

# Targeting BRD9 for Cancer Treatment: A New Strategy

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**Abstract:** Bromodomain-containing protein 9 (BRD9) is a newly identified subunit of the non-canonical barrier-to-autointegration factor (ncBAF) complex and a member of the bromodomain family IV. Studies have confirmed that BRD9 plays an oncogenic role in multiple cancer types, by regulating tumor cell growth. The tumor biological functions of BRD9 are mainly due to epigenetic modification mediated by its bromodomain. The bromodomain recruits the ncBAF complex to the promoter to regulate gene transcription. This review summarizes the potential mechanisms of action of BRD9 in carcinogenesis and the emerging strategies for targeting BRD9 for cancer therapeutics. Although the therapeutic potential of BRD9 has been exploited to some extent, research on the detailed biological mechanisms of BRD9 is still in its infancy. Therefore, targeting BRD9 to study its biological roles will be an attractive tool for cancer diagnosis and treatment, but it remains a great challenge.

**Keywords:** BRD9, ncBAF, bromodomain, cancer, inhibitor

## Introduction

The switch/sucrose non-fermentable (SWI/SNF) complex, a chromatin remodeling complex whose subunits are mutated in most malignant tumors, is one of the most common chromatin regulators in human malignancies.<sup>1</sup> It is typically divided into two categories based on the subunit composition and function: the barrier-to-autointegration factor (cBAF) complex and polybromo-associated BAF (PBAF) complex. The core subunits of the cBAF complex are BAF250a (*ARID1A*) and BAF250b (*ARID1B*), and those of the PBAF complex are BAF180 (*PBRM1*) and BAF200 (*ARID2*).<sup>2,3</sup> In addition to the core subunits, 7–15 auxiliary subunits such as BRM (*SMARCA2*), BRG1 (*SMARCA4*), BAF155 (*SMARCC1*), BAF170 (*SMARCC2*), and BAF47 (*SMARCB1*) participate in the assembly of the SWI/SNF complex.<sup>4</sup> Numerous studies have established that the SWI/SNF complex is altered in many tumor types. For example, in malignant rhabdoid tumors (MRT),<sup>5–7</sup> biallelic inactivation of *SMARCB1* was first reported, and thereafter, in myoepithelial tumors<sup>8</sup> and hepatoblastomas,<sup>9</sup> repeated mutations were reported. In adenoid cystic carcinoma,<sup>10</sup> *SMARCA2*, *SMARCE1*, and *ARID1A* genes were reported to be mutated. Several studies have revealed that *SMARCA4* undergoes mutations at different frequencies in Burkitt's lymphoma,<sup>11</sup> lung adenocarcinoma,<sup>12</sup> esophageal adenocarcinoma,<sup>13</sup> and medulloblastoma.<sup>14–16</sup> Moreover, researchers have found that the mutation frequency of *ARID1A*, which encodes the BAF250a subunit, is high in hepatocellular carcinoma,<sup>12,17</sup> gastric

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cancer,<sup>18,19</sup> bladder cancer,<sup>20,21</sup> colorectal cancer,<sup>22</sup> pancreatic cancer,<sup>23</sup> Burkitt's lymphoma,<sup>11</sup> and cholangiocarcinoma.<sup>24</sup> Overall, these studies have indicated that the SWI/SNF complex plays a critical role in the development and progression of human malignant tumors and could be a therapeutic target.

Notably, Wang et al<sup>25</sup> defined a third category of the SWI/SNF complex in mouse stem cells: the non-canonical BAF (ncBAF) complex. BRD9 and glioma tumor suppressor candidate gene 1 (*GLTSCR1*) or *GLTSCR1*-like (*GLTSCRIL*) are unique members of the ncBAF complex. In addition, the ncBAF complex contains the following BAF subunits: BAF155, BAF60, SS18, BAF53a, and BRG1/BRM.<sup>26</sup> Moreover, the ncBAF complex has not been reported to mutate repeatedly in cancer, unlike the cBAF and pBAF complexes. A study reported that prostate cancer cell line (PC3) proliferation and colony formation was dependent on *GLTSCR1* expression, and knocking out *GLTSCR1* could decrease PC3 cell proliferation and colony formation.<sup>26</sup> Meanwhile, another study demonstrated that BRD9 was highly expressed and required for in SMARCB1-deficient MRT cells.<sup>25</sup> In addition, researchers found that the protein level of BRD9 was significantly increased in acute myeloid leukemia (AML) cells than in CD34<sup>+</sup> cells.<sup>27</sup> Kang et al<sup>28</sup> confirmed the presence of BRD9 amplification on chromosome 5p in patients with non-small cell lung cancer (NSCLC) through high-resolution array comparative genomic hybridization analysis. A previous study revealed that the gene copy number of BRD9 was significantly increased in the 5p15.33 region in 12.5% (2/16) of patients with papillary thyroid carcinoma.<sup>29</sup> Similarly, based on single nucleotide polymorphism and fluorescence in situ hybridization analyses, Luigi Scotto et al<sup>30</sup> demonstrated that BRD9 protein was overexpressed in cervical cancer. In addition, studies have demonstrated that BRD9 acted as a co-factor to stabilize the structure of the SS18-SSX fusion and to maintain its oncogenic transcription in synovial sarcoma (SS).<sup>31–33</sup> These findings were in line with the finding that BRD9 and SS18-SSX were co-localized.<sup>34</sup> Furthermore, BRD9 has been inextricably linked to inflammation and type 2 diabetes due to  $\beta$ -cell dysfunction.<sup>35–37</sup> Wei et al<sup>38</sup> confirmed that BRD9 inhibitors could restore  $\beta$ -cell function and reduce inflammation to a certain extent. Based on Kyoto Encyclopedia of Genes and Genomes analysis and Gene Set Enrichment Analysis, researchers found that genes involved in oxidative phosphorylation and the ribosomal pathway were significantly upregulated in cancers

with BRD9 amplification, such as liver cancer and sarcoma.<sup>39</sup>

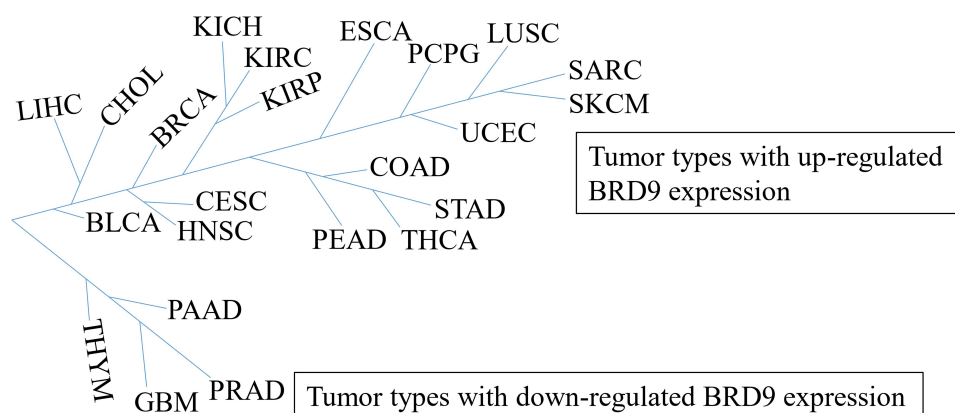
Interestingly, BRD9 appears to play a significant role in tumor suppression. *SF3B1* is an RNA splicing factor that is frequently mutated in various cancer types, such as myelodysplasia,<sup>40,41</sup> chronic lymphocytic leukemia,<sup>42</sup> and melanoma.<sup>43</sup> Inoue et al<sup>44</sup> suggested that mutant *SF3B1* recognized BRD9 introns and induced mis-splicing of BRD9, which ultimately led to the degradation of BRD9, and thus, promoted melanomagenesis. The whole exome sequencing revealed that BRD9 is one of the susceptibility genes for melanoma, and Gene Ontology analysis revealed that BRD9 is involved in cellular processes, such as DNA replication, DNA repair, and cell response to DNA damage stimuli.<sup>45</sup> Furthermore, Park et al<sup>46</sup> reported that the combination of BRD9 and lysine-specific histone demethylase 1 (LSD1) inhibitor may be a potential novel treatment for Merkel cell carcinoma (MCC), they claimed that LSD1 inhibition reduces the growth of MCC whereas inhibition reverses, at least partially, the anti-cancer benefit of LSD1 inhibition. Moreover, the AIPuFu database analysis revealed that BRD9 was differentially expressed in 23 malignancies (Figure 1); however, the function of BRD9 in these tumor types is yet to be determined, which will be interesting and meaningful.

Overall, these studies have indicated that BRD9 plays a critical role in tumor development. It is essential to explore the molecular mechanism of BRD9 in cancer progression, and targeting BRD9 will provide new directions for disease prevention and treatment.

## BRD9 Structure

BRD9 contains a bromodomain and a DUF3512 domain.<sup>27</sup> Although many researchers have focused on the bromodomain to determine the biological function of BRD9, few have studied the function of the DUF3512 domain. Till date, we only know that the DUF3512 domain is essential for the assembly of the ncBAF complex.<sup>25</sup>

"Epigenetics" first defined by Conrad Waddington, is a discipline that studies heritable changes in gene expression without involving changes in the nucleotide sequence of genes.<sup>47</sup> These changes include DNA modifications (such as DNA methylation), covalent histone modifications (such as histone methylation, phosphorylation, acetylation, and ubiquitination), and RNA-mediated gene silencing.<sup>48,49</sup> Functional bromodomains, usually approximately to 100 amino acids in length, can specifically recognize acetylated lysine residues on histone tails, and



**Figure 1** The tumor types with BRD9 differential expression. BRD9 is highly expressed in 19 cancer types including CHOL, LIHC, and BRCA, but is lowly expressed in four cancer types, such as THYM, PAAD, GBM and PRAD. According to the AIPuF database, the URL: <http://www.aipufu.com/index.html>.

recruit different chromatin-modifying factors to specific sites to participate in transcription regulation.<sup>50,51</sup> One common feature among all bromodomains: is that they have a hydrophobic pocket to which acetylated lysine residues bind. This hydrophobic region is formed between the helices  $\alpha Z$  and  $\alpha A$  (ZA loop) and between the helices  $\alpha B$  and  $\alpha C$  (BC loop).<sup>52</sup> Histone acetylation is involved in protein stabilization,<sup>48</sup> DNA repair,<sup>53</sup> signal transduction,<sup>54</sup> and post-translational modifications.<sup>55–57</sup> Studies have indicated that an acetylated lysine is recognized and immobilized on a conserved asparagine residue in the hydrophobic pocket.<sup>58,59</sup> The bromodomain family is divided into 8 subfamilies based on structural differences. BRD9, Bromodomain-containing protein 7 (BRD7), bromodomain and PHD finger containing 1 (BRPF1), bromodomain and PHD finger containing 2 (BRPF2), bromodomain and PHD finger containing 3 (BRPF3), ATPase family AAA domain containing 2 (ATAD2), and ATPase family AAA domain containing 2B (ATAD2B) belong to the bromodomain family IV.<sup>60</sup> The BRPF1 protein is a component of the MOZ/HAT complex, and its bromodomain recognizes H2AK5ac, H4K12ac, H3K14ac, H4K8ac, and H4K5ac.<sup>61</sup> BRPF2 and BRPF3 have high sequence similarity and are the subunits of the HBO1/HAT complex, which can acetylate histone H4.<sup>62</sup> The HBO1/HAT complex is reportedly involved in DNA transcription and replication, and these processes are inseparable from the contribution of BRPF2/BRPF3.<sup>63</sup> Although ATAD2 and ATAD2B are highly conserved, their functions appear to be quite different.<sup>64</sup> ATAD2 is mainly located in reproductive tissues,<sup>65,66</sup> and its bromodomain can recognize H4K5ac,<sup>67</sup> H4K12ac, and H4K5acK12ac;<sup>68</sup> ATAD2B is

expressed in neural tissues,<sup>69</sup> and its bromodomain and histone ligand have not been fully studied. BRD7 and BRD9 are the subunits of the PBAF and ncBAF complexes, respectively. Their bromodomains are highly homologous.<sup>70</sup> However, their roles in tumor progression are quite different. BRD7 has been reported as a tumor suppressor,<sup>71</sup> whereas BRD9 plays a role in cancer promotion.<sup>27</sup> Although few biological ligands for the BRD9 bromodomain are known, BRD9 has been demonstrated to bind to diacetylated H4K5acK8ac and dipropionylated H4K5prK8pr.<sup>72</sup>

## Potential Mechanisms of BRD9 BRD9-STAT5 Axis Participates in Tumor Progression

A recent study reported that the proliferation of AML cells depends on the function of BRD9.<sup>27</sup> BRD9 is enriched in the downstream region of the MYC promoter and drives its transcription. Further analysis of this process revealed that the role of BRD9 in AML depends on the recognition of the acetyl lysine region by the bromodomain. Several studies have demonstrated that proteins containing bromodomains play a pivotal role in epigenetic regulation,<sup>73,74</sup> because the bromodomain specifically recognizes acetylated lysines of histones and other proteins.<sup>51,74</sup> BRD9 is recruited to chromatin binding sites. Another study demonstrated that BRD9 was overexpressed in the AML cell line,<sup>75</sup> and acted as a key regulator of AML occurrence. The study revealed that the BRD9-STAT5 axis played an important role in the occurrence and maintenance of leukemia. In leukemia, BRD9 is overexpressed, and induces the activation of the signal transducer and

activator of transcription 5 (STAT5) pathway. The activation of STAT5 is known to promote the proliferation and survival of AML cells and the occurrence of inflammation.<sup>76–79</sup> Currently, no clinically effective STAT5 inhibitor is available for the treatment of leukemia.<sup>80</sup> Therefore, knocking down BRD9 to decrease the activation of STAT5 and induce apoptosis through the Caspase8 signaling cascade may be a possible therapeutic strategy.

## miR-140-3p-BRD9 Axis Participates in Tumor Progression

Lung cancer is one of the malignant tumors with high morbidity and mortality.<sup>81</sup> It is divided into three subclasses: lung carcinoid, Squamous cell lung cancer (SCLC) and NSCLC.<sup>82</sup> SCLC is a histological subtype of NSCLC. Patients with SCLC accounts for approximately one-third of those with NSCLC.<sup>83</sup> However, no clinically effective, targeted therapeutic strategy for SCLC has been found. Many studies have demonstrated that the differential expression of miRNAs in lung cancer makes miRNAs carcinogenic or suppressive. For example, in lung cancer, miR-342-3p<sup>84</sup> and miR-30d-5p<sup>85</sup> are inhibited in lung cancer, whereas miR-29b,<sup>86</sup> hsa-miR-3180, and miR-14,081 are highly expressed. Huang et al<sup>87</sup> demonstrated that miR-140-3p was downregulated in NSCLC cells and tissues, and regulated the process of NSCLC by directly targeting BRD9. A negative correlation exists between the expression level of BRD9 and that of miR-140-3p. miR-140-3p directly targets BRD9 mRNA, inhibiting its protein translation and consequently downregulating the expression level of C-myc, and suppressing the proliferation of SCLC. Therefore, the miR-140-3p-BRD9 axis may be a promising therapeutic approach for the clinical treatment of SCLC.

## Interaction Between the Phosphatidylinositol 3-Kinase Pathway and the Mitogen-Activated Protein Kinase Pathway Induces BRD9 Expression to Participate in Tumor Progression

Usually, tumor formation is closely related to a combination of multiple oncogenes or multiple oncogenic processes. A study reported that the activation of the phosphatidylinositol 3-kinase (PI3K) pathway was closely related to a variety of tumor biological processes,

such as tumor cell proliferation, migration, metabolism, and other important processes.<sup>88</sup> The *PI3KCA* gene catalyzes the activation of PI3K.<sup>89</sup> Studies have demonstrated that the kirsten rat sarcoma (*KRAS*) and *PIK3CA* genes are significantly associated with colorectal cancer,<sup>90</sup> lung cancer,<sup>91</sup> and breast cancer,<sup>92–94</sup> and their common mutations drive the malignant transformation. *KRAS* plays an indispensable role in the activation of the mitogen-activated protein kinase pathway.<sup>95</sup> A study<sup>96</sup> used double knock-in (DKI) breast epithelial (MCF-10A) cells harboring *PIK3CA* and *KRAS* to explore the interaction between *PIK3CA* and *KRAS*, and found that the carcinogenicity of *KRAS*-*PIK3CA* was because the *KRAS*-*PIK3CA* interaction induced the expression of BRD9. BRD9 regulated the proliferation and migration of DKI MCF-10A cells by combining with the MYC promoter.

## Cancer Therapeutics for Targeting BRD9

Recently, the BET family has been extensively studied as a therapeutic target, and bromodomain inhibitors as anti-tumor agents have demonstrated remarkable clinical effect.<sup>97–101</sup> Bromodomain inhibitors are divided into two categories: non-acetylated, and acetylated lysine mimetics. The former is a weak inhibitor, whereas the latter directly mimics the binding of an acetylated lysine to the bromodomain and competitively inhibits the binding of acetylated lysine residues to the hydrophobic binding pocket of the bromodomain.<sup>60</sup> Gradually, as the biological function of BRD9 in tumorigenesis becomes clear, targeting the bromodomain of BRD9 will become a new and effective tumor treatment method. For example, small-molecule inhibitors of the BRD9 bromodomain selectively suppress tumor cell proliferation and survival and induce apoptosis.<sup>27,75,102,103</sup> Indeed, scientists have researched and developed several effective BRD9 bromodomain inhibitors, such as BRD9 selective inhibitors (I-BRD9,<sup>104</sup> BI-7273,<sup>105</sup> and BI-9564<sup>106</sup>) and BRD7/9 inhibitors.<sup>107,108</sup> LP99 is the first reported selective BRD7/9 inhibitor that effectively inhibits the binding of BRD7/9 to acetylated histones in vivo and in vitro; Moreover, LP99 inhibits the secretion of proinflammatory cytokine IL-6. These results suggest a role of BRD9 in inflammation.<sup>109</sup> Notably, the probe compound of BRD9 designed by Crawford et al<sup>110</sup> can inhibit the expression of the drug resistance gene aldehyde dehydrogenase 1 family member A1 (*ALDH1A1*). Interestingly, both *ALDH1A1* and its

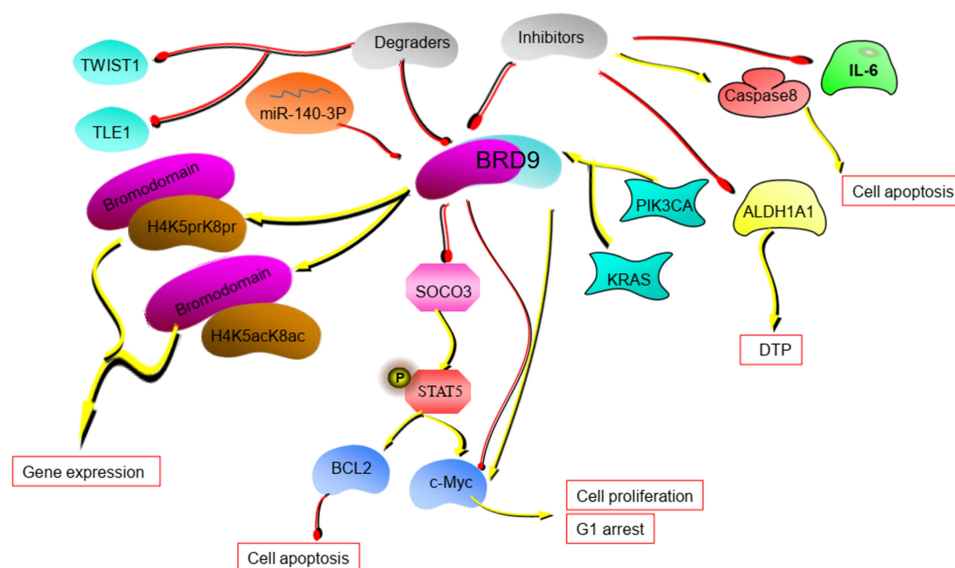
promoter are involved in the regulation of acetylation,<sup>111,112</sup> whereas the relationship between BRD9 and cancer resistance has not been described before. BRD9 inhibitors, BI-7273 and BI-9564, used to investigate the biological functions of BRD9 in vivo and in vitro were proven to be non-toxic by fragment-based screening.<sup>105,106</sup> Based on the structural design, I-BRD9 has been identified as a selective cytochemical probe for BRD9.<sup>113</sup> In addition, I-BRD9 downregulates cancer and immunology-related genes, such as *SAMSN1*,<sup>114</sup> *CLEC1*,<sup>115</sup> *FES*,<sup>116</sup> and *DUSP6*.<sup>117</sup> Studies on the selection mechanism of I-BRD9 for the BRD9 bromodomain have demonstrated that several residues in the ZA and ZB loops of the bromodomain, such as Asp144, Ile53, Lys91, Thr104, Pro82, Asn140, Asn100, and Phe44, can be used as important references for designing BRD9 inhibitors.<sup>104</sup> The imidazo [1,5-a] pyrazin-8 (7H) -one derivative was designed and synthesized using the interaction of the inhibitor with the Asn and Tyr residues to inhibit BRD9 activity.<sup>118</sup>

In addition to the synthesis and design of protein inhibitors, targeting protein degradation by hijacking the ubiquitin-proteasome system can be another therapeutic strategy.<sup>119,120</sup> Encouragingly, Remillard et al<sup>121</sup> designed the heterobifunctional ligand dBRD9, a direct chemical degrader for BRD9, which linked the BRD9 bromodomain and the cereblon E3 ubiquitin ligase complex. Thereafter, they designed VZ185, a highly effective and fast degrader for BRD9.<sup>122</sup> A previous study confirmed that BRD9 protein degraders are more effective than BRD9 bromodomain inhibitors.<sup>123</sup> These

data suggest that in addition to the bromodomain, other uncharacterized domains play vital roles in cancer.

## Conclusion

Recently, the role of the SWI/SNF complex has been extensively studied in various malignant cancers. Repeated mutations in the subunits of the SWI/SNF complex in cancer make it a promising therapeutic target. Based on different subunit combinations, the SWI/SNF complex is classified into three categories: the cBAF, PBAF, and ncBAF complexes. The ncBAF complex lacks SNF5 and ARID subunits. BRD9 is one of the subunits that make up the ncBAF complex and is a member of the bromodomain family IV. BRD9 has been found to be over-expressed in malignant cancers, such as MRT, AML, SS, and SCLC. BRD9 is especially important for maintaining the growth and proliferation of MRT and AML cells. Meanwhile, BRD9 plays an anti-tumor role in melanoma and MCC. BRD9 is closely related to the biological processes of cells, such as cell proliferation and apoptosis (Figure 2). It consists of a bromodomain and a DUF3512 domain. The deletion of the DUF3512 domain affects the assembly of the ncBAF complex. The bromodomain is required for the biological functions of BRD9 during tumor formation. Bromodomain-containing proteins are involved in epigenetic regulation. The regulatory mechanism involves the binding of the bromodomain to acetylated lysine residues on histones and non-histones, and the recruitment of molecular chaperones to regulate gene



**Figure 2** The potential mechanism of BRD9. BRD9 regulates tumor progression through the miR-140-3P-BRD9 axis and BRD9-STAT5 axis. BRD9 inhibitors and degraders can disrupt the tumor process. (The yellow lines in the figure represent the promotion between molecules, and the red lines represent the inhibition between molecules.).

transcription. Therefore, understanding the function of the bromodomain will aid in understanding the complex biological functions of BRD9. Currently, two treatment strategies targeting BRD9 are available. First, designing inhibitors to prevent the binding of bromodomains to acetylated lysine residues; and second, designing protein degraders to degrade proteins and inhibit their activity. Although the bromodomain inhibitors and degraders have demonstrated good therapeutic effect only to some extent, their great potential in cancer treatment has been demonstrated. However, the detailed mechanisms of the biological functions of BRD9 are unclear. We intend to focus on these mechanisms in our future research.

## Abbreviations

BRD9, bromodomain-containing protein 9; MRT, malignant rhabdoid tumor; ncBAF, non-canonical barrier-to-autointegration factor; SWI/SNF, switch/sucrose non-fermentable; cBAF, canonical barrier-to-autointegration factor; PBAF, polybromo-associated BAF; GLTSCR1, glioma tumor suppressor candidate gene 1; AML, acute myeloid leukemia; SS, synovial sarcoma; LIHC, Liver hepatocellular carcinoma; BLCA, bladder urothelial carcinoma; CHOL, cholangiocarcinoma; BRCA, breast invasive carcinoma; HNSC, head and neck squamous cell carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; KIRP, kidney renal papillary cell carcinoma; KIRC, kidney renal clear cell carcinoma; KICH, kidney Chromophobe; READ, rectum adenocarcinoma; COAD, colon adenocarcinoma; THCA, thyroid carcinoma; STAD, stomach adenocarcinoma; ESCA, esophageal carcinoma; PCPG, pheochromocytoma and paraganglioma; UCEC, uterine corpus endometrial carcinoma; LUSC, lung squamous cell carcinoma; SKCM, skin cutaneous melanoma; SARC, sarcoma; THYM, thymoma; PAAD, pancreatic adenocarcinoma; GBM, glioblastoma multiforme; PRAD, prostate adenocarcinoma; BRD7, bromodomain-containing protein 7; BRPF1, bromodomain and PHD finger containing 1; BRPF2, bromodomain and PHD finger containing 2; BRPF3, bromodomain and PHD finger containing 3; ATAD2, ATPase family AAA domain containing 2; ATAD2B, ATPase family AAA domain containing 2B; STAT5, signal transducer and activator of transcription 5; SCLC, squamous cell lung cancer; PI3K, phosphatidylinositol 3-kinase; KRAS, kirsten rat sarcoma; DKI, double knock-in; ALDH1A1, aldehyde dehydrogenase 1 family

member A1; LSD1, lysine-specific histone demethylase 1; MCC, Merkel cell carcinoma.

## Author Contributions

All the authors contributed for the preparation of this manuscript. XZ and LT were responsible for confirming the topic. XZ were responsible for writing the first draft of this article. LT and YL contributed to further editing and polishing the manuscript. All authors read and approved the final manuscript. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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