumor cells to acquire the related functions of immune evasion. PBRM1 recruits lysine demethylase 5C to upregulate IFNα gene expression and acts on IFN-stimulated gene factor 3 to inhibit RCC progression (46). Furthermore, PBRM1 has been found to bind directly to the RRM1 and RRM2 sites and promote the infiltration of CD4 T-cells in the peripheral tissues of RCC (47). As with anti-vascular targeting agents, anti-programmed cell death 1 agents are associated with improved clinical prognosis in patients with *PBRM1*-deficient mutated RCC (92). This suggests that *PBRM1*-deficient RCC is sensitive to targeted drugs and immune agents.

Other tumor suppressor BRDs in RCC

SMARCA2. SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin subfamily A member 2 (*SMARCA2*)S mutations are highly associated with VHL inactivation, an elevated tumor grade and a relatively poorer prognosis (93,94). RCC cells in the G2/M phase are promoted to undergo apoptosis and cell cycle arrest by *SMARCA2* mutations, not only by *SMARCA2* deletion but also by epigenetic silencing of SMARCA2. Therefore, the inhibition of *SMARCA2* transcription has a carcinogenic role (95), and the restoration of SMARCA2 expression by a HDAC3 inhibitor (RGFP966) effectively inhibited tumor progression in RCC (96). The restoration of the expression of tumor suppressor genes may thus be an effective strategy for the treatment of RCC.

5. Different functions of homologous BRD

General control of amino acid synthesis protein 5-like 2 (GCN5L2) and PCAF. GCN5L2 was the first histone acetyltransferase identified with an N-terminal structural domain, a conserved HAT structural domain and a C-terminal bromine structural domain (97). The aforementioned three structural domains are also found in PCAF, with only one molecular weight difference between the two (Fig. 2). The two proteins have approximately the same function, although PCAF can be methylated (98). Furthermore, both have opposite effects on RCC outcomes. The overexpression of GCN5L2 upregulates monocarboxylate transporter 1 (MCT1), thus promoting glycolysis in RCC cells. The proliferation of RCC cells with a high GCN5L2 expression may be significantly inhibited by an MCT1 inhibitor (AZD3965) (99).

PCAF is known as GCN5-related N-acetyltransferase in the lysine acetyltransferase family (100). As previously mentioned, PCAF (the EP300/CBP-associated factor) is a tumor suppressor gene in RCC (101). NADPH oxidase (NOX)4 functions as a mitochondrial energy sensor and the derived reactive oxygen species inhibit the acetylation of PCAF, promote metabolic reprogramming and enhance drug resistance in RCC cells (102). Promoting PACF expression or inhibiting NOX to reduce drug resistance in RCC may be a novel therapeutic approach.

Tripartite motif-containing (TRIM)24 and TRIM33. The TRIM family is a class of proteins with E3 ubiquitin ligase activity. Its members include a number of key biological processes, including autophagy, carcinogenic, intracellular signaling, protein ubiquitination and innate immunity (103). TRIM24 and TRIM33 form chromatin remodeling complexes with heterochromatin protein 1 and HDAC, with chromatin remodeling, mainly of different molecular weights (Fig. 2) (104). However, the two have distinct roles in the progression of RCC. In RCC, the transcription of TRIM24 is regulated by bone morphogenetic protein (BMP)8A, and the upregulation of TRIM24 by BMP8A enhances the Wnt-regulated Wnt signaling pathway, thus promoting proliferation, invasion, and metastasis and drug resistance (40,45).

In contrast to TRIM24, TRIM33 functions as a tumor suppressor in RCC and its overexpression inhibits β-linked proteins on the Wnt signaling pathway, which reduces the

Table II. Inhibitors.

Inhibitor	Target protein	Type of experiment	(Refs.)
CPTH2	EP300/CBP	Cell experiments	(35)
C646	EP300/CBP	Cell and animal experiments	(57)
HBS1	EP300/CBP	Cell and animal experiments	(58)
SF2523	BRD4, P13K	Cell and animal experiments	(67)
JQ1	BET	Cell and animal experiments	(36)
BDF1253	BET	Cell and animal experiments	(37)
PCC	BET	Cell experiments	(62)
OTX015	BRD2/3/4	Cell and animal experiments	(68)
AU1	BPTF	Cell and animal experiments	(44)
AZD3965	MCT1 (downstream signaling of GCN5L2 is blocked)	Cell and animal experiments	(99)
RGFP966	HDAC3 (expression of SMARCA2 returned to normal)	Cell and animal experiments	(96)
PLX51107	BRDT	Cell and animal experiments	(72)

CPTH2, a histone acetyltransferase inhibitor; C646, a selective small molecule inhibitor of EP300/CBP; AU1, GSK1379725A, a BRD PHD finger transcription factor antagonist; HBS1, a high-affinity ligand of cysteine-histidine-rich region 1, an EP300/CBP inhibitor; RGFP966, an inhibitor of histone deacetylase 3; SF2523, a PI3K/BRD4 inhibitor; JQ1, a BET inhibitor; BDF1253, a BET inhibitor; PLX51107, a BET inhibitor; PPC, a BET inhibitor; OTX015, a BET inhibitor; AZD3965, an inhibitor of monocarboxylate transporter 1. CPTH2, cyclopentylidene-[4-(4-chlorophenyl)thiazol-2-yl]hydrazone; PPC, physachenolide C; C646, ChemBridge#5838646; EP300, E1A binding protein P300; CBP, CREB binding protein; BET, BRD and extraterminal; BRD, bromodomain protein.

expression of cyclin D1 and C-MYC. Consequently, TRIM33 inhibits the growth of RCC and leads to the upregulation of E-calmodulin expression and the downregulation of N-calmodulin to reduce the EMT potential of RCC cells (103). In addition, the overexpression of TRIM33 significantly inhibits TGFβ-induced Smad activation, inhibiting RCC progression (105).

6. Clinical value of BRD

Large-scale studies have identified mutations in BRDs that cause dysfunction and lead to cancer development. BRDs are intimately involved in the regulation of gene transcription; therefore, the inhibition of BRD structural proteins is considered a strategy for targeting oncogenic transcription factors that have long been considered attractive drug targets, but cannot be directly regulated with small molecule inhibitors. This can also be tailored to the nature of the tumor, with different transcriptional repression. For instance, BET inhibition has been shown to block the association of MYC with BRD4 and MYC transcription (61,63). In anti-angiogenesis, the transcriptional expression of HIF, VEGF and VEGFA can be reduced by targeted inhibition of BRDs (33,34). In immunotherapy, immune checkpoints can be suppressed by targeting and inhibiting BRDs or activating BRDs to restore the transcriptional activity of antitumor factors (46-48). As presented in Table II, a large number of related drugs (Fig. S1) have been applied to basic studies on RCC and these have exhibited improved tumor-suppressive effects by directly inhibiting BRD or its downstream functional molecules. Targeting BRD structural proteins holds promise in clinical practice; however, to date, at least to the best of our knowledge, no clinical trials have been performed on RCC.

7. Conclusions and future perspectives

RCC is a common disease of the urinary system; however, its development process is highly complex, while research on BRDs has provided certain insight. BRDs are fully involved in the proliferation, angiogenesis and immune regulation of RCC, and supplement the signaling pathways of these cellular behaviors. Inhibiting the expression of these oncogenes or restoring the expression of those tumor suppressor genes may exert a notable inhibitory effect on RCC and may provide a potential solution for RCC resistance to VEGF-targeted drugs. Of note, the aforementioned studies on BRD molecules have revealed information regarding the promotion or inhibition of RCC; however, the specific underlying mechanisms remain to be fully elucidated and further in-depth research is required, as clinical trials on related inhibitors are lacking.

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Availability of data and materials

Data sharing is not applicable to this article, as no new data were generated or analyzed during the current study.

Authors' contributions

QW and HL wrote the manuscript. KL, WC and XZ acquired the data. JX and JG interpreted the data. JZ and XZ made substantial contributions to conception and design. All authors contributed to the article and approved the submitted version. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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