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Review

BIRC7 (baculoviral IAP repeat containing 7)

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Abstract

BIRC7, also known as livin, is a member of the Inhibitor of Apoptosis Protein (IAP) family and is linked to the prevention of cell death induced by apoptosis, by directly or indirectly preventing caspase activity. In general, as most IAPs, BIRC7 expression is not detectable in normal differentiated adult tissues, with the exception of placenta, spleen, lymph nodes and developing embryonic tissues. On the other hand, BIRC7 overexpression has been reported in a variety of tumor types, in which it is associated to malignancy and chemoresistance. Currently, there are some unanswered questions about BIRC7, including its interaction with caspases, a potential paradoxical role in the apoptotic process, and specific functions/affinities of the BIRC7α and BIRC7β splice variants. Moreover, several studies have demonstrated the value of BIRC7 as a therapeutic target in a number of cancer types. This review mainly focuses on the role of BIRC7 in cancer cell biology and its clinical significance, demonstrating aspects of its DNA/RNA and protein, as well as its relevance in cancer diagnosis and prognosis.

Keywords
BIRC7; Interact with caspases; Apoptosis; Breast cancer; Ampullary carcinoma; Neuroblastoma; Glioblastoma; Cervical carcinoma; Colorectal cancer; Esophageal carcinoma; Gastric cancer; Head and neck squamous cell carcinoma; Kidney cancer; Laryngeal cancer; Leukemia; Hepatocellular carcinoma; Lung cancer; Lymphoma; Melanoma; Mesothelioma; Oral squamous cell carcinoma; Ovarian cancer; Osteosarcoma; Pancreas cancer; Prostate cancer; Retinocytoma; Urinary tract cancer

Identity

Other names
ML-IAP, KIAP, RNF50, Livin, melanoma inhibitor of apoptosis protein, kidney inhibitor of apoptosis protein, livin inhibitor-of-apoptosis

HGNC (Hugo): BIRC7

Location: 20q13.3

DNA/RNA

Description

The BIRC7 gene is about 4.6 Kb (start: 63235883 bp and end: 63240507 bp; orientation: plus strand). There are two transcript variants deposited in the NCBI database (https://www.ncbi.nlm.nih.gov/gene). The transcript variant 1 (cDNA: 1334 bp) encodes the longer isoform (alpha; BIRC7α) (298 aa). The transcript variant 2 (cDNA: 1280 bp) presents an alternate in-frame splice site and encodes the shorter isoform (beta; BIRC7β) (280 aa). Isoform α blocks staurosporine-induced apoptosis and augments killing by natural killer (NK) cells, while isoform β blocks etoposide-induced apoptosis and protects

against NK cell. There is an additional transcript variant reported in Ensembl (http://www.ensembl.org/), which contains a cDNA of 593 bp, and generates a protein with 193 aa.

Protein

Description

The IAPs (Inhibitors of Apoptosis Proteins) are a family of proteins recognized, predominantly, for their role in preventing apoptotic cell death by directly or indirectly hindering caspase activity. Nevertheless, these proteins are further involved in other signaling pathways associated to cell survival, cell cycle and cell migration (Gyrd-Hansen & Meier, 2010; Owens et al., 2013; Plati, Bucur Khosravi-Far, 2011). The presence of, at least, one BIR domain (baculovirus IAP repeat), a conserved sequence of about 80 amino acid residues with Zn^{+2} in the center, which mediates the protein-protein interactions with caspases being essential for their anti-apoptotic activity, is the structural distinctive of the family (Budhidarmo & Day, 2015; Deveraux & Reed, 1999; Lopez; Meier, 2010). Eight IAPs have been identified within the human proteome - NAIP (BIRC1), cIAP1 (BIRC2), cIAP2 (BIRC3), XIAP (BIRC4), survivin (BIRC5), Apollon/Bruce (BIRC6), livin/ML-IAP (BIRC7) e ILP-2 (BIRC8), and these may present either one or three BIR domains arranged in their N-terminal portion (Budhidarmo & Day, 2015; Deveraux & Reed, 1999; Lopez Meier, 2010).

BIRC7 is a 39 kDa member of the IAP family, structured with a single BIR domain, added with a RING domain on the C-terminus portion, as firstly described by Vucic and colleagues in the year 2000 (Figure 1). Its BIR domain is globularly assembled, with four α-helixes and a three-strand anti-parallel β-sheet (Hinds et al., 1999). In turn, the RING-type zinc-finger domain, alike in other RING-bearing IAPs, has ubiquitin-ligase (E3) activity and, thus, is associated with the ubiquitination functionality; however further studies have demonstrated additional and yet unclear roles in addressing apoptotic activity (Ma et al., 2006).

A distinctive feature of this protein is that, unlike any other IAP, following a strong apoptotic incitement, BIRC7 is cleaved by CASP3 and CASP7 (caspases-3 and -7) at Asp52 to give a truncated form, which, paradoxically, promotes cell death (Nachmias et al., 2003).

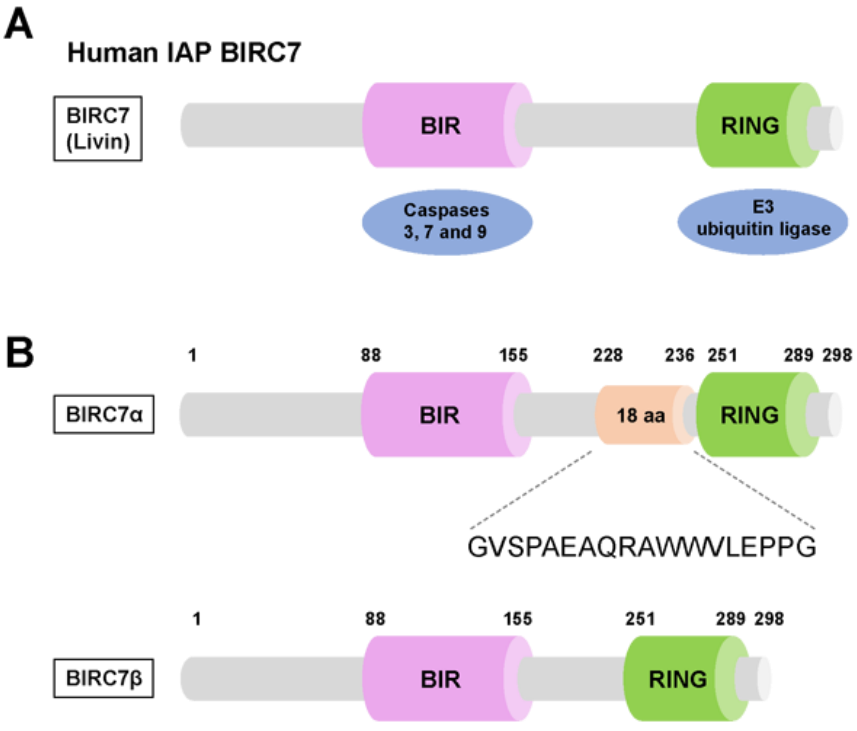

Figure 1. Structure of BIRC7 and its variants. BIRC7 (also known as livin) protein structure has 39 kDa and is composed of a single BIR domain containing approximately 70 amino acids (aa) and zinc binding residues. The protein nucleus is generally connected with a conserved cysteine and is rich in histidine, and is connected to its anti-apoptotic activity. Additionally, the RING domain, which gene covers 4.6 kb in chromosome 20, band q13, is composed by six introns and seven exons. Structurally, BIRC7-BIR forms a globular architecture preserved by four α-helices and an anti-parallel sheet of three filaments, as well as residues that form the hydrophobic nucleus. The RING domain is usually defined by seven cysteines and a histidine that can coordinate two zinc atoms in its carboxy terminal. BIRC7 has two similar variants, α and β, differing by 18 amino acids located between the BIR and RING domains, present only in the isoform α. Both isoforms have shown biological relevance to cancer.

By such trait, rather than merely an apoptosis inhibitor, BIRC7 may actually be allowed to a broader title, one of a cell death regulator. Furthermore, through alternative splicing of the mRNA, BIRC7 has two splice variants, BIRC7α and BIRC7β, which have different subcellular distribution and distinct anti-apoptosis properties. Still, the BIR and RING domains are identical in both isoforms, and their only structural difference is assumed by the 18 amino acids present between these domains in the α isoform, allowing the formation of an α-helix linker (Ashhab et al., 2001; Li et al., 2013a).

For BIRC7, there are currently a number of unanswered questions concerning the protein interaction with caspases, the paradoxical activities it can undertake during apoptosis and, also, on specific functions and affinities of the α and β variants. Still, taken the range of activities and regulatory motifs of the protein, BIRC7 has been regarded as an interesting target for cancer therapy. As this IAP displays such unique pro- and anti-apoptotic properties, a treatment strategy could involve the promotion of BIRC7 cleavage, directing accumulation of the truncated protein, in an attempt to tip the scale towards the pro-apoptotic effect, to counteract apoptosis resistance promoted by IAPs and other disrupted signaling pathways present in cancer cells (Wang et al., 2008). Other therapeutic opportunities include targeting BIRC7 at the transcriptional level using antisense oligonucleotides, thus, reducing the expression levels of the protein. Interestingly, antisense IAP therapy is also under clinical testing for XIAP and BIRC5, with promising candidates (Xia et al., 2002; Hu et al., 2003).

Expression

Much like most IAPs, BIRC7 has low or even no detectable expression in normal differentiated adult tissues, but is present in high levels in placenta, spleen, lymph nodes, developing/embryonic tissues and in a variety of tumor types (Li et al., 2013a). In fact, BIRC7 overexpression has been recorded in numerous cancers, however, it is best linked to the malignancy in which it was preferentially overexpressed when it was originally detected - melanoma -, justifying the attributed label of ML-IAP (melanoma inhibitor of apoptosis proteins) (Vucic et al., 2000). BIRC7 protein levels have been found upregulated in primary tumors as well as in various melanoma cell lines, whereas it was only detectable in negligible amounts in melanocytes or nevi. Still, in melanoma, high levels of BIRC7 have been associated to chemoresistance and poor prognosis, while intermediate levels (but not necessarily the total lack of BIRC7 expression) were related to a better prognosis - possibly due to the pro-death activity of the truncated forms of the protein (Gong et al., 2005; Lazar et al., 2012).

Gastric, prostate, bladder, breast, renal and liver carcinomas, along with neuroblastoma, leukemia, and lymphomas, as well as non-small cell lung, cervical, liver and pancreatic cancers have all been related to BIRC7 upregulation (Gazzaniga et al., 2003; Tanabe et al., 2004; Hariu et al., 2005; Kim et al., 2005; Wagener et al., 2007; Augello et al., 2009; Yuan et al., 2009; Wang et al., 2010; El-Mesallamy et al., 2011; Lazar et al., 2012). In neuroblastoma, bladder and gastric cancers, higher levels of BIRC7 expression could be pondered as a risk factor, once isoform α, but not β, was predominant in bladder cancerous tissue but neither isoform occurred in the healthy tissue (Gazzaniga et al., 2003). In gastric cancer, nearly half of the assessed patients expressed both isoforms in their tumorous tissue, however benign gastric lesions showed no detectable BIRC7 expression (Wang et al., 2010).

Moreover, Ashhab and colleagues (2001) assessed mRNA transcripts of BIRC7α and BIRC7β in a panel of human tumor cell lines and upregulation of both isoforms was detected in melanoma, colon, and prostate carcinoma cells. Nevertheless, when measured in normal fetal and adult tissues, different expression levels for each isoform suggests a specific pattern of splicing and expression related to histology. Notable levels of BIRC7β were found mainly in fetal kidney, spleen, and heart, whereas no BIRC7α was detected in fetal tissues. Adult tissues, such as heart, placenta, lung, spleen and ovary showed upregulation of both isoforms, while only the α isoform was detected in brain, skeletal muscle and lymphocytes (Ashhab et al., 2001).

Localisation

BIRC7 can be found both in the nucleus and in the cytoplasm, and the localization of this IAP has been compared to that of BIRC5 (Kasof Gomes, 2001). Nevertheless, full-length forms of both BIRC7 variants are present exclusively in the cytoplasm, while a peri-nuclear distribution is seen for the pro-apoptotic truncated forms of BIRC7 (t-livin), with prominent accumulation in the Golgi apparatus (Nachmias et al., 2007a). In fact, subcellular localization has been known to regulate the different roles of IAPs in the apoptosis process (Ambrosini et al., 1998). In this context, Nachmias and colleagues (2007) have demonstrated that the N-terminal region of t-livin directs the peri-nuclear distribution and this arrangement is essential, but not enough, to give t-livin its pro-apoptotic activity. The RING domain, whose purposes have been afflicted with much ambiguity among distinct IAPs, then fulfills the operative role in the properly localized t-livin's pro-apoptotic functions.

Point mutations to the RING domain resulted in proper peri-nuclear distribution and further Golgi

localization, but abrogated the pro-apoptotic effect of t-livin. However, RING-mutated full-length BIRC7 was found in both nucleus and cytoplasm, suggesting that RING domain, opposite to what was observed for the truncated forms, may affect the sub-cellular localization of full-length BIRC7 (Nachmias et al., 2007a). Moreover, while the occurrence of intact full-length BIRC7 in the cytoplasm directly correlates with resistance to apoptosis, the presence of t-livin in the nucleus is associated with increased cellular apoptosis.

Function

Most IAPs are thought to directly interact with caspases and block their activity (Kasof & Gomes, 2001), and the integrity of the BIR domain is necessary to achieve this effect. In fact, BIRC7 has been initially proposed to bind and inhibit CASP9, but not CASP1, CASP2, CASP3, CASP6, CASP7 or CASP8 (Vucic et al., 2000; Vucic et al., 2002). However, subsequent work carried out by the same group demonstrated that BIRC7 established a weaker interaction with caspases 3 and 9 when compared to that of XIAP (Vucic et al., 2005) (Figure 2). Moreover, three critical BIR residues were found responsible for BIRC7's lower caspase inhibition potency - Ser150, Gln167 and Glu168 - while XIAP's corresponding residues- Gly326, His343, and Leu344- rendered the latter IAP a stronger inhibitor. Once the critical residues were replaced for those of XIAP, the mutant BIRC7 actually showed greater inhibition towards caspase 9 than native XIAP (Vucic et al. 2005). Nevertheless, BIRC7 was demonstrated to bind with high affinity to the pivotal pro-apoptotic, IAP-antagonizer mitochondrial protein DIABLO (SMAC) through the BIR domain, while BIR-mutations were shown to abolish BIRC7-SMAC/DIABLO interaction (Ma et al., 2006). In this scenario, the anti-apoptotic function played by BIRC7 is essentially revealed through the sequestration of SMAC/DIABLO, thus abrogating the anti-IAP effect exerted by such protein (Chai et al., 2000; Liu et al., 2007). Furthermore, Ma and colleagues (2006) showed that BIRC7, in fact, resorts to the E3 ubiquitin ligase function of the RING domain to target SMAC/DIABLO for degradation through the ubiquitin-proteasome pathway.

BIRC7 has prompted apoptosis blockage induced by a number of death receptors, such as FAS, TNFRSF1A (TNFR1), TNFRSF10A (DR4) and TNFRSF10B (DR5) (Vucic et al., 2000), and has been associated to other proteins that are within the apoptotic pathway, thus inducing further indirect caspase inhibition. Similar to XIAP, the ability of BIRC7 to activate MAPK8 (JNK1), a protective pathway against apoptosis induced by TNF (TNF-&alpha); and interleukin, was verified by the MAP3K7 / TAB1 (TAK1/TAB1) signaling cascade (Sanna et al., 2002; Chen et al., 2010). Moreover, BIRC7 may play a role in the WNT/ CTNNB1 (Wnt/β-catenin) signaling pathway, a key component of gene activation with outcomes on tumor development through the activity of TCF (T-cell factor) transcription factors (Uematsu et al., 2003). Indeed, Yuan and collaborators (2007) confirmed BIRC7 to be a target of the β-catenin/TCF complex, suggesting their transcriptional regulation by upon BIRC7 (Yuan et al., 2007). Recent studies have also demonstrated a role for BIRC7 in regulating the epithelial-mesenchymal transition in colorectal cancer cells, favoring metastasis by the activation of the p38/ GSK3B pathway (Han et al., 2017).

BIRC7 overexpression has been also associated with tumor aggressiveness, chemoresistance and reduced sensitivity to radiation, while silencing of BIRC7 has been shown to lessen such features, both in vitro and in vivo. When SMMC-7721 cells were transfected with BIRC7 siRNA, mRNA and protein levels of both splice variants, BIRC7α and β, were greatly downregulated. Moreover, transfected cells displayed G1-arrest and a diminished S-phase cell count, reduced invasiveness, and re-established a response to apoptotic stimuli (Liu et al., 2010). BIRC7-silenced SCG-7901 cells, in turn, regained sensitivity to cytotoxic chemotherapy drugs, such as 5-fluorouracil (5-FU) and cisplatin (Wang et al., 2010). In xenograft models, HCT116 tumors treated with BIRC7 siRNA presented reduced volume in a dose-dependent fashion, while mice maintained healthy body weight and no signs of toxicity (Oh et al., 2011). Animal models were also used to demonstrate the differential effects of BIRC7 isoforms in tumorigenesis. BIRC7α was shown to promote tumor progression, whereas those expressing BIRC7β inhibited tumor growth due to high degrees of cleavage, mediated by natural killer (NK) cells activity, of this variant into t-livin, which has a pro-apoptotic effect. Nevertheless, the expression of a mutated BIRC7β with lowered inclination to undergo cleavage restored a positive effect of tumor growth (Abd-Elrahman et al., 2009). In turn, it was also established that, while BIRC7α enhanced killing by NK cells, the β variant took on a modest protective effect against apoptosis induced by NK cells, however, in Jurkat cells, this action occurred alongside a concurrent inhibitory trigger, and not self-sufficiently. Nevertheless, when both isoforms were detected in melanoma cells, a low killing rate was observed (Nachimas et al., 2007b).

The paradoxical pro-apoptotic effects of BIRC7, although baring intact BIR domains, are exerted by the truncated forms of both variants; still, t-livin β was found to give a stronger, however less stable, pro-apoptotic effect than t-livin α. t-Livin occurs around the cell nucleus, although not sturdily bound to that, and accumulates in the Golgi apparatus.

Resorting to mutagenesis and co-localization studies, Nachmias and colleagues further demonstrated that an intact RING domain and merely the first N-terminal glycine (G53) residue were sufficiently responsible for t-livin's localization to Golgi apparatus and also for its pro-apoptotic function, while deletion of either of these regions resulted in restoration of anti-apoptotic effect (Nachimas et al., 2007a). Additionally, t-livin has also been termed a flexible inducer of cell death once Shiloach and colleagues (2014) recognized its capacity of inciting necrosis, like in 293T cells, or apoptosis, like in A549 and MelA1, and such distinction may be possibly linked to TP53 status. Moreover, once the BIR domain was deleted from t-livin, the prior necrotic effect observed in 293T cells was replaced by an apoptotic effect, regardless of its inactive TP53. Both effects, apoptosis and necrosis, were linked to activation of JNK pathway.
However, once the BIR domain was deleted from t-livin, 293T cells failed to express JNK, suggesting a role for BIR in activation of this pathway. In MelA1 cells, when these were treated with a pan-caspase inhibitor, t-livin-induced cell death was only partially abrogated, implying an aptitude of t-livin to induce cell death in situations where the apoptotic process is compromised (Shiloach et al., 2014).

Homology

BIRC7 has a high homology among different species (Table 1).

% Identity for: *Homo sapiens* BIRC7	Symbol	Protein	DNA
vs. *X. tropicalis*	birc7	55.4	58.2
vs. *D. rerio*	birc7	60.3	62.7
vs. *G. gallus*	BIRC7	55.4	58.2
vs. *D. rerio*	birc7	59.1	65.0
vs. *G. gallus*	BIRC7	60.3	62.7
vs. *X. tropicalis*	birc7	59.1	65.0

Table 1. Comparative identity of human BIRC7 with other species (Source: http://www.ncbi.nlm.nih.gov/homologene)

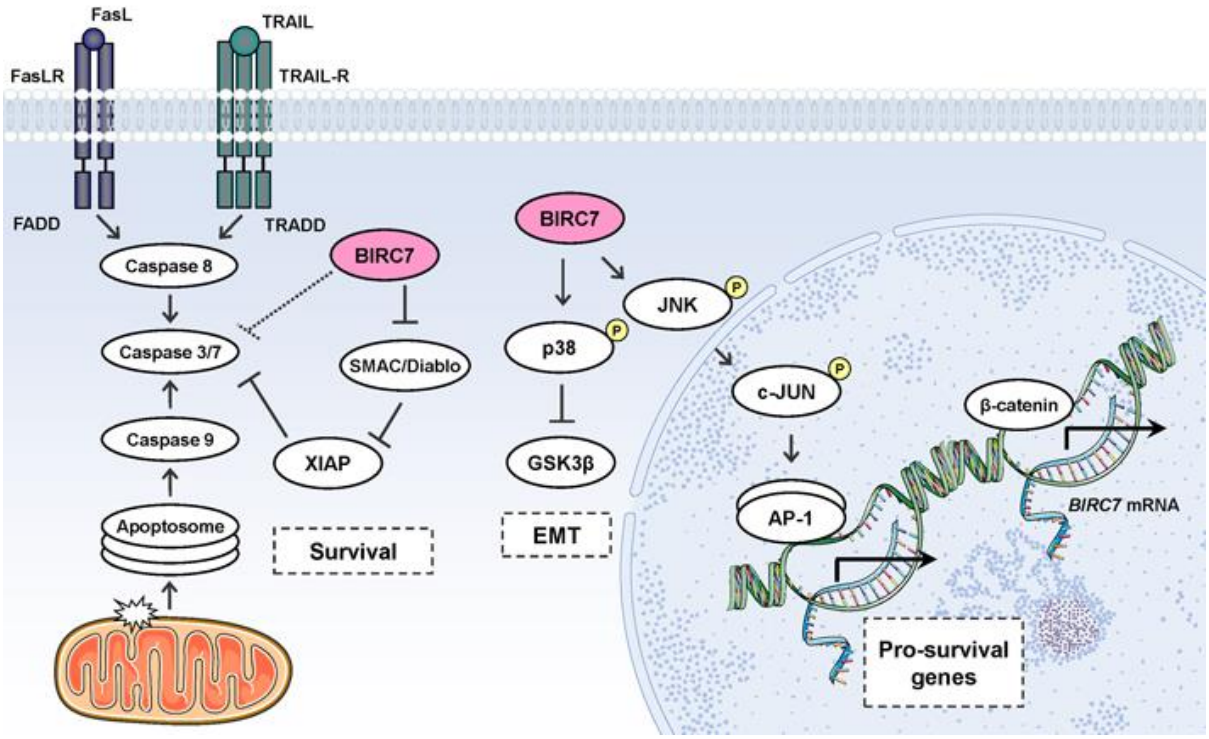

Figure 2. Suggested mechanisms of action of BIRC7 on apoptosis regulation. BIRC7 (livin) acts on cytoplasm and nucleus and is involved different cellular functions: cell survival, epithelial mesenchymal transition and up-regulation of pro-survival genes. In cytoplasm, BIRC7 modulates apoptosis pathway by indirectly regulating caspases 3 and 7. BIRC7 may block SMAC/DIABLO, a factor released by mitochondria, which subsequently inhibit the BIRC4 (XIAP). Also, BIRC7 induces the phosphorylation of P38, inhibiting GSK3B. It also induces the phosphorylation of JNK, mediating the translocation of C-JUN to the nucleus that induces the transcription of genes involved in pro-survival such as AP-1.

Mutations

Somatic

Recurrent mutations in the BIRC7 gene are rare. Among the 48,467 unique samples reported in COSMIC (Catalogue of Somatic Mutations in Cancer; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic), only 99 presented BIRC7 mutations (71 missense substitutions, 26 synonymous substitutions, 2 nonsense substitutions, and 1 frameshift insertion). Similar findings are reported in cBioPortal (http://www.cbioportal.org), in which, among the 10,967 cancer samples accessed, somatic mutations in BIRC7 were shown in merely 0.5% of the tested samples (corresponding to 59 mutations, of which 54 are missense substitutions, 4 truncated genes, and 1 other mutation). BIRC7 gene has been localized to the long arm of chromosome 20 on 20q13.3, a region frequently amplified in melanomas and other malignancies (Vucic et al., 2000; Ibrahim et al., 2014; Choi et al., 2019);

Implicated in

Ampullary carcinoma

In ampullary carcinoma, BIRC7 was detected in 46.5% of cases, in which its expression was found predominantly in the cytoplasm, and only in 2.8% in the nucleus. High BIRC7 expression positively correlated with cell differentiation, tumor-node-metastasis (TNM) staging, and lymph node metastasis. BIRC7 expression correlated negatively with caspase 3 levels and positively with Ki-67 levels, demonstratinsg a decrease in apoptosis rate and an increase in cell proliferation in this cancer type. In addition, survival of patients with high BIRC7 expression was shorter compared with that of patients with low BIRC7 expression (Xue et al., 2013).

Breast cancer

The investigation of BIRC7 gene expression in 8 breast cancer cell lines revealed that this gene was expressed in all cells assessed. At least 6 out of the 8 breast cancer cell lines (BT549, MDA-MB-435, MDA-MB-231, MDA-MB-468, MCF-7, SK-BR-3 and ZR-75-30) showed relatively increased BIRC7 mRNA and protein expression compared to the non-malignant breast cell line, HBL100. Moreover, BIRC7 expression was found in higher levels in invasive breast cancer cells, when compared to non-invasive ones (Fan et al., 2013, Crnkovic-Mertens et al., 2010).

Clinicopathological studies revealed that the expression levels of BIRC7 in breast cancer tissues (62%) are higher than that of adjacent (35%) and normal breast tissues (25%). Still, the expression of BIRC7 in breast cancer is not closely related to age, menopause status, histological grade, ESR1 (estrogen receptor), or PGR (progesterone receptor) status. However, expression of BIRC7 is higher in breast cancers classified under histological grade III when compared to grades I and II (88.9% vs. 46.9%). Similarly, the positive expression rate of BIRC7 in TNM in breast cancer stages III and IV (87.5%) was higher than in other stages (50%). In breast cancer cells, BIRC7 gene silencing induced G0/G1 cell cycle arrest. BIRC7 was highly expressed in high-invasive breast cancer cells and promoted breast cancer cell migration and invasion via the activation of AKT signaling and induction of epithelial-mesenchymal transition (EMT) in vitro and in vivo (Li et al., 2012).

EMT is a key step in tumor progression via the induction of a highly invasive phenotype, and its molecular mechanisms have been extensively studied. The loss of epithelial markers such as CDH1 (E-cadherin), and the gain of mesenchymal markers such as CDH2 (N-cadherin) and VIM (vimentin) are the hallmarks of EMT. Overexpression of BIRC7 resulted in a similar loss of epithelial markers and a gain of mesenchymal markers, suggesting that BIRC7 was actively involved in the EMT process in breast cancer cells. These results suggested that BIRC7 participates of EMT by altering expression and activation of proteins involved in metastasis (Li et al., 2013b).

Together, these findings indicate that BIRC7 promoted the progression and metastasis of breast cancer through the regulation of EMT by activating the p38/GSK3β pathway. A deeper understanding of the role of BIRC7-induced EMT in breast cancer may provide effective targets for therapy, especially in triple-negative breast cancer (Han et al., 2017, Etti et al., 2017).

Central nervous system cancer

BIRC7 overexpression was reported in cerebral neoplasms, including neuroblastomas, glioblastomas, and tumors derived from neural crest cells. In most brain tumors, upregulation of BIRC7 expression was associated with radio- and chemotherapeutics resistance (Dasgupta et al., 2010).

In neuroblastomas, 80% of cases presented high BIRC7 expression. Experimental findings indicate that BIRC7 may play a role in drug-resistance in neuroblastoma, particularly in aggressive and MYCN amplified tumors. These data strongly support that therapeutic targeting of BIRC7 to block its antiapoptotic effect could be an interesting strategy for the treatment of this disease (Dasgupta et al., 2010).

In glioblastoma multiforme, the tumor hypoxia-induced BIRC7 expression may represent a pathway for resistance to radio- and chemotherapeutics, since experimental studies showed that siRNA directed

against BIRC7 inhibited tumor growth (Hsieh et al., 2014; Yuan et al., 2011).

Cervical carcinoma

Cervical cancer is one of the common gynecologic malignancies, and resistance to cisplatin is a concern in the clinical practice. In functional studies using the human cervical adenocarcinoma cell line, HeLa (which highly expresses BIRC7), inhibition of expression of BIRC7 by RNAi enhanced the activity of caspase 3, reduced BCL2 expression, and increased BAX, further inducing apoptosis and improving the effects of cisplatin (Yu Wang, 2009).

Colorectal cancer

BIRC7 expression was detected in 54.1% of patients with colorectal cancer, specifically on the base of colorectal crypts in adenoma and throughout the epithelium in carcinoma, while such protein was not detected in normal colorectal mucosa (Xi et al., 2011), (Wang et al., 2014). A high BIRC7 expression rate was negatively associated to overall survival, but showed no correlation with age, gender, degrees of differentiation, and TNM staging in this malignancy (Xi et al., 2011; Myung et al, 2013).

In primary tumors, BIRC7 expression was significantly increased compared with adjacent or distant normal mucosa, in which expression was independently related to survival outcomes in patients with rectal cancer (Ding et al., 2013). In addition, BIRC7 was related to pathological grade, extent of invasion and amount of lymph node metastasis, contributing to poor prognosis of mid-distal rectal cancer following surgery (Su et al., 2017).

Overexpression of BIRC7 induced proliferation, migration, and invasion of cancer colorectal cells, which was reverted by BIRC7 depletion. Moreover, this overexpression promoted EMT, as evidenced by a decrease in E-cadherin expression and an increase in mesenchymal markers, including vimentin, SNAI2 (SLUG), and SNAI1 (SNAIL) (Ge et al., 2016). Additionally, knockdown of BIRC7 promoted cell cycle arrest by decreasing CCND1 36 and CCND3 (cyclins D1 and D3), CDK4 and CDK6, and by inducing CDKN1B (p27) expression.

Moreover, MAPK signaling cascades were significantly blocked by knockdown of BIRC7 (Myung et al, 2013), while BIRC7 silencing using siRNA also decreased cell proliferation and clonogenicity and increased apoptosis rates (Zou et al., 2014).

In colorectal cancer cell lines, BIRC7 expression was attributed to cisplatin resistance. BIRC7 mRNA levels was upregulated after cisplatin treatment in a dose- dependent manner.

By contrast, knockdown of BIRC7 by siRNA rendered colon cancer cells more sensitive to cisplatin, reinforcing its involvement in chemoresistance (Ding et al., 2013). BIRC7 knockdown also improved the sensitivity of colorectal cells to 5-FU (Liu et al., 2018). Colorectal cancer chemoresistance in HCT-8/V due to overexpression of this protein has also been attributed in response to vincristine (VCR), etoposide (VP-16), and 5-FU (Wang et al., 2010).

Esophageal carcinoma

BIRC7 expression was associated with tumor staging and progression in human esophageal carcinoma. Moreover, a positive correlation with VEGFA expression has also been demonstrated in these tumor types (Chen et al., 2008).

Gastric cancer

BIRC7 expression was found in 52.5% of gastric cancer samples, compared to 6.7% in that of adjacent normal gastric tissues (Liang et al., 2012). Similar results were described by Ou et al. (2014), who revealed that BIRC7 expression was elevated in tumors (64.1%) when compared to adjacent non-cancer tissues (30.8%) obtained from patients with gastric cancer. Both studies found a positive correlation of BIRC7 expression with tumor differentiation and lymph node metastasis.

Furthermore, Ou et al. (2014) demonstrated that BIRC7 depletion inhibited cell proliferation and invasion and induced apoptosis - showed by decreased expression of p38 MAPK, VEGF, and MMP2 and increased expression of caspase 3 in vitro. This feature also induced cell cycle arrest, with a decrease of cyclin D1 and CDK4 and CDK6, and an increase in expression of CDKN1A (p21) and CDKN1B (p27) (Chung et al., 2013). Comparably, in vivo assessments proved tumor size had decreased after treatment with siRNA (Oh et al., 2011) or shRNA (Ou et al., 2014) targeting BIRC7.

Head and neck squamous cell carcinoma

Yoon et al. (2017) demonstrated that BIRC7 is involved in chemoresistance in head and neck squamous cell carcinoma (HNSCC). This was evidenced in experiments using human HNSCC cell lines, where depletion of BIRC7 enhanced cytotoxicity of cisplatin, 5-FU, and docetaxel. Additionally, the authors detected elevated expression of cleaved caspases-3 and -7 and PARP1, when compared with control cells, after chemotherapy treatment, suggesting that reduction of BIRC7 levels is associated to sensitization to apoptosis (Yoon et al., 2017).

Kidney cancer

According to Xu et al. (2010), overexpression of BIRC7 was detected in 40.7% of the cases of renal cell carcinoma (RCC). Similarly, studies carried out by Zang et al. (2013) revealed BIRC7 was detected in 44% of cases of RCC. Furthermore, when

metastatic lymph nodes were detected, cases with overexpression of BIRC7 came up to 59% (Wagener et al., 2007).
Clinical studies indicated that tissues from advanced stages of RCC have greater expression of BIRC7 (Wang et al., 2016). Functional studies strongly suggested that BIRC7 is a bridge for apoptosis and autophagy. Silencing of BIRC7 induced apoptosis and autophagic cell death while also increasing sensitivity to cisplatin in RCC cells (Wang et al., 2016).

Laryngeal cancer

Studies have reported that BIRC7 inhibits cell apoptosis via modulation of caspase 3, caspase 7 and PARP1 in human larynx and pharynx carcinoma cells. In laryngohypopharyngeal carcinoma (LHSCC), BIRC7 expression was predominantly identified in tumors (36.7%) when compared to the adjacent healthy mucosa. Additionally, induction of apoptosis by BIRC7 knockdown occurred through activation of caspases-3 and 7 and PARP1. Such data indicate that BIRC7 induces tumorigenic activities in LHSCC, such as resistance to apoptosis. Thus, BIRC7 silencing may be useful for therapeutic intervention against tumor progression in LHSCC (Kuang et al., 2017, Liu et al., 2016).
In patients with nasopharyngeal carcinoma (NPC), high expression levels of BIRC7 occurred in 65.1% of cases, suggesting BIRC7 to be implicated in progression of such disease. Thus, this may be a useful prognostic biomarker for NPC (Kuang et al., 2017, Liu et al., 2016). Nevertheless, observational studies have shown that the efficacy of radiotherapy is greater in patients who did not express BIRC7 compared to those with BIRC7 overexpression, indicating that BIRC7 may be associated with a poor prognosis for NPC and LHSCC (Kuang et al., 2017, Liu et al., 2016).

Leukemia

Overexpression of BIRC7 was found in approximately 81% of patients with acute myeloid leukemia (AML), and a positive correlation between the expression of BIRC7 and high white blood cell counts was reported (Zareifar et al., 2018). In AML, genetic aberrations were found to activate BIRC7-related signal transduction pathways, resulting in greater proliferation and/or survival of leukemia progenitor cells by affecting transcription factors or transcription coactivation components, resulting in differentiated blocking and/or aberrant acquisition of self-renewal properties by hematopoietic progenitor cells (Dohner et al., 2008; Hanahan et al., 2000; Zareifar et al., 2018).
Additionally, levels of BIRC7 expression in acute lymphoblastic leukemia (ALL) were also shown to be elevated. Such feature may be attributed to the different mutations that occurred in the two types of leukemia that further lead to leukemogenesis (Ibrahim et al., 2014; Choi et al., 2019).
Overexpression of BIRC7 protein in newly diagnosed children with acute leukemia suggested an important role for this protein in carcinogenesis and progression of such disease (Lv et al., 2015). Yang et al. (2010) also suggested that the expression of BIRC7α and BIRC7β may be associated with genesis and development of acute leukemia in childhood, and that this could be used as a molecular marker of childhood acute leukemia. In addition, BIRC7 can be used as a new target for leukemia treatment, as RNAi technology effectively inhibited expression of BIRC7 (Yang et al., 2010; Yan et al., 2011; Ibrahim et al., 2014).

Liver cancer

BIRC7 mRNAs were significantly increased in samples from hepatocellular carcinoma patients compared to their normal hepatic tissues (Augello et al., 2009), hepatitis, and hepatic cirrhosis tissues (Guo et al., 2013).
BIRC7 inhibition, by shRNA, promoted apoptosis in hepatocellular carcinoma cell line HepG2, which was even more evident with a combinatory strategy using the co-transfection with a shRNA targeting BIRC5 (Xu et al., 2014). Additionally, another study demonstrated that inhibition of BIRC7 using shRNA increased chemosensitivity of HepG2 cells (Liu et al., 2015).
Similar results were obtained in other hepatocellular carcinoma cell line, SMMC-7721, using BIRC7 siRNA. Inhibition of BIRC7 sensitized cells to pro-apoptotic stimuli associated with caspase 3 activation and, moreover, promoted cell growth inhibition specifically by mitotic arrest. In addition, BIRC7 depletion reduced the invasive capacity of hepatocellular carcinoma cells, demonstrating that BIRC7 is not only involved in resistance to apoptosis, but also in cell proliferation and invasiveness (Liu et al., 2010).
BIRC7 not only provided resistance to hepatocellular carcinoma cells, but also significantly contributed to cell proliferation and invasion (Liu, 2010). In addition, clinical studies showed that overexpression of BIRC7α isoform correlates with a high risk of relapse in liver cancer (Liu, 2007; Liu, 2010).
Inhibition of BIRC7 gene expression was associated with a strong increase in apoptotic response in the presence of pro-apoptotic agents, indicating that BIRC7 depletion led to sensitization to apoptotic stimuli (Mazumder, 2008; Liu, 2010). Moreover, negative regulation of BIRC7 expression induced cell cycle arrest at the G0/G1 phase, indicating that BIRC7 modulation may be a potential targeted approach for the treatment of liver cancer (Wang, 2008; Liu, 2010)

Lung cancer

High levels of BIRC7 were detected in approximately 61.5% of cases of non-small cell lung cancer (NSCLC). Conversely, BIRC7 overexpression was associated with poor prognosis and lymph node metastasis (Crnkovic-Mertens et al., 2006; Yuan et al., 2008).
Functional studies showed that silencing of BIRC7 increased the efficiency of chemotherapy or radiotherapy in pulmonary adenocarcinomas. In addition, this protein is portrayed as a potential predictive biomarker for the prognosis of lung adenocarcinoma besides a promising strategy for drug-resistant lung adenocarcinoma (Yang et al., 2014; Wu et al., 2016; Liang et al., 2017).

Lymphoma

The expression of BIRC7 in non-Hodgkins lymphoma (NHL) was significantly higher than in lymph node samples in classical Hodgkins lymphomas (CHL). This difference in BIRC7 expression was also observed when comparing two NHL subtypes - large B-cell lymphoma (DLBCL) and large cell anaplastic lymphoma for CHL - where a significantly higher expression of BIRC7 occurred in DLBCL (Tanhaei et al., 2014; Ziaei et al, 2015; Browne et al., 2003).
BIRC7 plays a critical role in the pathogenesis of lymphomas and was detected in 40% of cases Hodgkin's lymphoma and 48% in cases of Burkitt's lymphoma, indicating that BIRC7 could be a potential marker and therapeutic target for these diseases (Abd-Elrahamn et al., 2009; Kalungi et al., 2012).

Melanoma

BIRC7 is also named Melanoma-Inhibitor Apoptosis Protein (ML-IAP) due to the first paper that reported an elevated expression of this IAP in melanoma cell lines, when compared to that of some lymphomas, fetal kidney, fetal liver, testis and thymus. The study further demonstrated that BIRC7 mRNA was highly expressed in melanoma cell lines but not in normal human melanocytes. Moreover, such expression was consistent with a resistant phenotype to chemotherapeutic agents, also becoming the first work to demonstrate the importance of BIRC7 on chemoresistance (Vucic et al., 2000).
BIRC7 showed low occurrence in nevi (15%), however an increased expression in melanoma (47.6 - 70.7%), in which these levels came up to 95% in metastatic melanoma, suggesting this protein to be involved in melanoma progression (Hartman Czyz, 2013). In this scenario, high BIRC7 levels were associated with a poor prognosis in melanoma (Lazar et al., 2012). Still, silencing of BIRC7 induced apoptosis, by activation of caspase 3, and cell cycle arrest at the G0/G1 phase, thus inhibiting proliferation of LiBr melanoma cells (Wang et al., 2007).DISEASE

Mesothelioma

BIRC7 protein was expressed in 18% of malignant pleural mesothelioma (MPM) and was usually found in the nucleus of these cells. Only BIRC2 (IAP1) and BIRC7 proteins were expressed in the nucleus of MPM tumors (Gordon et al., 2007).

Oral squamous cell carcinoma

BIRC7 was increased in human oral squamous cell carcinoma (OSCC) tissues compared with the adjoining healthy mucosa. Additionally, BIRC7 knockdown reduced cell invasion, migration, and proliferation in the human OSCC cells, while also promoting apoptosis, evidenced by activation of caspases (Lee et al., 2014).

Ovarian cancer

Elevated expression levels of BIRC7 isoforms were detected in human epithelial ovarian cancer (EOC) in comparison to benign ovarian neoplasms. Moreover, depletion of BIRC7 levels by shRNA result in profound pro-apoptotic and antiproliferative effects, and was associated with the activation of caspase signaling, increased apoptosis and recovered sensitivity to chemotherapy drugs (Liu et al., 2012).

Osteosarcoma

BIRC7 expression was upregulated in 58.7% of human osteosarcoma tissue, which, in turn, showed a significant correlation with microvascular density, suggesting that regulation of BIRC7 expression could further control the physiological repair of pathological angiogenesis in osteosarcomas (Li et al, 2014; Guan, 2015)
As BIRC7 has rarely been found in osteochondroma tissues, this feature may be indicative of a specificity of such protein to osteosarcomas. In invasive osteosarcomas metastatic tissues, BIRC7 was notoriously elevated, suggesting that the higher levels of this protein conferred anti-apoptotic effects and endurance of these tumor cells (Li et al, 2012). In this context, BIRC7 may serve as a promising therapeutic target for the treatment of osteosarcomas. Furthermore, expression of BIRC7 was related to a poor prognosis of osteosarcoma and its detection may play an important role in evaluation of this type of cancer (Li et al, 2012; Li et al, 2014; Sun et al., 2018).

Pancreas cancer

BIRC7 was shown to be overexpressed in 25% of pancreatic cancer cases. Additionally, this protein displayed strong reactivity in tumor tissues by in situ hybridization studies. Such reactivity was not found in all ducts, indicating heterogeneity for BIRC7 expression is not merely related to tumor type or

origin, but also in different areas of a same tumor (Lopes et al., 2007, Liu et al., 2011).
In PANC-1 cells, pharmacological studies have shown oxymatrine-induced apoptosis to be related to downregulation of BIRC7 and upregulation of the BAX / BCL2 ratio (Lopes et al., 2007, Liu et al., 2011).

Prostate cancer

Expression of BIRC7β was detected in 51.9% of cases of testicular germ cell tumor, whereas 28.2% of cases of such pathology expressed BIRC7α (Kempkensteffen et al., 2008).
In prostate carcinoma tissues, BIRC7 overexpression was associated with high-grade clinical stages of the disease and metastasis. This protein plays an important role in initiation of prostate cancer and promotes cell proliferation by regulating the G1/S cell cycle transition. BIRC7 has been related with invasion of cancer cells in the surrounding prostate tissue by affecting NF-KB signaling pathway and expressions of FN1 and CXCR4, resulting in inhibition of PTK2 (FAK) and SRC, and of ITGA5 and ITGB3 (integrins a5 and b3) (Ye et al, 2011; Chen et al., 2012)

Retinocytoma

BIRC7 was found to be upregulated in retinocytoma compared to the normal control group. Treatment with topotecan induced apoptosis through the inhibition of BIRC7 expression (Zhang et al., 2013).

Urinary tract cancer

BIRC7 expression was upregulated in urinary tract cancers - bladder transitional cell carcinoma (TCC) and bladder squamous cell carcinoma (SCC) -when paralleled with corresponding adjacent non-neoplastic tissues. Such elevated expression was significantly associated with higher tumor grades and staging, suggesting BIRC7 contributes to the progression of bladder carcinoma (Gayyeda Tawfiekb, 2015).

To be noted

Pharmacological advances targeting BIRC7 in cancer:

Treatment with siRNA targeting BIRC7 significantly suppressed cancer cell growth and enhanced cytotoxicity of typical anticancer drugs such as 5-FU and oxaliplatin (L-OHP) in colorectal cancer, demonstrating such protein to be a relevant target in oncology (Oh et al., 2016). Similarly, a study using a protamine single-chain antibody fusion protein (anti-MM scFv-tP) to deliver BIRC7 siRNA to melanoma LiBr cells revealed suppression of cell proliferation and induction of apoptosis, both in vitro and in vivo (Wang et al., 2017).
A synthetic oligonucleotide containing unmethylated CpG oligodeoxynucleotides (CpG-ODN) was evaluated in combination with 5-FU in the hepatocellular carcinoma cell line HepG2 and verified that such treatment decreased cell viability, increased apoptosis and induced cell cycle arrest at the S phase when compared with CpG-ODN or 5-FU alone. Alongside, expression of mRNA for BIRC7 decreased in cells treated with CpG-ODN alone or in combination with 5-FU, but increased in cells treated with 5-FU alone (Liang et al., 2013).
Supplementation diets rich in n-3 polyunsaturated fatty acids (PUFAs) have been associated with a reduced risk for several types of cancer which, in turn, has been linked to their effect in reducing the levels of expression of IAP family members associated with chemotherapy resistance and cancer malignancy, such as BIRC7 and BIRC5 (Slagsvold et al., 2010).
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