Gene of the month: BCOR

Alessandro Pietro Aldera,[1,2] Dhirendra Govender [1,3]

[1]Anatomical Pathology, University of Cape Town, Cape Town, South Africa
[2]Anatomical Pathology—Groote Schuur Hospital, National Health Laboratory Service, Cape Town, South Africa
[3]Anatomical Pathology, Pathcare Cape Town, Cape Town, Western Cape, South Africa

Correspondence to
Dr Alessandro Pietro Aldera, D7 Anatomical Pathology, Groote Schuur Hospital, Cape Town 7925, South Africa; alessandro.aldera@nhls.ac.za

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ABSTRACT

BCL-6 transcriptional corepressor (*BCOR*) gene is located at Xp11.4 and encodes a protein which is involved in transcriptional repression in association with BCL-6 and epigenetic silencing through polycomb repressive complex 1 (PRC1). *BCOR* mutations are being identified in an increasing number of tumours which are diverse in their anatomical location and clinical setting. Interestingly, these tumours share similar and overlapping histological features, namely small round blue cell morphology and a myxoid background with delicate capillary channels. Clear cell sarcoma of the kidney, primitive myxoid mesenchymal tumour of infancy and central nervous system high-grade neuroepithelial tumour with *BCOR* alteration all share similar internal tandem duplications in the polycomb-group really interesting new gene (RING) finger homolog ubiquitin-likefold discriminator domain of *BCOR*. Translocations resulting in *BCOR* fusion with *CCNB3*, *MAML3* and *ZC3H7B* have been identified in undifferentiated round cell sarcoma. Subsets of high-grade endometrial stromal sarcoma and ossifying fibromyxoid tumour which have a more aggressive clinical course have been shown to harbour *ZC3H7B-BCOR* fusions. BCOR immunohistochemistry is an established marker with diagnostic utility.

STRUCTURE

BCL-6 transcriptional corepressor (*BCOR*) gene is located at Xp11.4 and comprises 16 exons encoding a ubiquitously expressed transcriptional repressor.[1] The principle BCOR protein isoform comprises a canonical sequence of 1755 amino acids with a molecular weight of 192 kDa.[2] BCOR protein contains two main functional binding domains. The BCL-6 binding domain allows binding to the POZ domain of BCL-6 and augments its function as a repressor of transcription.[1] Polycomb-group RING finger homolog (PCGF) ubiquitin-like fold discriminator (PUFD), a common domain occurring in proteins involved in histone modification, allows binding to the RING finger and WD40-associated ubiquitin-like domain of PCGF proteins.

FUNCTION

BCOR protein functions as a transcriptional corepressor in association with BCL-6 and is also involved in histone modification when bound to polycomb repressive complex 1 (PRC1). PRC1 is a molecular complex involved in transcriptional repression through the epigenetic modification of histones (figure 1). PRC1 functions by adding an ubiquitin moiety to histone H2A at Lys119 (H2AK119).[3] PRCs silence several genes, including *HOX* group genes.[3 4] BCOR participates in one of the non-canonical PRC1 complexes, PRC1.1, by binding to PCGF1. PRC1.1 comprises the scaffold RING1A/B and PCGF1 heterodimer and RYBP or YAF2, SKP1, USP7 and KDM28.[4] KDM28 is involved in the recruitment and binding of chromatin to the PRC1.1 complex at non-methylated CpG islands.[5]

In addition to its role in carcinogenesis, *BCOR* appears to be involved in early embryonic development and the differentiation of embryonic stem cells into ectoderm, mesoderm and haematopoietic lineages.[6]

ROLE IN DISEASE

BCOR is being increasingly recognised as a partner fusion gene in a variety of mesenchymal neoplasms (table 1). Internal tandem duplications (ITD) in the PUFD region have also been described in clear cell sarcoma of the kidney (CCSK), primitive myxoid mesenchymal tumour of infancy (PMMTI) and central nervous system high-grade neuroepithelial tumour with BCOR alteration (CNS HGNET-BCOR).

Clear cell sarcoma of the kidney

CCSK is an uncommon aggressive paediatric renal neoplasm which was first separated from Wilms tumour by Kidd in 1970 and noted to have a propensity for bone metastases, leading to its former designation 'bone metastasising renal tumour of childhood'.[7] CCSK represents the second most common malignant paediatric renal tumour.[8] Most tumours occur between the ages of 2 and 3 years, with a male predominance (male-to-female ratio of 2:1). CCSK is known for its diversity of histological appearances, and its ability to mimic virtually all other paediatric renal tumours. Traditionally, the role of immunohistochemistry in the diagnosis of CCSK has largely been to exclude other entities in the differential diagnosis. Recently, BCOR immunohistochemistry has emerged as a sensitive and specific marker to diagnosis CCSK.[9 10]

Somatic *BCOR* ITD have been found in approximately 70% of CCSK. Three groups have identified the *BCOR* ITD at the 3' part of the exon 16 coding sequence.[11–13] ITD sequences located at the C-terminal may affect the PUFD domain conformation of the BCOR protein. The additional stretch of amino acids (ITD) in the PUFD domain might interfere with PCGF1 binding and thus could affect the PRC1-related epigenetic modifications.

High-grade endometrial stromal sarcoma

Endometrial stromal sarcomas (ESS) are uncommon malignant neoplasms of the female genital tract which typically affect women in the fifth decade

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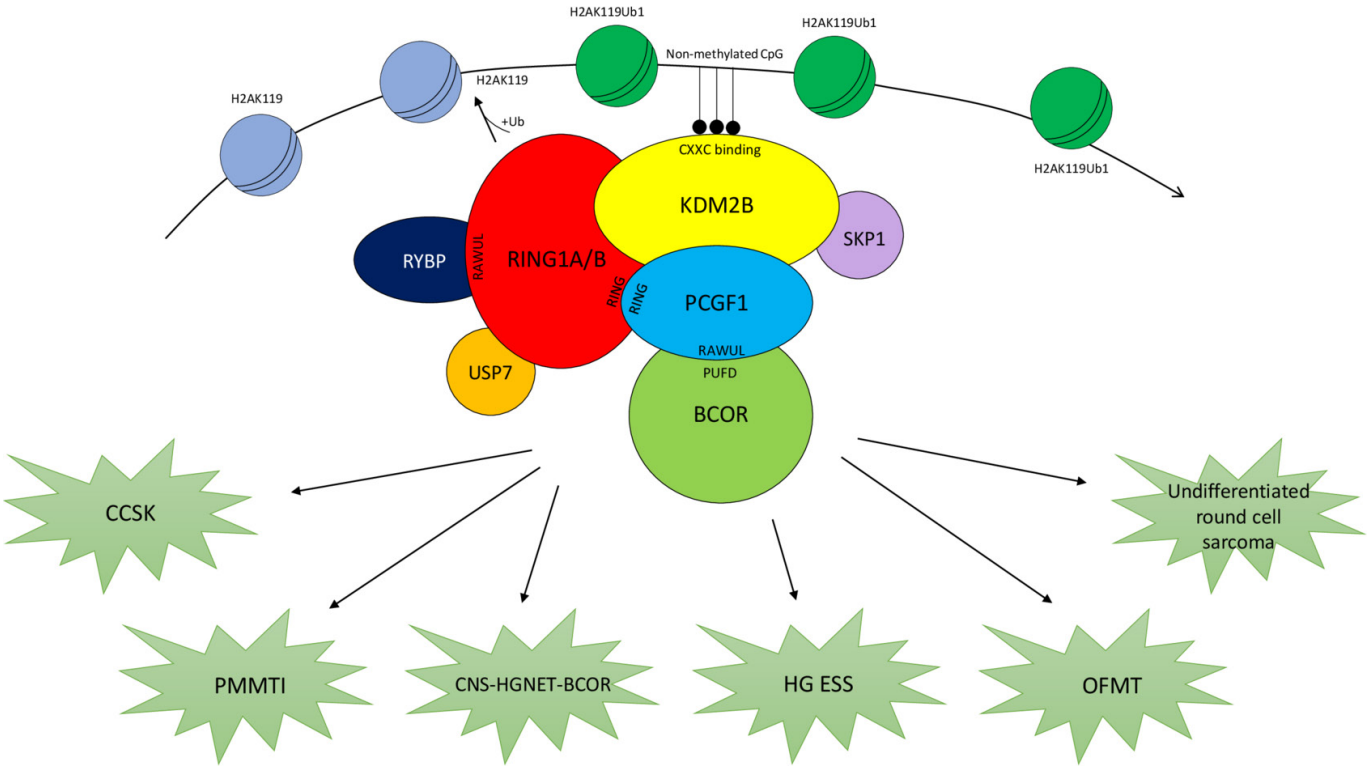

Figure 1 BCOR binds to the PRC1.1 via the RAWUL domain of PCGF protein. PRC1.1 comprises the RING1A/B and PCGF1 heterodimer and RYBP or YAF2, SKP1, USP7 and KDM28 proteins. The function of PRC1.1 is to repress transcription by the ubiquitination of histone H2A at Lys119. CCSK, clear cell sarcoma of the kidney; HG ESS, high-grade endometrial stromal sarcoma; CNS HGNET-BCOR, central nervous system high-grade neuroepithelial tumour with *BCOR* alteration; OFMT, ossifying fibromyxoid tumour; PCGF, polycomb-group RING finger homolog; PMMTI, primitive myxoid mesenchymal tumour of infancy; PRC1.1, polycomb repressive complex 1.1; RAWUL, RING finger and WD40-associated ubiquitin-like domain.

and often present with abnormal vaginal bleeding.[14] In 2012, Lee *et al* described a high-grade form of ESS which demonstrates variable histology, with cellular constituents ranging from spindled to small round cells.[15] It lacks the pleomorphism seen in undifferentiated uterine sarcoma. The most common genetic aberration occurring in high-grade ESS is t(10;17) resulting in *YWHAE-NUTM2* fusion, and this corresponds to the more classic spindle cell morphology.[16] Tumours with more myxoid stroma and composed of shorter more fusiform or round cells have recently been found to harbour *ZC3H7B-BCOR* gene fusions.[17] The latter tumours have a more aggressive clinical course. BCOR immunohistochemical staining may serve as a sensitive and specific surrogate for identifying high grade ESS, regardless of the underlying genetic alteration.[18]

Table 1 *BCOR* alterations and the neoplasms associated with them

BCOR alteration	Associated neoplasms
BCOR ITD	Clear cell sarcoma of the kidney Primitive myxoid mesenchymal tumour of infancy CNS-HGNET-BCOR
BCOR-CCNB3	Undifferentiated round cell sarcoma
BCOR-MAML3	Undifferentiated round cell sarcoma
ZC3H7B-BCOR	Undifferentiated round cell sarcoma High-grade endometrial stromal sarcoma Ossifying fibromyxoid tumour
BCOR-RARα	Acute myeloid leukaemia

BCOR, BCL-6 transcriptional corepressor; CNS-HGNET-BCOR, central nervous system high-grade neuroepithelial tumour with BCOR alteration; ITD, internal tandem duplications.

Primitive myxoid mesenchymal tumour of infancy

PMMTI is an intermediate grade mesenchymal neoplasm of proposed fibroblastic-myofibroblastic derivation. PMMTI occurs in the soft tissues of the trunk, extremities and head and neck of young infants.[19] Histologically, PMMTI is composed of sheets of round cells arranged in a vaguely nodular pattern within a myxoid background with a delicate arborising capillary network. Recently, mutually exclusive *YWHAE-NUTM2B* fusions and *BCOR* ITD similar to those found in CCSK have been described in PMMTI.[20 21] *BCOR* ITD was found in 86% of cases of PMMTI in the study by Kao *et al*.[20] These ITDs were in-frame and located in the last exon of *BCOR*, but were variable in the number of nucleotides and genomic positions. These genetic alterations are useful diagnostically in distinguishing PMMTI from its histological differential diagnosis, congenital infantile fibrosarcoma which is characterised by a recurrent *ETV6-NTRK3* fusion. Some observers now consider these tumours to represent the soft tissue counterpart of CCSK.[20]

Undifferentiated round cell sarcoma

Small round blue cell tumours (SRBCT) are a heterogeneous group of neoplasms which are often difficult to diagnose. The most common genetic alteration in this family of tumours is *EWSR1* rearrangement. *EWSR1*-negative SRBCT are associated with *CIC-DUX4* fusions in approximately two thirds of cases. The majority of the remaining cases show *BCOR* rearrangements. BCOR-rearranged sarcomas show a striking male predominance.[22]

Pierron *et al* identified *BCOR-CCNB3* fusion in a subset of *EWSR1*-negative SRBCT with Ewing sarcoma (ES)-like

morphology.[23] This results from an X-chromosomal paracentric inversion linking the *BCOR* sequence to exon 5 of *CCNB3*. *BCOR-CCNB3* sarcomas occur predominantly in children and present in the bone.[24 25] Whether these tumours represent standalone entities or should be added to the ES family of tumours is still unresolved. Nevertheless, it is important to distinguish these tumours from ES from a clinical and therapeutic standpoint.

More recently, Specht *et al* studied 75 SBBCTs that were negative for *EWSR1*, *FUS*, *SYT*, *CIC* and *BCOR-CCNB3* inversion.[26] They identified two recurrent *BCOR*-related fusions involving *MAML3* and *ZC3H7B* partner genes. In contrast with *BCOR-CCNB3* sarcomas, these tumours were found to occur in adults (mean age of 35 years at diagnosis) and present more commonly in the deep soft tissues. These tumours were shown to follow an aggressive clinical course. Histological evaluation showed a spindle cell component in the majority of cases which differs from ES and the *BCOR-CCNB3* sarcoma.

Ossifying fibromyxoid tumour

Ossifying fibromyxoid tumour (OFMT) is an uncommon rarely metastasising soft tissue neoplasm first described by Enzinger *et al* in 1989.[27] Arising typically in the extremities or trunk, OFMT is characterised histologically by a peripheral circumferential bony shell and cords and nests of bland small neoplastic cells embedded within a fibromyxoid stroma. OFMTs are currently classified as typical, atypical and malignant, based on cellularity, nuclear grade and mitotic rate.[28] It is now recognised that OFMT is a translocation-associated neoplasm with recurrent rearrangements of the *PFH1* gene. The most common fusion is *PFH1-EP400* which was described in 44% of the 39 OFMTs examined by Antonescu *et al*.[29] Recently, small numbers of OFMTs have been shown to harbour other translocations including *ZC3H7B-BCOR* and *MEAF6-PHF1*.[29] These tumours were more likely to be S100 negative and behave in a malignant manner. *EPC1-PHF1* fusion has also been described. *ZC3H7B-BCOR*, *MEAF6-PHF1* and *EPC1-PHF1* fusions have also been reported in ESS.

CNS HGNET-BCOR

CNS HGNET-BCOR is a rare aggressive brain tumour first described by Sturm *et al* in 2016 while examining the molecular profiles of central nervous system primitive neuroectodermal tumours.[30] CNS HGNET-BCOR occur predominantly in young children, but have also been described in adolescents and young adults. The tumours show perivascular anuclear zones, which may evoke consideration of astroblastoma or ependymoma. These tumours demonstrate in-frame ITDs in BCOR which are identical to those described in CCSK.[13] Treatment of these uncommon tumours is challenging and protocols are not well defined. Coactivation of the wingless-related integration site (Wnt) and sonic hedgehog signalling pathways have been identified in CNS HGNET-BCOR.[30 31] Novel therapeutic approaches targeting these pathways such as arsenic trioxide with radiotherapy are being investigated.[32]

Other tumours and conditions

Germline *BCOR* loss of function mutations has been described in X linked oculofaciocardiodental syndromes.[33] Somatic mutations of *BCOR* have been detected in a small subset of acute myeloid leukaemia, myelodysplastic syndrome and chronic myelomonocytic leukaemia.[34]

Take home messages

- BCL-6 transcriptional corepressor (*BCOR*) is located at Xp11.4 and is involved in cancer by internal tandem duplications (ITD) or as a partner fusion gene.
- BCOR functions as a corepressor when bound to BCL-6 and also forms part of the polycomb repressive complex 1 which ubiquitinates H2AK119 causing epigenetic silencing.
- Clear cell sarcoma of the kidney, primitive myxoid mesenchymal tumour of infancy and central nervous system high-grade neuroepithelial tumour with *BCOR* alteration are morphologically similar tumours which share *BCOR* ITD.
- Subsets of undifferentiated round cell sarcoma, high-grade endometrial stromal sarcoma and ossifying fibromyxoid tumour show *ZC3H7B-BCOR* fusion.
- Undifferentiated round cell sarcoma can also show *BCOR* fusions with either *CCNB3* or *MAML3*.
- BCOR immunohistochemistry can be used diagnostically to separate some of these tumours from their histological mimics.

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ORCID iD
Dhirendra Govender http://orcid.org/0000-0003-1487-8255

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