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Gene Section

Review

BRD3 (bromodomain containing 3)

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Abstract

BRD3 is a ubiquitously expressed member of the bromodomain and extraterminal motif (BET) family of proteins that use their tandem N-terminal bromodomains to associate with acetylated histones and transcription factors. Translocations involving BRD3 and NUT generate oncogenic fusion proteins that drive NUT midline carcinoma (NMC), an aggressive squamous cell malignancy. In addition, small molecule inhibitors that target the bromodomain-acetyl lysine interaction of all BET proteins are in clinical development for both hematologic malignancies and diverse solid tumors.

Keywords
BRD3, ORFX, RING3L, bromodomain-containing protein 3, RING3-like protein, BRD3-NUT, NUT midline carcinoma

Identity

Other names: ORFX, RING3L

HGNC (Hugo): BRD3

Location: 9q34.2

DNA/RNA

Description

BRD3 maps to chromosome 9 on the reverse strand and spans 37.7kb. The gene consists of 12 exons, with the translation initiation codon present in exon 2 and the stop codon in exon 12. BRD3 exhibits a high degree of homology to BRD2, which sits in the MHC locus. In addition to BRD3, chr9q34 contains other MHC-homologous genes, suggesting that BRD2 and BRD3 may have arisen through a gene duplication event (Kasahara et al., 1996; Thorpe et al., 1997).

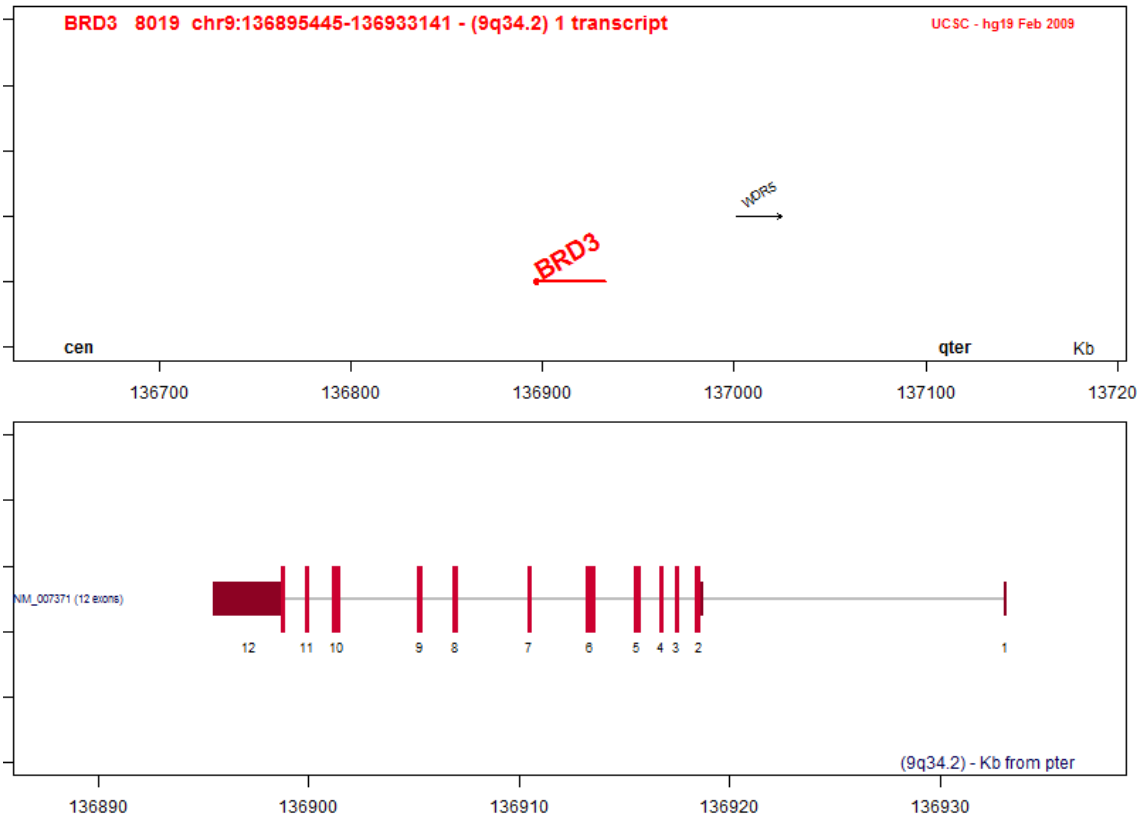
Transcription

BRD3 mRNA (NM_007371.3) is 5,673 base pairs in length. It is expressed across at least fifty adult and fetal tissues (Thorpe et al., 1997). BRD3 has an expression pattern that is similar to BRD2, although the expression levels vary between cell and tissue type.
It is not known how BRD3 expression is regulated. An alternatively spliced transcript with a predicted structure missing the C-terminal 170 amino acids has been reported, however there is no experimental validation of this shorter isoform (UniProtKB Q15059-2).

Protein

Description

BRD3 is a member of the bromodomain and extraterminal motif (BET) family of proteins that includes BRD2, BRD4 and BRDT. BET family members, including BRD3, possess conserved tandem amino-terminal bromodomains that bind to acetylated lysine residues on histones and other proteins.



The conserved extraterminal (ET) motif facilitates interactions with several transcriptional regulatory complexes (Rahman et al., 2011), and may be important for the association of BRD3 with viral proteins such as Kaposi's sarcoma-associated herpesvirus (KSHV) latency-associated nuclear antigen (LANA-1) (Ottinger et al., 2006). BRD3 contains two additional domains conserved in other BET family members, motif A and motif B (Paillisson et al., 2007). It has been reported that motif B is important for homo- and heterodimerization of BET proteins, as well as their association with mitotic chromosomes (Garcia-Gutierrez et al., 2012). The function of motif A is unknown.

Expression

Based on antibody staining, BRD3 is ubiquitously expressed in most tissues, including in cell lines generated from normal and malignant myeloid and lymphoid cells and non-hematopoietic tumors. Most primary tissues demonstrate significant expression, with the exception of lymphoid tissues, which were observed to have lower relative levels (Uhlen et al., 2015).

Localisation

BRD3 is a predominantly nuclear protein (Uhlen et al., 2015) that binds to chromatin (LeRoy et al., 2008; Lamonica et al., 2011; Stonestrom et al., 2015). Like other members of the BET family, BRD3 localizes to mitotic chromosomes (Garcia-Gutierrez et al., 2012) although the functional significance of this has not been determined. In a murine erythroid cell line BRD3 was found to exhibit strong colocalization with enhancers and promoters bound by the hematopoietic transcription factor GATA1 (Lamonica et al., 2011; Stonestrom et al., 2015).

Although BRD3 is broadly expressed, little is known about BRD3 chromatin occupancy in other tissues or its association with other tissue-specific transcription factors.

Function

Like BRD2 (Kanno et al., 2004) and BRD4 (Dey et al., 2003), BRD3 is associated with acetylated lysines on histones H3 and H4 (LeRoy et al., 2008). BRD3 was shown to activate transcription in vitro by promoting RNA polymerase II activity on nucleosomal templates in a manner that required the bromodomain-acetyl lysine interaction (LeRoy et al., 2008).

Proteomic analysis of BET proteins indicates that BRD3 can bind to transcription elongation complexes such as PTEF-b and PAF (Dawson et al., 2011).

In addition, the extraterminal (ET) domain of BRD3 can associate with the histone methyltransferase NSD3 and a component of the

Nucleosome Remodeling and Deacetylase (NuRD) complex, CHD4, suggesting that BRD3 has transcriptional regulatory function in vivo as well (Rahman et al., 2011).
BRD3 has also interacts with an acetylated peptide of the hematopoietic transcription factor GATA1 (Gamsjaeger et al., 2011; Lamonica et al., 2011). However, despite strong colocalization at GATA1-occupied sites genome-wide in an erythroid cell line, BRD3 depletion affected GATA1-mediated gene expression only in the setting of BRD2 loss. In addition, overexpression of BRD3 is able to partially rescue the erythroid maturation defects observed with BRD2 deficiency, suggesting that the functions of BRD2 and BRD3 are additive and at least partially redundant in erythroid cells, with BRD2 being the dominant protein (Stonestrom et al., 2015). It remains unclear how BRD2 and BRD3 can substitute for one another and whether BRD3 can functionally replace BRD2 at all genes. While knockout of BRD2 or BRD4 in mice results in early embryonic lethality (Houzelstein et al., 2002; Gyuris et al., 2009; Shang et al., 2009), a BRD3 knockout mouse has not been reported.

Homology

BRD3 shares functional domains with BRD2, BRD4, and BRDT. The tandem amino-terminal bromodomains, BD1 and BD2, are highly conserved between BET family members. Indeed BD1 of BRD3 is more similar to the first bromodomains of other BET proteins than it is to BD2 (Florence and Faller, 2002; Belkina and Denis, 2012). However, BET bromodomains - both BD1 and BD2 - can be selectively targeted with competitive small molecule inhibitors such as JQ1 (Filippakopoulos et al., 2010) and I-BET (Dawson et al., 2011), and thus are structurally distinct from other bromodomain-containing proteins. The carboxy-terminal extraterminal (ET) domain is about 80% conserved among BET proteins and facilitates shared protein-protein interactions with chromatin modifying proteins (Rahman et al., 2011). The remainder of the C-terminus is more divergent; however, little is understood about how this region contributes to BRD3-specific functions.
BRD3, like the other BET proteins, is evolutionarily conserved in diverse species including mice and zebrafish (NCBI). In addition BET homologs exist in Drosophila as FS(1)H (Haynes et al., 1992), and in yeast, where BDF1 and BDF2 also exhibit functional redundancy (Matangkasombut and Buratowski, 2000).

Mutations

Although there are 459 SNPs associated with the Brd3 mRNA transcript, only a small fraction have been validated and at present there are no clinically significant variants reported (dbSNP). Translocations involving BRD3 and Nuclear protein in testes (NUT) are found in NUT midline carcinoma (French et al., 2008), a rare squamous cell malignancy described below.

Implicated in

NUT midline carcinoma

Disease

NUT midline carcinomas (NMCs) are rare but lethal tumors consisting of undifferentiated or poorly differentiated squamous cells. Two thirds of NMCs result from a translocation of NUTM1 to the 3' end of BRD4 (t(15;19)(q14;p13) (French et al., 2003). The remaining NMCs involve a similar translocation to BRD3 (French et al., 2008) or WHSC1L1 (NSD3) (t(8;15)(p11;q14) WHSC1L1/NUTM1)(French et al., 2014).

Prognosis

The first two patients in whom this translocation was described lived 148 weeks and 8 weeks post diagnosis, respectively (French et al., 2008). Median survival of all NMCs is 6.7 months (Bauer et al., 2012).

Cytogenetics

BRD3/NUT fusion proteins are generated from a translocation involving t(9;15)(q34;q14). NMC typically involves only a single cytogenetic abnormality, in contrast to other carcinomas (French, 2010).

Abnormal protein

The predicted protein based on the mRNA analysis above is expected to contain the majority of the BRD3 protein, including the tandem bromodomains and the ET motif, attached to a version of NUT lacking the first 6 amino acids (French et al., 2008). This protein is structurally similar to that reported for BRD4-NUT (French et al., 2003). The BRD3-NUT and BRD4-NUT fusion proteins were noted to reside within the nucleus in a speckled pattern, in contrast to NUT alone, which was either cytoplasmic or nuclear. This suggests that the chromatin binding function of BRD3 and BRD4 inappropriately targets NUT to the nucleus (French et al., 2008). The reciprocal translocation product NUT-BRD3 exhibits no detectable expression (French et al., 2008).

Oncogenesis

The exact mechanism by which BRD3-NUT facilitates oncogenesis is not understood, but treatment of NMC cells with a BET-specific bromodomain inhibitor causes NMC cells to differentiate, suggesting that the fusion protein blocks the cells in an undifferentiated, proliferative state (Filippakopoulos et al., 2010). Deregulation of MYC expression by BRD3-NUT is one potential

mechanism (Grayson et al., 2013). NUT is also known to interact with the histone acetyltransferase p300. This suggests that BRD-NUT fusion proteins can inappropriately bind p300 and redirect its activity away from its normal targets, resulting in decreased transcription of genes important for differentiation (Reynoird et al., 2010; Schwartz et al., 2011).

Prostate cancer

Disease

Depletion of BRD3 in androgen-receptor positive prostate cancer cell lines inhibited growth and invasion, suggesting that BRD3 promotes a malignant phenotype. BRD2 and BRD4 depletion had similar effects, suggesting shared functionality in this disease (Asangani et al., 2015).

Oncogenesis

It is not known how BRD3 promotes prostate cancer cell growth or whether this function is also important in human patients. In cell lines, BRD2, BRD3, and BRD4 can associate with the androgen receptor (AR), and global BET inhibition reduces AR chromatin binding (Asangani et al., 2015). Thus one possible mechanism is that BRD3, along with BRD2 and BRD4, may act to load or stabilize AR at its target sites.

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