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Gene Section
Review

BIRC6 (Baculoviral IAP repeat-containing 6)

Sze Ue Iris Luk, Yuzhuo Wang

The Vancouver Prostate Centre, Vancouver General Hospital and Department of Urologic Sciences, the University of British Columbia, Vancouver, BC, Canada (SUI), Department of Experimental Therapeutics, BC Cancer Agency, Vancouver, BC, Canada (YW)

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Abstract

The BIRC6 gene (BRUCE/APOLLON) encodes the cytoplasmic protein BIRC6 in mammals, consisting of a single N-terminal baculoviral IAP repeat (BIR) domain and a C-terminal ubiquitin-conjugating (UBC) domain. Of the huge protein size at 528 kDa, BIRC6 demonstrated pleiotropic functions including inhibition of apoptosis, cytoprotection, regulation of cytokinesis, mitosis, autophagy and neutrophil differentiation. With the BIR domain, BIRC6 is defined as a member of the Inhibitor of Apoptosis (IAP) family. Through its BIR domain, BIRC6 binds to active caspases, including caspases-3, 6, 7 and 9 and accounts for its ability to inhibit the caspase cascade and ultimately apoptosis. The UBC domain has chimeric E2/E3 ubiquitin ligase activity where it facilitates proteosomal degradation of various proteins, including pro-apoptotic proteins p53, caspases, Smac and mitotic regulator cyclin A. More importantly, the UBC domain plays an indispensable role in embryonic development in mammals and spermatogenesis in Drosophila. Increasing evidence supports the cancer promoting role of BIRC6. Elevated BIRC6 expression has been found in a variety of cancers and was shown to contribute to treatment resistance.

Keywords
BIRC6, Apollon, BRUCE, Inhibitor of Apoptosis, BIR, UBC, E2/E3 ligase.

Identity

Other names: APOLLON, BRUCE

HGNC (Hugo): BIRC6

Location: 2p22.3

Local order

- CARD12 (caspase recruitment domain family member 12) (encoded on minus strand, 32303029-32344427)
- YIPF4 (YIP1 domain family member 4) (32356483-32385159)
- **BIRC6** (32435234-32697467)
- TTC27 (tetratricopeptide repeat domain 27) (32706633-32899620)
- LTBP1 (latent transforming growth factor beta binding protein 1) (33025896-33478077)

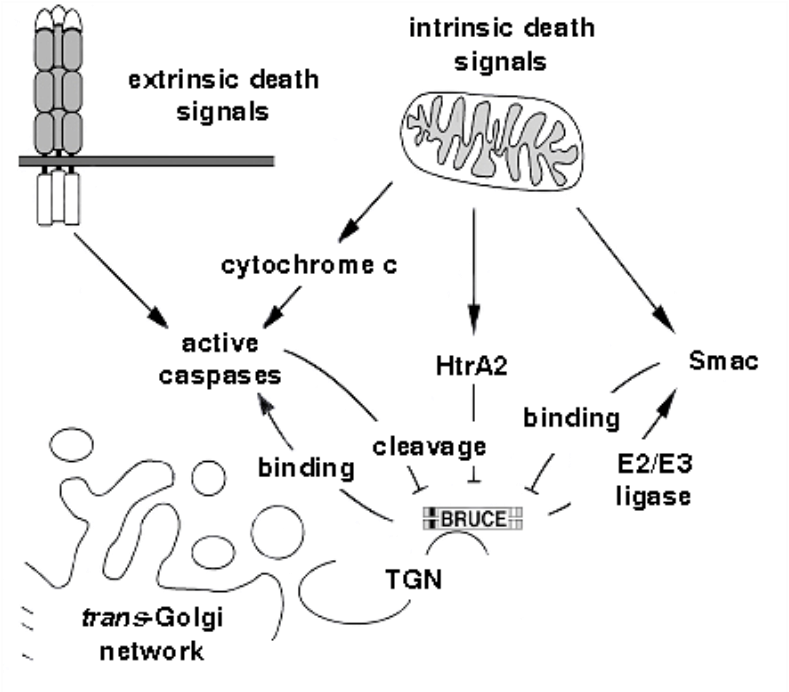
DNA/RNA

Description

The BIRC6 gene comprises 75 exons resulting in a transcript of 16066 bps. The ATG is in the first exon.

Transcription

Only one variant of BIRC6 has been found so far which comprises 14490 bps. There are several synonymous and nonsynonymous SNPs reported for BIRC6 (E589K, L1742F, R2187T, T2646S, T3708N, E3864K, Q4323H, N4324Y, S4325C, N4326T, P4329R).



BIRC6 is a component of the apoptosis regulatory network. Multiple protein-protein interactions allow a switch from apoptosis inhibition to inactivation in later steps in apoptosis. BIRC6's action on activated caspases and other pro-apoptotic molecules might be restricted to the trans-Golgi network and the vesicular system.

Pseudogene

Not known. There is evidence for a processed pseudogene in M. musculus.

Protein

Description

BIRC6 contains two functionally validated domains: A N-terminal BIR repeat (SMART SM00238, aa: 256-332) and a C-terminal UBC domain (SMART SM00212, aa: 4548 - 4712). The BIR repeat is needed for interactions with caspases and IAP-binding motif (IBM) containing proteins (HtrA2, Smac). The UBC domain can form a thiolester linkage with ubiquitin transferred by E1.
Between aa 1589-1633 a coiled-coil region can be found.

Expression

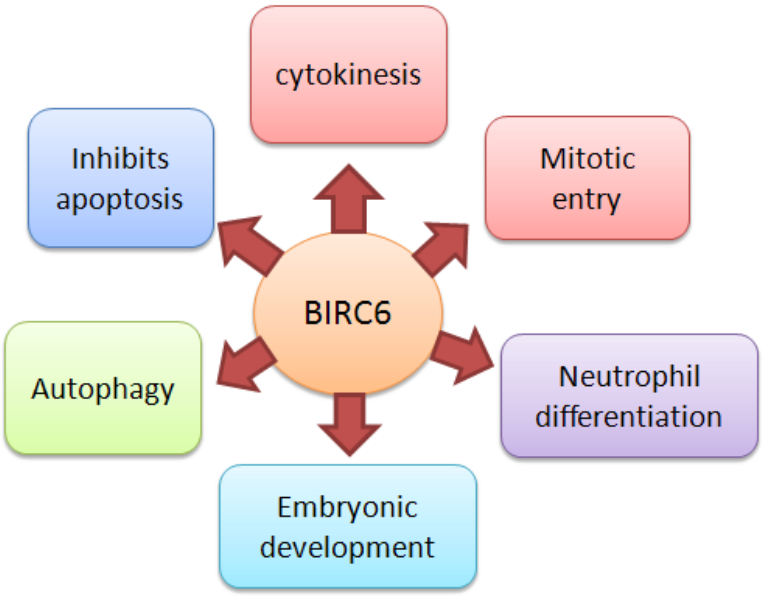
BIRC6 is highly expressed in brain, testis, lymphatic cells and secretory organs and also found in any other tissues (Hauser et al., 1998). It is highly expressed in the mouse embryos up to E11 and then transcript levels drop. Single-cell RNA cytometry analysis revealed a bi-modal distributed Birc6 mRNA expression heterogeneity within mouse hematopoietic stem cell (HSC) population. Upon ageing, BIRC6-high expressing HSC cells were shown to out-compete Birc6-low cells (Dimov et al., 2014). BIRC6 is frequently elevated in various cancer tissues.

Localisation

Localized to membranes of the trans Golgi network (TGN) and the endosomal system (Hauser et al., 1998). BIRC6 relocalizes considerably during the cell cycle. It concentrates in a pericentriolar compartment in interphase, moves partially to spindle poles in metaphase, and finally localizes to the spindle midzone and the midbody in telophase and during cytokinesis (Pohl and Jentsch, 2008).

Function

Inhibitor of apoptosis. BIRC6 is a peripheral membrane protein of the trans-Golgi network that protects cells from apoptosis by functioning as an inhibitor of apoptosis protein (IAP). BIRC6 can bind and inhibit activated caspases CASP-3, CASP-6, CASP-7, CASP-8 and CASP-9. Furthermore it ubiquitylates caspase-9, HtrA2 (a pro-apoptotic serine protease) and DIABLO/Smac (a competitor for caspase-IAP interactions) thereby targeting them for proteasomal degradation. The ubiquityltion reactions do not require an ubiquitin E3 ligase making BIRC6 a chimeric E2/E3 ubiquitin ligase (Bartke et al., 2004; Hao et al., 2004). More importantly, distinct from other IAP members, BIRC6 is able to antagonize both precursor and mature forms of Smac and caspase-9. The ability to antagonize precursor apoptotic molecules represents an important mechanism for the prevention of apoptosis under normal conditions (Qiu and Goldberg, 2005).



Summary of the pleiotropic functions of BIRC6.

On the other hand, BIRC6 also inhibits apoptosis via negatively regulating p53 protein levels by facilitating its degradation via ubiquitination (Ren et al., 2005; Tang et al., 2014).

BIRC6 and treatment resistance. Silencing of BIRC6 has been shown to sensitize cancer cells to various anticancer agents, including 5-fluorouracil (in cervical, fibrosarcoma and breast cancer cells) (Chu et al., 2008), oxaliplatin and cisplatin (in colonospheres) (Van Houdt et al., 2011), MEK inhibitor, BRAFV600E-specific inhibitor and soluble or membrane-bound TRAIL (in melanoma cells) (Tassi et al., 2012), cisplatin (in non-small cell lung cancer and glioma) (Dong et al., 2013; Chen et al., 1999), camptothecin (glioma) (Chen et al., 1999) and sorafenib (in hepatoma) (Tang et al., 2014).

Essential in embryonic development. Targeted disruption of BIRC6 in mice caused embryonic and neonatal lethality. BIRC6 homozygous-mutant embryos which did not express BIRC6 all died immediately after birth. At E18.5, viable mutant embryos had normal appearance, but were significantly smaller (10-20% less body weight) than control littermates. Macroscopic analysis of mutant embryos at E15.5 revealed that more than half of them had severely defective angiogenesis that often coincided with severe oedema (Hao et al., 2004). Consistantly, BIRC6 knock-out mice showed retarded growth and poor vascularization from E13.5 and perinatal lethality (Lotz et al., 2004). BIRC6 mutant mice were embryonic lethal (Hitz et al., 2000; Ren et al., 2005).

Regulator of cytokinesis. BIRC6 is a major regulator of abscission, the final stage of cytokinesis. During cytokinesis, BIRC6 moves from the vesicular system to the midbody ring and serves as a platform for the membrane delivery machinery and mitotic regulators. Depletion of BIRC6 in cell cultures causes defective abscission and cytokinesis-associated apoptosis, accompanied by a block of vesicular targeting and defective formation of the midbody and the midbody ring. BIRC6 coordinates multiple steps required for abscission including the relocalization of ubiquitin from midbody microtubules to the midbody ring during cytokinesis (Pohl and Jentsch, 2008).

Novel regulator of mitosis. BIRC6 interacts with cyclin A and promotes its degradation in early mitosis. BIRC6 also interacts with APC/C, and it facilitates cyclin A ubiquitylation. The elimination of cyclin A and cyclin B are essential for entry into mitosis. BIRC6 -deficient MEF cells exhibit earlier replicative senescence, large nuclei with excess centrosome, and mitotic delay. BIRC6 facilitates the ubiquitylation of CYCLIN A by recruiting it to APC/C without the need of a functional UBC domain, suggesting its role as a substrate recognition subunit in a complex of ubiquitin ligase (Kikuchi et al., 2014).

BIRC6 and autophagy. Functional BIRC6 is required to inhibit autophagy under nutrient-rich conditions in D. melanogaster oogenesis. Lack of BIRC6 function in BIR-domain deleted flies resulted in an increase in both autophagic punctate and TUNEL staining in germaria and degenerating midstage egg chambers (Hou et al., 2008). On the contrary, recent evidence suggested that BIRC6 may promote autophagy in prostate cancer cells. Silencing of BIRC6 was showed to decrease Beclin-1 protein, LC3 cleavage and reduce LC3 punctate formation (Low et al., 2013).

Regulation of BIRC6

Despite the ability of BIRC6 to target caspases, Smac and HtrA2, BIRC6 is also negatively regulated by these pro-apoptotic molecules. Caspase-3 and HtrA2 are capable of cleaving BIRC6 and inhibit its anti-apoptotic function. Smac inhibits the IAP function of BIRC6 by its ability to block BIRC6-caspase binding (Bartke et al., 2004; Sekine et al., 2005). Nrdp1, a RING finger containing ubiquitin ligase, promotes proteasomal degradation of BIRC6 (Qiu et al., 2004).

Epstein-Barr Virus (EBV) microRNAs (miRNAs) processed from the BHRF1 and BamHI A rightward (BART) transcript, miR-BART15-3p, targets the 3' untranslated region (UTR) of BIRC6. miR-BART15-3p inhibits the translation of BIRC6 protein in EBV-infected gastric carcinoma cells and contributes to host cells apoptosis induction (Choi et al., 2013). In muscle, prostaglandin F2a upregulates BIRC6 which promotes muscle cell survival and growth (Jansen and Pavlath, 2008).

Homology

- ubc-17 (C. elegans)
- IAP6 (A. gambiae)
- Bruce (D. melanogaster)
- BIRC6 (X. tropicalis)
- Birc6 (M. musculus)

Mutations

There are several synonymous and nonsynonymous SNPs reported for BIRC6 (E589K, L1742F, R2187T, T2646S, T3708N, E3864K, Q4323H, N4324Y, S4325C, N4326T, P4329R).

Implicated in

Myelodysplastic syndromes

Bone marrow cells of myelodysplastic syndromes exhibit significant expression of BIRC6 (Abe et al., 2005).

Childhood acute myeloid leukemia

Prognosis

BIRC6 elevation associated with poor prognosis in childhood de novo Acute Myeloid Leukemia: BIRC6 overexpression (>median expression) was associated with an unfavorable day 7 response to induction chemotherapy and also associated with a poorer 3-year relapse-free survival rate (Sung et al., 2007).

Acute myeloid leukemia

BIRC6 mRNA expression was associated with the differentiation status of AML cells.

BIRC6 mRNA expression was induced upon neutrophil differentiation of AML cells, whereas knocking-down BIRC6 attenuates neutrophil differentiation of APL cells without altering cell survival.

Cytogenetics

AML patient samples with the t(8;21), the t(15;17) or a complex karyotype express BIRC6 significantly lower than normal human granulocytes (Schläfli et al., 2012).

Colorectal cancer

BIRC6 expression increased in colorectal cancer tissue and stem-like cells enriched colonosphere.

BIRC6 mRNA expression was significantly up-regulated in primary colorectal cancer tissues compared with normal mucosa (Bianchini et al., 2006). Moreover, BIRC6 protein highly up-regulated in patient derived colonosphere compared with differentiated counterpart. Knockdown of BIRC6 sensitized colonosphere against the chemotherapeutic drugs oxaliplatin and cisplatin in vitro. (Van Houdt et al, 2011).

Brain cancers

Elevated expression in brain cancers.

BIRC6 knockdown induces apoptosis in neuroblastoma cells and associated with increased DIABLO protein expression in cytoplasm (Lamers et al., 2012). It is also overexpressed in glioma cell lines (SF-268, SNB-78) (Chen et al., 1999).

Cytogenetics

Frequent gain of the BIRC6 gene on chromosome 2 neuroblastoma tumors, which resulted in increased BIRC6 mRNA expression (Lamers et al., 2012).

Melanoma

BIRC6 is constitutively expressed in melanoma and promote resistance to antitumor agents.

BIRC6 was constitutively expressed by melanoma cells, in vitro and in patient samples, and at higher levels than in benign melanocytic lesions. Melanoma susceptibility to apoptosis by cytotoxic drugs fotemustine and target-specific inhibitors (MEK inhibitor and BRAFV600E-specific inhibitor) correlated with down-modulation of BIRC6 protein. The antitumor agents promoted BIRC6 downmodulation, is caspase independent and proteasome dependent. Moreover, targeting of BIRC6, by siRNA, significantly enhanced caspase-dependent melanoma apoptosis in response to cytotoxic drugs, MEK, and BRAFV600E inhibitors and soluble or membrane-bound TRAIL (Tassi et al., 2012).

Non-small cell lung cancer (NSCLC)

Elevated expression in non-small cell lung cancer (NSCLC).

BIRC6 down-regulation inhibited growth of the NSCLC cells and sensitized the cells to cisplatin in vitro.

Prognosis

Elevated BIRC6 protein expression in NSCLC tissues was associated with poor 3-year relapse-free patient survival, regional lymph node metastasis, and advanced pathological tumor, node, metastasis stage. (Dong et al., 2013).

Prostate cancer

BIRC6 is elevated in advanced prostate cancer and important in promoting growth and suppressing apoptosis.
Elevated BIRC6 protein expression was found in prostate cancer cell lines and clinical specimens compared to benign tissue. In particular, increased BIRC6 expression was associated with Gleason 6-8 cancers, castration resistance, higher clinical T stages and correlates with the presence of poor prognostic factors including PSA recurrence, lymph node metastasis and prostatic capsule invasion (Low et al., 2013; Luk et al., 2014).

Epithelial ovarian cancer

Elevated expression and poor prognostic factor in epithelial ovarian cancer.
BIRC6 expression was higher in the epithelial ovarian cancer (EOC) tissue than in normal control tissue at protein level.

Prognosis
BIRC6 was an independent significant predictor for overall survival and disease-free survival. Cytoplasmic BIRC6 expression is associated with EOC differentiation (Wang et al., 2014).

Hepatocellular carcinoma (HCC)

BIRC6 promotes hepatocellular carcinogenesis and associates with poor patient survival and prognosis.
BIRC6 knockdown suppressed hepatoma cell proliferation, caused G1/S arrest and sensitized hepatoma cells to sorafenib-induced apoptosis in vitro and in vivo.

Prognosis
BIRC6 overexpression was significantly correlated with serum alanine aminotransferase level and HCC vascular invasion in patient samples. Patients with BIRC6 positive expression in tumor tissue had a poor survival and a high rate of recurrence (Tang et al., 2014).

Breast cancer

BIRC6 promotes cell growth and inhibiting apoptosis in breast cancer cells with wild type p53.
BIRC6 knockdown resulted in a marked decline of cell growth and an increased rate of apoptosis in wild-type p53 ZR75.1 cells, which was associated with p53 stabilisation and activation of the mitochondrial-dependent apoptotic pathway. A less pronounced anti-proliferative and pro-apoptotic effects were observed in mutant p53 breast cancer cells (Lopergolo et al., 2009).

Pseudoexfoliative glaucoma (PEXG)

Polymorphism in the BIRC6 Gene plays a protective role in Pseudoexfoliative Glaucoma.

Prognosis
TT allele of the rs2754511 in the BIRC6 gene plays a protective role in PEXG patients of the Pakistani population (Ayub et al., 2014).

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