

Review Article

BRD7: a novel tumor suppressor gene in different cancers

Xin Yu^{1*}, Zheng Li^{2*}, Jianxiang Shen²

¹Department of Dermatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100042, China; ²Department of Orthopedics Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100042, China. *Equal contributors.

Received October 13, 2015; Accepted November 24, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: BRD7 (bromodomain 7), also known as celtix-1, was first identified in nasopharyngeal carcinoma (NPC) cells in 2000. BRD7 is a crucial component of both functional p53 and BRCA1 (breast cancer 1, early onset) pathways. Recently, the BRD7 tumor suppressor status has been fully established. Previous studies demonstrated that BRD7 was downregulated in human breast cancer and the downregulation often associates with tumor progression. The expression of BRD7 was downregulated in various cancers, including breast cancer, NPC, gastric cancer, colorectal carcinoma, ovarian cancer, and prostate cancer. Moreover, BRD7 inhibited cancer cell growth and metastasis and promote apoptosis in vitro and in vivo via downregulating AKT pathway. In addition, BRD7 may regulate many signaling pathways including ras-raf-MEK-ERK and RB/E2F. In this review, we provide an overview of current knowledge concerning the role of BRD7 in tumor development and progression. To our knowledge, this is the first review about the role of this novel tumor suppressor gene BRD7 in tumor development and progression.

Keywords: BRD7, tumor suppressor gene, cancers

Introduction

Tumor suppressor genes (TSGs) are defined as genes whose mutation predisposes the animal to cancer. TSGs encode for a protein that inhibits tumor development through blocking cell proliferation and/or contributing to the maintenance of genome stability [1, 2]. Transcriptional regulation is a process that converts the genetic codes into RNA synthesis. The bromodomain is an evolutionally conserved sequence existing in more than 40 proteins. It can regulate gene transcription through binding to acetylated histones in chromosomal [3]. BRD7 (bromodomain 7), a novel bromodomain-containing protein of about 75 kD (BRD7), also known as celtix-1, is a subunit of polybromo-associated BRG1-associated factor (PBAF)-specific Swi/Snf chromatin remodeling complexes [4]. BRD7 can bind to the four core histones, and deletion of its bromodomain abolishes these interactions [5, 6]. BRD7 is a crucial component of both functional p53 and BRCA1 (breast cancer 1, early onset) pathways [7, 8]. It is essential for the transcriptional activation of target genes of P53, including P21, HDM2 and TIGAR.

Accumulating evidence has demonstrated that BRD7 is involved in the development of multiple cancers, serving as a tumor suppressor gene. It is downregulated in many types of cancers, including breast cancer, nasopharyngeal carcinoma (NPC), gastric cancer, colorectal carcinoma, ovarian cancer, and prostate cancer. BRD7 expression was deleted in more than 3,000 tumor samples and cell lines from 54 cancer subtypes, strongly indicating the role of BRD7 as a TSG [9]. It could inhibit cancer development through multiple mechanisms.

BRD7: structural features and functions

Bromodomain-containing proteins (BCPs) are large families of proteins involving in chromatin remodeling, transcriptional control, and methyl or acetyltransferase activity [10]. BCPs consist of an evolutionally conserved domain, bromodomain (Brd), which contains a motif of 59-63 amino acids, flanked by structurally conserved sequences to domain of 110 amino acids [3, 6]. BRD7 was first identified in 2000 as a member of the BCPs family downregulated in Nasopharyngeal carcinoma (NPC) cells by cDNA

BRD7: a novel suppressor gene

Representational Difference Analysis [11]. BRD7 expression is mainly localized in the nucleus as shown by immunofluorescence [12, 13]. The coding sequences of BRD7 gene include 2,213 bp of nucleotides. BRD7 is predicted to encode a protein of 651 amino acids with a molecular weight of 74 kDa. BRD7 was mainly distributed in nucleus with a functional nuclear localization signal (NLS) sequence ranging from amino acid 65 to 96 [13].

BRD7 was ubiquitously expressed in human tissues, including brain, heart, lung, colon and breast [13, 14]. Researchers have showed that BRD7 play significant roles in cell cycle control and transcriptional regulation, involving in cellular growth, apoptosis, cell cycle, and mobility [15]. For instance, overexpression of BRD7 could arrest cycle progression from G1 to S phase by regulating cell cycle-related molecules in NPC [13]. During eukaryotic transcription, the epigenetic information in chromatin is interpreted by proteins with domains for recognizing the histone codes. By binding to acetylated histone H3, BRD7 protein can transcriptionally regulate its target genes and cell cycle [6]. BRD7 inhibits basic transcription in several viral and cellular promoters in the nucleus. BRD7 influences gene regulation by interacting with other transcription factors [16, 17]. For example, BRD7 protein associates with transcriptionally active chromatin in the nucleus through interacting with interferon regulatory factor 2 [12]. More importantly, the interaction between BRD7 and p53 and p300 is required for a subset of p53-regulated gene expressions [7]. In addition, BRD7 can bind to BRCA1 in breast cancer cells [8]. In addition, BRD7 may regulate many signaling pathways including ras-raf-MEK-ERK and RB/E2F [18]. Although BRD7 is implicated in target gene repression, its mechanism remains unclear.

BRD7 status in human cancers

Recently, accumulating studies have found that BRD7 expression is decreased or lost in human cancers, consistent with its role as a tumor suppressor gene. In this section, we will summarize the current studies on the expression of BRD7 in different human malignancies.

Nasopharyngeal carcinoma (NPC)

BRD7 was first identified as an NPC-associated gene in 2000 since it was decreased in both

NPC biopsies and cell lines than in normal nasopharyngeal epithelial tissues [12]. Since then, several studies have demonstrated that BRD7 act as tumor suppressor/susceptibility genes in different stages of NPC. Overexpression of BRD7 inhibited cell proliferation and capability to form colonies, blocking the cell cycle progression from G1 to S phase. In addition, it was proved that BRD7 decreased NPC cells growth through inhibiting β -catenin and ERK1/2 pathways [19]. In order to investigate the underlying mechanisms of decreased BRD7 expression in NPC, Liu et al. showed that DNA methylation could decrease BRD7 expression in NPC cells through silencing BRD7 promoter activity and inhibiting its binding to nuclear protein (possibly Sp1) [20]. In addition, the methylation frequency of BRD7 promoter was higher in the tissue and blood samples from NPC patients than that from normal controls, indicating the potential role of DNA methylation of BRD7 promoter as a diagnostic marker in NPC. Wu et al. [21]. found that BRD7 could increase BRD2-induced NPC cell apoptosis. In addition, BRD7 blocked cell cycle progression through G0/G1 by suppressing ras/MEK/ERK, Rb/E2F and Wnt signaling pathways [15, 22]. In summary, BRD7 was decreased in NPC and functioned as a TSG. BRD7 may be potential diagnostic and treatment targets for NPC in the future.

Breast cancer

BRD7 is a binding partner of BRCA1 and involved in the regulation of approximately 30% of BRCA1 targets [8]. BRD7 is required for the BRCA1-mediated transcriptional regulation of the estrogen receptor. Depletion of BRCA1 or BRD7 resulted in loss of ER α expression in breast cancer cells, as well as resistance to fulvestrant treatment [8]. BRD7 was downregulated and even deleted in p53-wild-type, but not mutant, breast cancer cells [23]. However, sequence analysis proved that BRD7 was not a frequent high-penetrance breast cancer susceptibility gene since its variants only represented rare polymorphisms [24]. In addition, another study proved that no pathogenic BRD7 germ-line mutations were found in German patients with familial breast cancer and the 40 Triple Negative Breast Cancer (TNBC) patients, ruling out the role of BRD7 in the genetic predisposition to breast cancer [25].

Pancreatic cancer (PC)

A two-stage case-control study was conducted to investigate the associations between 14

BRD7: a novel suppressor gene

common variants in 6 genes (SMARCA4, SMCRB1, PBRM1, BRD7, ARID1, and ARID2) and the risk of PC. Variant rs11644043, in the 8th intron of BRD7 gene, demonstrated consistent significant association with increased risk of PC in both discovery and validation stages [26]. The study suggested variants in BRD7 might contribute to the susceptibility of PC in the Chinese population

Colorectal cancer (CRC)

Zhang et al. reported no significant difference of mRNA expression levels of BRD7 between the gastric/colorectal cancer tissues and the corresponding normal tissues [27]. However, a recent study by Wu et al. showed that BRD7 expression level was lower in 117 cancer tissues and CRC cell lines compared with that in normal colon epithelial cells and adjacent non-cancerous tissue samples [28]. In addition, expression level of BRD7 was positively correlated with clinical stage and TNM classification in CRC patients. Low/none BRD7 expression indicated shorter overall survival time and served as an independent prognostic factor for CRC patients.

Prostate cancer

Tripartite motif 24 (TRIM24) could enhance transcriptional activity of androgen receptor (AR) in prostate cancer cells through interaction with AR [29]. TRIM24 could also bind to BRD7 and negatively regulate cell proliferation and growth. By binding to TRIM24, BRD7 was found to inhibit prostate cancer cells growth and repress the AR transactivation activity [29]. These findings indicate that BRD7 plays a role in AR-mediated transcription in prostate cancer.

Ovarian cancer

BRD7 expression was decreased in the ovarian cancer tissues compared with normal controls. In addition, high-grade serous cancer demonstrated lower expression of BRD7 than low-grade serous cancer. Transfection of BRD7 to ovarian cancer cells suppressed cell viability and invasion and increased apoptosis. Furthermore, BRD7 decreased tumor weight in vivo in orthotopic mouse model. Moreover, the tumor suppressive effects of BRD7 are p53-independent. BRD7 can negatively regu-

late β -catenin pathway, decreasing its accumulation in the nucleus. In conclusions, BRD7 played a tumor suppressor role in epithelial ovarian cancers through inhibiting β -catenin pathway [30].

Endometrial carcinoma

A recent study by Park et al. showed that interaction between miR-200c and BRD7 played significant roles in growth of endometrial cancer cells. MiR-200c was upregulated in endometrial carcinoma. In addition, anti-miR or pre-miR-200c could regulate cell survival, proliferation, and apoptosis in endometrial cancer cells. Furthermore, miR-200c regulated the translocation of β -catenin from the cytoplasm to the nucleus through inhibiting the expression of BRD7, leading to increased expression of cyclin D1 and c-myc [31].

Osteosarcoma

Osteosarcoma is the most common type of primary malignant bone tumor in childhood and adolescence. BRD7 acted as a tumor suppressor in osteosarcoma, inhibiting the G1/S transition during cell cycle. In addition, BRD7 could be regulated by anaphase-promoting complex/cyclosome (APC/C), which could directly bind and degrade BRD7. BRD7 mutant resistant to degradation by APC/C is more efficient than the wild-type protein at suppressing proliferation, colony formation, and tumor growth of osteosarcoma in vitro and in vivo. Furthermore, protein levels of BRD7 were inversely correlated with Cdh1 or Cdc20, and lower BRD7 expression was associated with poor prognosis in patients with osteosarcoma [32, 33]. Furthermore, the BRD7 mutant resistant to degradation by APC/C showed more efficient at inhibiting proliferation, colony formation, and tumor growth of osteosarcoma both in vitro and in vivo compared with the wild-type protein. ProTAME, an inhibitor of APC/C, combined with chemotherapeutic drugs, can efficiently targets osteosarcoma in vitro. Therefore, APC/C-BRD7 pathway may be a novel therapeutic strategy for osteosarcoma.

Glioma

BRD7 was highly expressed in gliomas and its expression level was negatively correlated with LRRC4 expression. In addition, transcriptional

BRD7: a novel suppressor gene

Table 1. BRD7 expressions in human cancers

Cancer type	Expression	Role in tumor	References
Nasopharyngeal carcinoma	Decreased	tumor suppressor	12, 19, 20, 21
Breast Cancer	Depletion, decreased polymorphisms	tumor suppressor	8, 23, 24, 25
Pancreatic cancer	Variants		26
Colorectal cancer	Decreased	tumor suppressor	27, 28
Prostate cancer		tumor suppressor	29
Ovarian cancer	Decreased	tumor suppressor	30
Endometrial carcinoma	Decreased	tumor suppressor	31
Osteosarcoma	Decreased	tumor suppressor	32, 33
Glioma	Decreased	tumor suppressor	33
Oral squamous cell carcinomas	Methylation		35

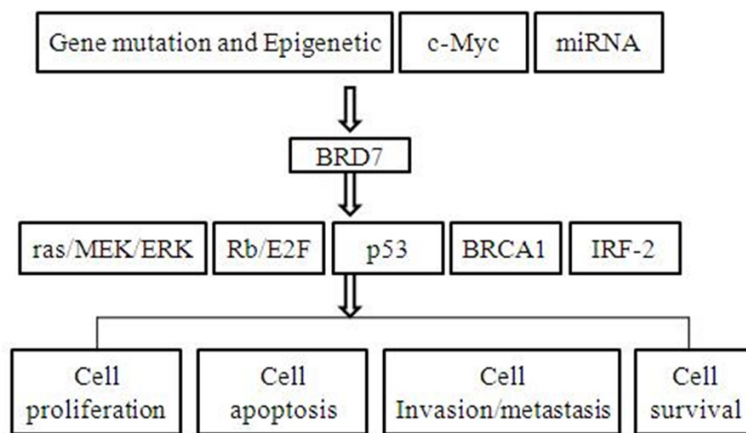


Figure 1. Proposed model of tumorigenesis due to loss or decreased BRD7 expression. Reduced BRD7 expression caused by gene mutations or epigenetic changes, c-Myc and miRNA, induced cell apoptosis, suppressed cell survival, proliferation, invasion and metastasis by ras/MEK/ERK pathway or other genes.

regulation of BRD7 was dependent on miR-182 and miR-381. Previous studies showed that LRRC4 was a direct target gene of miR-381 and miR-182, both of which were involved in pathological malignant progression [33]. The silencing of miR-182 and miR-381 decreased the proliferation in vitro and growth of glioma cell in vivo by intracranial transplanted tumor model in rats.

Oral squamous cell carcinomas

Promoter hypermethylation of TSG resulted in gene silencing, which is the most frequent event in carcinogenesis [34]. Using methylation sensitive enzyme technique, methylation of BRD7 promoter region was observed in 17/20 (74%) well differentiated oral squamous cell carcinoma samples, suggesting that the meth-

ylation of BRD7 is frequent in cancers [35] (Table 1).

Mechanisms of BRD7 tumor suppressive functions

Brd7 may contribute to cancer development through various mechanisms. Firstly, BRD7 regulates cell cycle progression through regulating cell cycle associated crucial molecules. For example, BRD7 could inhibit NPC cell growth and arrest them in G0/G1 phase through regulating gene transcriptions involved in ras/MEK/ERK and Rb/E2F pathways [18]. In addition, c-Myc could negatively regulate expression of BRD7

gene. The promoter activity of BRD7 was negatively associated with c-Myc expression[36, 37]. Moreover, BRD7 acted its tumor suppressive role by interaction with p53. BRD7 was required for efficient p53-mediated transcription of a subset of target genes [7, 9]. BRD7 could also bind to BRCA1, which was required for the BRCA1-mediated transcriptional regulation of the estrogen receptor in breast cancer. Depletion of BRCA1 or BRD7 resulted in loss of ER α expression in breast cancer cells and resistance to fulvestrant treatment [8]. Moreover, BRD7 protein could also interact with nuclear transcription factor Interferon Regulatory Factor-2 (IRF-2), which was involved in the transcriptional control at the G1/S-phase transition of the cell cycle [12]. The adenovirus nuclear protein, E1B-AP5 is a member of the nuclear rib nucleoprotein family involved in mRNA process-

BRD7: a novel suppressor gene

ing and transport. BRD7 could form a complex with E1B-AP5, thereby affecting its transcription activity [5]. BRD7 interacted with three core subunits of the polycomb repressor complex 2 (PRC2) including SUZ12 [16]. Furthermore, BRD7 co-localized on tumor-suppressor genes ST7 and retinoblastoma-like protein 2 (RBL2) promoters, correlating with hypermethylation of H3R8, H4R3 and H3K27 in patient-derived mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) cell lines [16]. BRD2 mainly localizes in nucleus in two distribution patterns, diffused and dotted, and BRD2 has distinct roles in initiating apoptosis, and the dotted distribution pattern of BRD2 in nucleus may be a morphologic marker of cell apoptosis. BRD7 could interact with the region from amino acid 430 to 798 of BRD2 [38]. The promoter region of the BRD7 gene was responsive to several transcriptional factors, including Sp1, E2F, and E2F6, indicating that those transcriptional factors were associated with the BRD7 promoter activity [37]. Interaction of BRD7 to acetylated histone H3 is the underlying molecular mechanism of BRD7's transcriptional regulation role on its target genes and cell cycle inhibition role in NPC cells. Bromodomain-deleted BRD7 mutant could not inhibit E2F3 promoter activity and cell cycle G1-S progression because of the loss of affinity with acetylated histone H3 (Figure 1) [6].

Implications in cancer management

BRD7 was deregulated in a multiple human cancers and provides a potential target for anti-cancer therapies. Firstly, BRD7 can act as molecular biomarkers for cancer diagnosis. By detecting the BRD7 levels, such as alterations in gene and protein levels, the risk of cancer development and progression, as well as the prognosis can be predicted. In addition, since BRD7 was decreased in many cancers, re-introduction of BRD7 gene or to stabilization of BRD7 protein level may be an attractive strategy for cancer management. Restoration of its tumor suppressing function may inhibit tumor growth, serving as a potential target for cancer therapy.

Conclusions and future directions

In summary, BRD7, decreased in a various human malignances, plays a tumor suppressive role in carcinogenesis. BRD7 exerts its

tumor suppressor function through regulating several gene transcription involved in cell cycle progression, such as p53, c-myc, IRF-2 and E2F3 [16, 36]. All of those genes are involved in the tumorigenesis and might be the underlying mechanism for the tumor suppressive functions of BRD7. Although recent studies have characterized the molecular mechanisms of BRD7 in transcriptional regulation, studies on the molecular mechanism that lead to the deregulations of BRD7 were relatively limited. Further investigations are required to identify the status of BRD7 in other cancers as well as its molecular functions. In addition, more in vivo experiments are needed to confirm the tumor suppressive role of BRD7 in mouse models.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (NSFC) (Grant Numbers: 81401847).

Disclosure of conflict of interest

None.

Address correspondence to: Jianxiong Shen, Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100042, China. Tel: 86-010-69152812; Fax: 86-010-69152812; E-mail: shenjianxiong@med-mail.com.cn

References

- [1] Blagosklonny MV. Molecular theory of cancer. *Cancer Biol Ther* 2005; 4: 621-627.
- [2] Zhao H, Wang J, Han Y, Huang Z, Ying J, Bi X, Zhao J, Fang Y, Zhou H, Zhou J, Li Z, Zhang Y, Yang X, Yan T, Wang L, Torbenson MS and Cai J. ARID2: a new tumor suppressor gene in hepatocellular carcinoma. *Oncotarget* 2011; 2: 886-891.
- [3] Dhalluin C, Carlson JE, Zeng L, He C, Aggarwal AK and Zhou MM. Structure and ligand of a histone acetyltransferase bromodomain. *Nature* 1999; 399: 491-496.
- [4] Kaeser MD, Aslanian A, Dong MQ, Yates JR, 3rd and Emerson BM. BRD7, a novel PBAF-specific SWI/SNF subunit, is required for target gene activation and repression in embryonic stem cells. *J Biol Chem* 2008; 283: 32254-32263.
- [5] Kzhyshkowska J, Rusch A, Wolf H and Dobner T. Regulation of transcription by the heteroge-

BRD7: a novel suppressor gene

- neous nuclear ribonucleoprotein E1B-AP5 is mediated by complex formation with the novel bromodomain-containing protein BRD7. *Biochem J* 2003; 371: 385-393.
- [6] Peng C, Zhou J, Liu HY, Zhou M, Wang LL, Zhang QH, Yang YX, Xiong W, Shen SR, Li XL and Li GY. The transcriptional regulation role of BRD7 by binding to acetylated histone through bromodomain. *J Cell Biochem* 2006; 97: 882-892.
- [7] Drost J, Mantovani F, Tocco F, Elkon R, Comel A, Holstege H, Kerkhoven R, Jonkers J, Voorhoeve PM, Agami R and Del Sal G. BRD7 is a candidate tumour suppressor gene required for p53 function. *Nat Cell Biol* 2010; 12: 380-389.
- [8] Harte MT, O'Brien GJ, Ryan NM, Gorski JJ, Savage KI, Crawford NT, Mullan PB and Harkin DP. BRD7, a subunit of SWI/SNF complexes, binds directly to BRCA1 and regulates BRCA1-dependent transcription. *Cancer Res* 2010; 70: 2538-2547.
- [9] Burrows AE, Smogorzewska A and Elledge SJ. Polybromo-associated BRG1-associated factor components BRD7 and BAF180 are critical regulators of p53 required for induction of replicative senescence. *Proc Natl Acad Sci U S A* 2010; 107: 14280-14285.
- [10] Chen R, Yik JH, Lew QJ and Chao SH. Brd4 and HEXIM1: multiple roles in P-TEFb regulation and cancer. *Biomed Res Int* 2014; 2014: 232870.
- [11] Yu Y, Zhang BC, Xie Y, Cao L, Zhou M, Zhan FH and Li GY. Analysis and Molecular Cloning of Differentially Expressing Genes in Nasopharyngeal Carcinoma. *Sheng Wu Hua Xue Yu Sheng Wu Wu Li Xue Bao (Shanghai)* 2000; 32: 327-332.
- [12] Staal A, Enserink JM, Stein JL, Stein GS and van Wijnen AJ. Molecular characterization of celtix-1, a bromodomain protein interacting with the transcription factor interferon regulatory factor 2. *J Cell Physiol* 2000; 185: 269-279.
- [13] Zhou M, Liu H, Xu X, Zhou H, Li X, Peng C, Shen S, Xiong W, Ma J, Zeng Z, Fang S, Nie X, Yang Y, Zhou J, Xiang J, Cao L, Peng S, Li S and Li G. Identification of nuclear localization signal that governs nuclear import of BRD7 and its essential roles in inhibiting cell cycle progression. *J Cell Biochem* 2006; 98: 920-930.
- [14] Peng C, Zhou M, Zhang QH, Tang K and Li GY. Analysis of bromodomain of BRD-7 gene and its prokaryotic expression. *Ai Zheng* 2002; 21: 1167-1172.
- [15] Wu M, Li X, Li X and Li G. Signaling Transduction Network Mediated by Tumor Suppressor/Susceptibility Genes in NPC. *Curr Genomics* 2009; 10: 216-222.
- [16] Tae S, Karkhanis V, Velasco K, Yaneva M, Erdjument-Bromage H, Tempst P and Sif S. Bromodomain protein 7 interacts with PRMT5 and PRC2, and is involved in transcriptional repression of their target genes. *Nucleic Acids Res* 2011; 39: 5424-5438.
- [17] Yu Y, Zhu S, Zhang B, Zhou M, Li X and Li G. Screening of BRD7 interacting proteins by yeast two-hybrid system. *Sci China C Life Sci* 2002; 45: 546-552.
- [18] Zhou J, Ma J, Zhang BC, Li XL, Shen SR, Zhu SG, Xiong W, Liu HY, Huang H, Zhou M and Li GY. BRD7, a novel bromodomain gene, inhibits G1-S progression by transcriptionally regulating some important molecules involved in ras/MEK/ERK and Rb/E2F pathways. *J Cell Physiol* 2004; 200: 89-98.
- [19] Peng C, Liu HY, Zhou M, Zhang LM, Li XL, Shen SR and Li GY. BRD7 suppresses the growth of Nasopharyngeal Carcinoma cells (HNE1) through negatively regulating beta-catenin and ERK pathways. *Mol Cell Biochem* 2007; 303: 141-149.
- [20] Liu H, Zhang L, Niu Z, Zhou M, Peng C, Li X, Deng T, Shi L, Tan Y and Li G. Promoter methylation inhibits BRD7 expression in human nasopharyngeal carcinoma cells. *BMC Cancer* 2008; 8: 253.
- [21] Wu M, Li X and Li G. Signaling Transduction Network Mediated by Tumor Suppressor/Susceptibility Genes in NPC. *Curr Genomics* 2009; 10: 216-222.
- [22] Wang H, Zhao R, Zhou M, Guo C, Liu Y, Jiang S, Li X, Xiong W, Ma J, Peng S, Li X, Schmitt DC, Tan M and Li G. Preparation of polyclonal antibody highly specific for mouse BRD7 protein and its application. *Acta Biochim Biophys Sin (Shanghai)* 2014; 46: 163-166.
- [23] Beroukhi R, Mermel CH, Porter D, Wei G, Raychaudhuri S, Donovan J, Barretina J, Boehm JS, Dobson J, Urashima M, McHenry KT, Pinchback RM, Ligon AH, Cho YJ, Haery L, Greulich H, Reich M, Winckler W, Lawrence MS, Weir BA, Tanaka KE, Chiang DY, Bass AJ, Loo A, Hoffman C, Prensner J, Liefeld T, Gao Q, Yecies D, Signoretti S, Maher E, Kaye FJ, Sasaki H, Tepper JE, Fletcher JA, Taberner J, Baselga J, Tsao MS, Demichelis F, Rubin MA, Janne PA, Daly MJ, Nucera C, Levine RL, Ebert BL, Gabriel S, Rustgi AK, Antonescu CR, Ladanyi M, Letai A, Garraway LA, Loda M, Beer DG, True LD, Okamoto A, Pomeroy SL, Singer S, Golub TR, Lander ES, Getz G, Sellers WR and Meyerson M. The landscape of somatic copy-number alteration across human cancers. *Nature* 2010; 463: 899-905.
- [24] Penkert J, Schlegelberger B, Steinemann D and Gadzicki D. No evidence for breast cancer susceptibility associated with variants of

BRD7: a novel suppressor gene

- BRD7, a component of p53 and BRCA1 pathways. *Fam Cancer* 2012; 11: 601-606.
- [25] Pern F, Bogdanova N, Schurmann P, Lin M, Ay A, Langer F, Hillemanns P, Christiansen H, Park-Simon TW and Dork T. Mutation analysis of BRCA1, BRCA2, PALB2 and BRD7 in a hospital-based series of German patients with triple-negative breast cancer. *PLoS One* 2012; 7: e47993.
- [26] Zhu B, Tian J, Zhong R, Tian Y, Chen W, Qian J, Zou L, Xiao M, Shen N, Yang H, Lou J, Qiu Q, Ke J, Lu X, Song W, Li H, Liu L, Wang L and Miao X. Genetic variants in the SWI/SNF complex and smoking collaborate to modify the risk of pancreatic cancer in a Chinese population. *Mol Carcinog* 2015; 54: 761-8.
- [27] Zhang XM, Wang XY, Sheng SR, Wang JR and Li J. Expression of tumor related genes NGX6, NAG-7, BRD7 in gastric and colorectal cancer. *World J Gastroenterol* 2003; 9: 1729-1733.
- [28] Wu WJ, Hu KS, Chen DL, Zeng ZL, Luo HY, Wang F, Wang DS, Wang ZQ, He F and Xu RH. Prognostic relevance of BRD7 expression in colorectal carcinoma. *Eur J Clin Invest* 2013; 43: 131-140.
- [29] Kikuchi M, Okumura F, Tsukiyama T, Watanabe M, Miyajima N, Tanaka J, Imamura M and Hatakeyama S. TRIM24 mediates ligand-dependent activation of androgen receptor and is repressed by a bromodomain-containing protein, BRD7, in prostate cancer cells. *Biochim Biophys Acta* 2009; 1793: 1828-1836.
- [30] Park YA, Lee JW, Kim HS, Lee YY, Kim TJ, Choi CH, Choi JJ, Jeon HK, Cho YJ, Ryu JY, Kim BG and Bae DS. Tumor suppressive effects of bromodomain-containing protein 7 (BRD7) in epithelial ovarian carcinoma. *Clin Cancer Res* 2014; 20: 565-575.
- [31] Park YA, Lee JW, Choi JJ, Jeon HK, Cho Y, Choi C, Kim TJ, Lee NW, Kim BG and Bae DS. The interactions between MicroRNA-200c and BRD7 in endometrial carcinoma. *Gynecol Oncol* 2012; 124: 125-133.
- [32] Hu K, Liao D, Wu W, Han AJ, Shi HJ, Wang F, Wang X, Zhong L, Duan T, Wu Y, Cao J, Tang J, Sang Y, Wang L, Lv X, Xu S, Zhang RH, Deng WG, Li SP, Zeng YX and Kang T. Targeting the anaphase-promoting complex/cyclosome (APC/C)- bromodomain containing 7 (BRD7) pathway for human osteosarcoma. *Oncotarget* 2014; 5: 3088-3100.
- [33] Tang H, Wang Z, Liu Q, Liu X, Wu M and Li G. Disturbing miR-182 and -381 inhibits BRD7 transcription and glioma growth by directly targeting LRRC4. *PLoS One* 2014; 9: e84146.
- [34] Kim SJ, Hwang JA, Ro JY, Lee YS and Chun KH. Galectin-7 is epigenetically-regulated tumor suppressor in gastric cancer. *Oncotarget* 2013; 4: 1461-1471.
- [35] Balasubramanian A, Subramaniam R, Narayanan V, Annamalai T and Ramanathan A. BRD7 promoter hypermethylation as an indicator of well differentiated oral squamous cell carcinomas. *Asian Pac J Cancer Prev* 2015; 16: 1615-1619.
- [36] Liu H, Zhou M, Luo X, Zhang L, Niu Z, Peng C, Ma J, Peng S, Zhou H, Xiang B, Li X, Li S, He J, Li X and Li G. Transcriptional regulation of BRD7 expression by Sp1 and c-Myc. *BMC Mol Biol* 2008; 9: 111.
- [37] Liu H, Peng C, Zhou M, Zhou J, Shen S, Zhou H, Xiong W, Luo X, Peng S, Niu Z, Ouyang J, Li X and Li G. Cloning and characterization of the BRD7 gene promoter. *DNA Cell Biol* 2006; 25: 346-358.
- [38] Zhou M, Xu XJ, Zhou HD, Liu HY, He JJ, Li XL, Peng C, Xiong W, Fan SQ, Lu JH, Ouyang J, Shen SR, Xiang B and Li GY. BRD2 is one of BRD7-interacting proteins and its over-expression could initiate apoptosis. *Mol Cell Biochem* 2006; 292: 205-212.