Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

# Gene Section

## Review

# BIRC5 (baculoviral IAP repeat containing 5)

**Paola Cristina Branco, Paula Christine Jimenez, João Agostinho Machado-Neto, Letícia Veras Costa-Lotufo**

Department of Pharmacology, Institute of Biomedical Sciences of the University of São Paulo, São Paulo, pbranco@usp.br (PCB); jamchadoneto@usp.br (JAM-N); costalotufo@usp.br (LVC-L) Brazil; Department of Marine Sciences, Federal University of Sao Paulo, Santos, paulacjimenez@gmail.com (PCJ), Brazil.

Published in Atlas Database: January 2019

Online updated version : http://AtlasGeneticsOncology.org/Genes/BIRC5ID797ch17q25.html

Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/70468/01-2019-BIRC5ID797ch17q25.pdf

DOI: 10.4267/2042/70468



## Abstract

BIRC5, also known as survivin, has been implicated in cell cycle progression and apoptosis avoidance. BIRC5 is highly expressed in embryonic tissues, however very low or absent in adult tissues. BIRC5 overexpression has been frequently associated to cancer development, a poor prognosis and chemoresistance. Besides that, different BIRC5 isoforms has been characterized and related to better or worse chemotherapy responses depending on the isoform and the cancer type. So far, many efforts have been conducted in order to deplete BIRC5 in cancer cells, including gene therapy, pharmacological and nanotechnological approaches. In this review, we will discuss the role of BIRC5 in cancer cell biology and its clinical significance, demonstrating its DNA/RNA and protein aspects, also its relevance for diagnosis and prognosis, and advances as a target for the treatment of different cancer types.

**Keywords**
BIRC5; Cell cycle progression; Apoptosis; Cancer

## Identity

**Other names:** API4, EPR-1

**HGNC (Hugo):** BIRC5

## DNA/RNA

### *Description*

The entire BIRC5 gene is approximately 11.4 Kb (start: 78214186 and end: 78225636 bp; orientation: Plus strand).

### *Transcription*

There are three transcript variants deposited in the NCBI database (https://www.ncbi.nlm.nih.gov/gene).
In general, they present three exons (exon 1, 2 and 3) that are responsible for encoding the BIR domain, which is conserved in all BIRC family members, and the exon 4 that is related to the coiled-coil (CC) domain.
Variant 1 is the predominant transcript (cDNA: 2574 bp), and encodes isoform 1 (142 amino acids [aa]).
Variant 2 lacks an exon in the 3' coding region, which results in a frameshift (cDNA: 2537 bp) and, thus, in a changed protein (143 aa) with a different C-terminus from that of isoform 1 (isoform 2, also known survivin-ΔEx3). Variant 3 exhibits an alternate in-frame segment (cDNA: 2724 bp) and generates a longer (165 aa) and distinct protein (isoform 3, also known survivin-2B), compared to isoform 1.

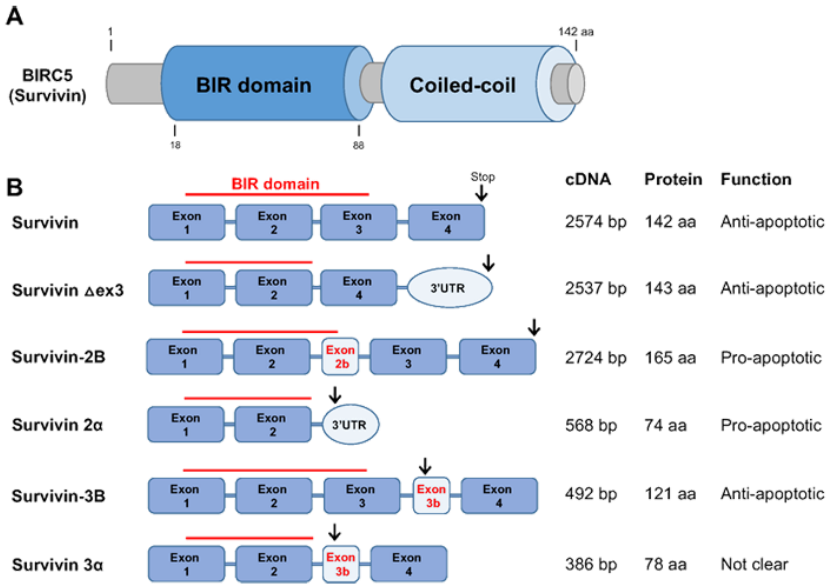


**Figure 1.** BIRC5 structure and its splices variants. BIRC5 (also kwon as survivin) presents at least five variants with biological relevance for cancer. A. The protein structure of the most common variant observed presents 142 aa and is composed of a BIR domain that is responsible for its anti-apoptotic activity and a coiled coil. B. The BIRC5 pre mRNA of the most common expressed variant is composed of 3 exons that codifies the BIR domain and the exon 4 that codifies the coiled coil. This variant present anti-apoptotic activity. Survivin Ex3 has its exon 3 deleted and an insertion of a 3'UTR, this isoform codes a protein of 143 aa and also exerts anti-apoptotic functions. Survivin-2B presents an insertion of an exon 2b located between exon 2 and exon 3, generates a protein of 165 aa with pro-apoptotic characteristics. Survivin-2α is characterized by the presence of exon 1 and 2 and the insertion of a 3'UTR, this isoform codifies a protein of 74 aa with pro-apoptotic functions. Survivin-3B presents the insertion of exon 3 b between exon 3 and exon 4, which generates a protein of 165 aa with anti-apoptotic properties. Survivin-3α presents a deletion of exon 3 and generates a protein of 78 aa whose function remain controversial. Arrows indicate the stop codon. UTR- untranslated region. Red line indicates the BIR structure.

Moreover, three additional transcript variants are reported in Ensembl (http://www.ensembl.org/): a transcript variant containing 568 bp, which generates a protein of 74 aa (also known as Survivin-2α); a transcript variant with 492 bp (cDNA) that produces a protein of 121 aa (also known as Survivin-3B); and a transcript variant comprised of 386 bp (cDNA) that gives a protein of 78 aa (also known as Survivin-3α) (Figure 1).

# Protein

## *Description*

The IAPs (Inhibitors of Apoptosis Proteins) are a family of proteins primarily known for inhibiting caspase activity, either directly or indirectly, thus preventing apoptotic cell death (Gyrd-Hansen and Meier, 2010). Still, the IAPs are further implicated in key roles in other processes, such as cell cycle, cell migration, inflammation and, even, in the innate immune response (de Almagro and Vucic, 2012).

Structurally, members of the IAPs are characterized by the presence of at least one BIR (Baculovirus IAP repeat) domain, which contains nearly 80 amino acid residues and carries $Zn^{2+}$ in the center. Such domain is a highly conserved sequence that mediates protein-protein interactions, an essential feature for their anti-apoptotic function. Within the eight human IAPs recognized ( NAIP [BIRC1], BIRC2 [cIAP1], BIRC3 [cIAP2], XIAP [BIRC4], survivin [BIRC5], BIRC6 [bruce], BIRC7 [livin] and BIRC8 [ILP-2]) there may be between one and three BIR domains, typically arranged in their N-terminal portion (Budhidarmo and Day, 2015; Lopez and Meier, 2010).

BIRC5 (survivin), the smallest among the IAPs (16.5 kDa), was discovered in 1997 (Ambrosini et al., 1997), is 142 amino acids (aa) long and has a single BIR domain (Peery et al., 2017). This protein is presented as a stable loop-shaped homodimer, formed by interactions of the N-terminal region through a predominantly hydrophobic interface (Chantalat et al., 2000; Verdecia et al., 2000). Furthermore, on the C-terminal portion, survivin carries an alpha-helix CC (coiled coil) domain, its unique structure (Chantalat et al., 2000; Coumar et al., 2013) which convenes the ability to associate to microtubules and a range of other proteins involved, mainly, in the process of mitosis, and further allowing for translocation among the different cellular compartments, such as mitochondria, cytoplasm and nucleus (Rodel et al., 2012) (Figure 1).

Since BIRC5 is connected to a diverse network of biochemical processes and therefore has remarkable multifunctionality, its modulation in cancer therapy continues to be extensively explored. Several survivin inhibitors have been identified by in vitro and in silico methods, such as antisense oligonucleotides, siRNA, dominant-negative

mutants, peptidomimetic molecules and other small inhibitory molecules, and even as anticancer vaccine (Fenstermaker et al., 2016; Sarvagalla et al., 2016).

## Expression

BIRC5 is normally expressed in embryonic tissues and during fetal development, as well as in fast dividing normal cells (like bone marrow stem cells, basal epithelial cells and thymocytes, even if at lower concentrations), but is virtually undetectable in fully differentiated and healthy adult tissues (Adida et al., 1998; Sah et al., 2006; Stauber et al., 2007). Throughout the cell cycle, BIRC5 is expressed only during mitosis, in a highly regulated manner comprising the chromosomal passenger complex (CPC), as it interacts with tubulin and kinetochores during metaphase, then participates in central spindle organization and cytokinesis, throughout anaphase (Szafer-Glusman et al., 2011).

However, BIRC5 is expressed in cells that undergo malignant transformation, being overexpressed in numerous tumors (Altieri, 2001; LaCasse et al., 2008). Recent studies evidenced that transcriptional activation is not the only cause for BIRC5 overexpression, but also post-transcriptional regulation, specially coordinated by many alternative polyadenylation (APA) sites. For instance, in ovarian cancer, aberrant APA leads to shortening of the 3'-UTR region, enabling escape from negative regulation of miRNAs and causing up-regulation of BIRC5 (He et al., 2016).

Clinically, overexpression of BIRC5 has been correlated with a poor prognosis of cancer, resistance to apoptosis induced by chemotherapy, decreased survival of patients and greater chances of relapse (Islam et al., 2000; Rodel et al., 2012).

## Localisation

BIRC5 is located both in the cytoplasm and in the nucleus. Nuclear expression has been associated with a poor prognosis and chemoresistance (Du et al., 2015), which may differ among the different types of cancers (Shintani et al., 2013). BIRC5 splice variants were also related to subcellular localization. This has been shown in samples from acute myeloid leukemia patients, where wild-type survivin and the 2B splice variant were expressed in the nucleus, cytoplasm or both, whereas the ΔEx3 isoform was only expressed in the nucleus (Serrano-Lopez et al., 2013). However, considering pro-survival factors, localization is not the only relevant feature: it has been recently demonstrated that BIRC5 can be packaged into extracellular vesicles (endosomes) and its delivery may be guided by antiapoptosis stimuli from cancer cells and tumor microenvironment, inducing pro-survival competences in fibroblasts after treatment with paclitaxel. Conversely, knockdown of BIRC5 in those vesicles promoted increased cell sensitivity to chemotherapeutic agents (Kreger et al., 2016).

## Function

Studies have shown that overexpression of BIRC5 inhibits both the intrinsic and extrinsic pathways of apoptosis and the depletion of survivin in human cell culture impairs apoptosis and triggers cell division defects (Li et al., 1998; Roy et al., 2015). The antiapoptotic mechanism of BIRC5 still needs to be better clarified, however, both the direct or indirect binding of BIRC5 to caspases are proposed (Figure 2) (Altieri, 2013; Garg et al., 2016; Li et al., 1998). Evidences also indicate that BIRC5 binds to XIAP, one of the best studied IAPs, forming a complex that protects XIAP against ubiquitination and proteosomal degradation.

This complex then activates multiple signaling pathways, including NF-κB, inhibits caspases CASP3, CASP7 and CASP9, suppresses apoptosis and accelerates tumor progression. Other cytoprotective mechanisms have been proposed for BIRC5, including the ability of mitochondrial BIRC5 to sequester the pro-apoptotic DIABLO (Smac) protein from its binding to BIRC4 (also known as XIAP), or even preventing its release from mitochondria (Altieri, 2013; Coumar et al., 2013; Song et al., 2003).

Interaction of BIRC5 with CDK4 has been associated with progression of the cell cycle. In mitosis, BIRC5 plays a key role in integrating the transient chromosome complex (CPC), along with INCENP, CDCA8 (borealin) and AURKB, which controls the formation and stabilization of the mitotic spindle (Altieri, 2013; Coumar et al., 2013). Activation of Wnt signaling induces β-catenin ( CTNNB1) and BIRC5 nuclear translocation, which contributes in mitotic spindle formation, further regulating CPC, β-catenin, STAT3 and HIF1A (Figure 2). BIRC5 also appears to be involved in the cellular response to stress through the interaction with various chaperones, such as AIP, HSPD1 (HSP60) and HSP90AA1 (HSP90) (Altieri, 2013; Fortugno et al., 2003). Moreover, BIRC5 also partakes in the process of autophagy (Wang et al., 2011) and in DNA repair among several tumor cell lines (Jiang et al., 2009).

BIRC5 has also been shown to induce cell motility, metastasis and increased colonization capacity by AKT-mediated upregulation of the α5 integrin pathway in a melanoma model (McKenzie et al., 2013).

Additionally, BIRC5 plays an important role in angiogenesis, contributing to endothelial cell proliferation and migration, which was then linked to increased β-catenin protein levels that consequently promotes an elevated expression of BIRC5 and VEGF (Fernandez et al., 2014).

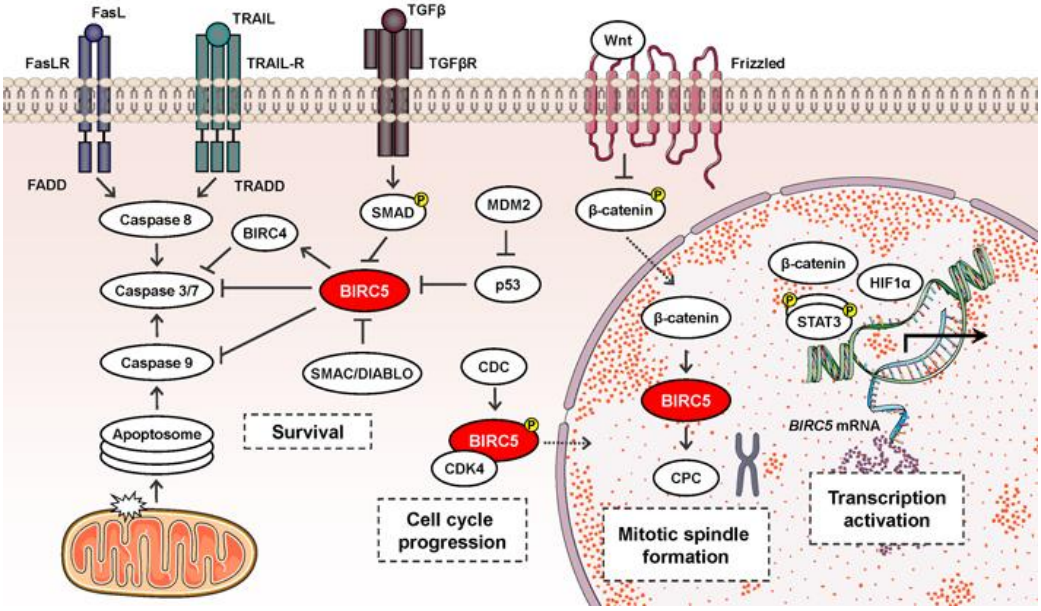


**Figure 2.** BIRC5: a multitask protein. BIRC5 (survivin) acts on cytoplasm and nucleus and is involved different cellular functions: cell survival, cell cycle progression, mitotic spindle formation and transcription activation. In cytoplasm, BIRC5 modulates apoptosis pathway by binding to and blocking initiator caspase 9 and effectors caspases 3 and 7, demonstrating to be involved in extrinsic and intrinsic apoptosis and contributing to cell survival. BIRC5 may be blocked by SMAC/DIABLO, a factor released by mitochondria. Also BIRC5 potentiates apoptosis inhibition through stabilization of BIRC4 (also kwon as XIAP). TGF-β signaling negatively regulates BIRC 5 by phosphorylating SMAD protein. p53-mediated signaling also downregulates BIRC5 functions. CDC phosphorylates BIRC5 and promotes its binding to CDK4 that may be translocated to nucleus, and thus promotes cell cycle progression. In nucleus, BIRC5 is involved in the mitotic spindle formation modulated by Wnt pathway through the phosphorylation inhibiton and nuclear translocation of β-catenin activating BIRC5 and associated to other proteins (not shown) form the Chromosomal Passenger Complex (CPC). The transcription activation of BIRC5 mRNA is mainly promoted by β-catenin, STAT3 (signal transducer and activator of transcription-3) and HIF 1 α (hypoxia-inducible factor-1α).

BIRC5 is also directly involved in enhancing anoikis resistance through miR-141/KLF12/Sp1/survivin axis. It is a consensus that anoikis resistance is crucial for establishing a metastatic niche and consequently promoting cancer progression and dissemination (Mak et al., 2017). Dissimilar functions have been attributed to the different isoforms of BIRC5. Survivin-2α and survivin-2B portray a proapoptotic activity profile, whereas Survivin-ΔEx3 and Survivin-3B show prominent antiapoptotic activity, with similar activities to those of survivin itself. These distinct variants can predict aggressiveness of cancer phenotype, thus contributing to prognosis (Caldas et al., 2005). BIRC5 can be released from tumor cells in exosomes (Khan et al., 2011). This information provided new insights into biomarkers for determination of early diagnosis and also to predict prognosis. In this context, the splice variant survivin-2B, in breast cancer, was shown to be expressed mostly in primary tumors and exclusively in early stage disease. Conversely, Survivin-ΔEx3 variant was most commonly expressed in late stages of breast cancer (Khan et al., 2014). Survivin-2B has been further reported to promote cell death in some cancer cells by promoting autophagy followed by cell death induced by accumulation and stabilization of IKBKB (IKKB) in the nucleus (Shi et al., 2014).

## Homology

The BIRC5 gene is highly homologous among different species, as shown in Table 1, which demonstrates the comparison of variant 1 among different species.

| % Identity for: *Homo sapiens* BIRC5 | Symbol | Protein | DNA |
|---|---|---|---|
| *vs. P. troglodytes* | *BIRC5* | 98.3 | 98.8 |
| *vs. M. mulatta* | *BIRC5* | 97.9 | 97.9 |
| *vs. C. lupus* | *BIRC5* | 90.8 | 90.1 |
| *vs. B. taurus* | *BIRC5* | 90.1 | 90.1 |
| *vs. M. musculus* | *Birc5* | 83.6 | 82.6 |
| *vs. R. norvegicus* | *Birc5* | 83.0 | 81.3 |
| *vs. G. gallus* | *BIRC5* | 60.6 | 65.7 |
| *vs. X. tropicalis* | *birc5.2* | 57.8 | 64.2 |
| *vs. D. rerio* | *Birc5a* | 54.3 | 58.0 |

**Table 1.** Comparative identity of human BIRC5 with other species (Source: http://www.ncbi.nlm.nih.gov/homologene)

# Mutations

## Somatic

Recurrent mutations in the BIRC5 gene are rare. Among the 47,119 unique samples reported in COSMIC (Catalogue of Somatic Mutations in Cancer; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic), only 43 presented BIRC5 mutations (29 missense substitutions, 8 synonymous substitutions, 3 nonsense substitutions and 2 frameshift insertions). Similar findings are reported in cBioPortal (http://www.cbioportal.org) among the 55,481 cancer samples accessed, that show somatic mutations in BIRC5 occur in merely 0.2% of the tested samples (corresponding to 116 mutations, of which 65 are missense substitutions, 50 truncated genes or 1 other mutation). When mutations, amplifications, deep deletions and multiple alterations were considered, the total of cancer samples with any type of genetic alteration in BIRC5 was 969 (1.7%).

# Implicated in

## Angiosarcoma

In a cohort including 85 samples from angiosarcoma patients and 88 controls (54 hemangioma and 34 pyogenic granuloma), nuclear BIRC5 expression was observed in all angiosarcoma patients, but in fewer than 7% of the control group. This data indicates that BIRC5 expression may be used as a diagnosis tool in angiosarcoma (Tsuneki et al., 2017). In addition, genetic or pharmacological BIRC5 inhibition reduces cell proliferation in ISO-HAS-B human angiosarcoma cells (Tsuneki et al., 2017).

## Brain cancer

Western blot analysis revealed that BIRC5 was expressed in 60.3% of glioma samples, which was associated with a reduced apoptosis ratio and high-grade tumors (Bae et al., 2017). In agreement, samples obtained from gliosarcoma patients presented elevated expression of BIRC5 in the nucleus of tumor cells collected from brain lesions, when compared to normal brain cells (Chen et al., 2010).

BIRC5 expression was also associated to radioresistance: ionization of glioblastoma cell lines promoted BIRC5 upregulation, which mediated dedifferentiation to a stem-like phenotype and, consequently, induced a radioresistant phenotype (Dahan et al., 2014).

Treatment of glioma cells with the survivin inhibitor YM155 overcomes resistance to TRAIL-induced apoptosis, by downregulating MCL1 and BIRC5 (Premkumar et al., 2013). In glioblastoma cell lines, YM155 treatment reduced BIRC5 expression, and induced apoptosis and DNA fragmentation (Lai et al., 2012). Similar results were reported by Jane and colleagues (Jane et al., 2013), where YM155 downregulated BIRC5 and MCL1 expression and inhibited cell growth in malignant human glioma cells. Interestingly, in resistant glioma cell lines attributed to EGFR activation, YM155 alone did not present any significant effects, however in combination with ABT-373, a BH3-only mimetic that targets the prosurvival members of the BCL2 family, a synergic effect mediated by caspase activation was observed (Jane et al., 2013). Depletion of BIRC5 levels mediated by parthenolide treatment induced apoptosis and cell cycle arrest in glioblastoma cell lines (Tang et al., 2015). Cucurbitacin-I, another natural product, induced cell death in malignant glioma cells, while promoting $G_2$/M accumulation, depletion of p-STAT3, p-STAT5, p-JAK1 and p- JAK2 levels, and downregulation of AURKA, AURKB and BIRC5 (Premkumar et al., 2015). Medulloblastoma also presents elevated level of BIRC5 expression, as observed for other brain cancers. Similarly, antagonists of BIRC5 impaired proliferation and survival of both murine and human medulloblastoma cells (Brun et al., 2015). High BIRC5 expression was associated to advanced stages and sporadic tumors in patients aged greater than 12 months (Islam et al., 2000), which negatively impacted clinical outcomes (Azuhata et al., 2001). In addition, BIRC5/p53 and BIRC5/FAS ratios have been implicated in neuroblastoma prognosis (Sandler et al., 2002; Tajiri et al., 2001). In neuroblastoma and oligodendroglioma cell lines, BIRC5 silencing reduced cell viability while further inducing mitotic catastrophe and cell death by caspase-dependent and -independent pathways (Shankar et al., 2001).

## Breast cancer

BIRC5 protein expression was found in 78% of high-grade and 21.4% of low-grade patients with ductal carcinoma in situ, indicating that BIRC5 expression is associated with an advanced stage phenotype in breast cancer (Chade et al., 2018). In addition, increased

Estrogen positive breast cancer subtypes have been connected to increased BIRC5 regulation, w levels of BIRC5 mRNA (2.24 fold) were observed in whole blood samples from breast cancer patients when compared to healthy donors (Wang et al., 2016).

Estrogen positive breast cancer subtypes have been connected to increased BIRC5 regulation, which was reverted by treatment with the natural compound myricetin, enhancing apoptosis (Jiao and Zhang, 2016). In triple negative breast cancer, chemoresistance and metastasis were associated to elevated DEPTOR protein expression that, in turn, induced a higher expression of BIRC5, both in vitro

and in vivo (Parvani et al., 2015). Survivin and survivin-ΔEx3 were overexpressed and associated to chemoresistance in non-responder samples using ex vivo organotypic cultures of primary human breast tumors (Faversani et al., 2014). Using shRNA targeting BIRC5 splice variants isoforms, Zheng and colleagues (Zheng et al., 2011) demonstrated that apoptosis rates were improved considerably by survivin depletion, but survivin-ΔEx3 isoform silencing only moderately inhibited cell survival and growth in a breast cancer model.

In breast cancer cells, combined therapy using panobinostat with gemcitabine markedly diminished BIRC5 expression (Budman et al., 2012). Similarly, SMAC mimetics (BV6, Birinapant) and BH3-mimetics (ABT-737/263) combined with paclitaxel treatment demonstrated positive results regarding BIRC5 downregulation (Panayotopoulou et al., 2017).

Chemoresistance was also related to the extracellular LGALS1 (galectin-1) expression that, moreover, contributes to cancer progression and doxorubicin resistance in triple negative breast cancer. It must be stated, herein, that galectin-1 expression is mediated by STAT3 activation, which is a transcription factor that culminates in BIRC5 upregulation, corroborating the role of BIRC5 in chemoresistance in breast cancer cells (Nam et al., 2017). The function for STAT3 in BIRC5 upregulation in breast cancer cells was also confirmed by Wang and colleagues (Wang et al., 2015), who demonstrated that MIR204 inhibits STAT3 activation and BIRC5 expression.

BIRC5 also participates on the invasive phenotype by regulating the expression of the vascular endothelial growth factor-C ( VEGFC) at both protein and mRNA levels, which culminates in a raised metastasis rate in breast cancer (Cai et al., 2012). In agreement, elevated BIRC5 expression was associated with poor prognostic in stage II/III breast cancer patients (Hamy et al., 2016). The authors proposed that BIRC5 expression might be theranostic, and suggest that high BIRC5-expressing breast cancer patients would be randomized to receive BIRC5 targeting drugs (Hamy et al., 2016).

A recent study that evaluate the transcriptome of primary breast cancer patients, demonstrated that, along with NEK2 and TOP2A, BIRC5 gene was amplified in obese breast cancer patients, reinforcing that this gene may be druggable for this population (Nuncia-Cantarero et al., 2018). One factor that may explain such observation is the synthesis of visfatin, an adipokine secreted by adipocytes, macrophages and inflamed endothelial tissue, which was found to be increased in obese and breast cancer patients, while exerting a protective effect on BIRC5, raising its levels and, thus, contributing to tumor progression (Gholinejad et al., 2017).

In breast cancer cell lines, including triple negative phenotype and tamoxifen-resistant cells, YM155, a BIRC5 inhibitor, as previously mentioned, reduces cell viability, with $IC_{50}$ values in the low nanomolar range, and induced autophagy (Cheng et al., 2015).

In breast cancer cell lines, ABT-263 (navitoclax), a BCL2 family protein inhibitor, promoted a negative modulation of BIRC5 levels in MDA-MB-231, but not in MCF-7, which was associated with a higher sensitivity to the drug (Lee et al., 2018).

## Cervical carcinoma

In a recent meta-analysis including eleven studies and a total of 865 cervical carcinoma patients, Cheng and colleagues (Cheng et al., 2016) reported that elevated BIRC5 expression was positively associated with aggressive clinicopathological features, lymph node metastasis and poor survival outcomes.

## Colorectal cancer

Immunohistochemical analysis evidenced that patients with colorectal adenocarcinomas exhibited higher BIRC5 levels compared to adjacent non-tumor colorectal mucosa. In the same study, the authors demonstrated that BIRC5 silencing, by siRNA, suppressed survival and cell invasion, and induced cell cycle G0/G1 arrest and apoptosis in colorectal cancer cells (Wang et al., 2017b). BIRC5 splice variants were also evaluated in colorectal cancer, and the distribution of mRNA observed was the following: 48% of wild-type survivin, 38% of survivin-2B isoform and 29% of survivin-ΔEx3 isoform. The mRNA expression of wild-survivin and survivin-ΔEx3 was related with tumor size and invasion, respectively (Pavlidou et al., 2011). In contrast, BIRC5 levels were not associated with patients with advanced colorectal adenoma (Choi et al., 2017).

Elevated expression of BIRC5 was also correlated with levels of CD133+, which is associated to chemoresistance to 5-fluorouracil, in colon cancer cells. The elevated expression of BIRC5 induced by activation of the CXCL12/ CXCR4 signaling pathway in cells exposed to radiation may be a crucial factor for the acquisition of chemoresistance in this cancer type (Wang et al., 2017a). However, no association was found between expression of BIRC5 and invasion, lymph node metastasis, nor histologic differentiation (Li et al., 2017). Survivin depletion by the EpCAM-aptamer-guided BIRC5 RNAi enhanced colorectal cancer stem cells sensitivity to 5-FU and oxaliplatin, further inducing apoptosis, reducing tumor growth and improving the overall survival in a colorectal cancer xenograft model (AlShamaileh et al., 2017).

The use of natural products was also implicated in reduction of BIRC5 levels, such as tanshinone I, an active compound from traditional Chinese herbal

medicine (Lu et al., 2016), and the Pinus roxburghii essential oil (Sajid et al., 2018). Additionally, treatment with tamoxifen β-estradiol or a combination of these two agents promoted decreased BIRC5 levels and impaired cell migration in colorectal cancer cells (Ou et al., 2017). In colon cancer cells, dimethoxy curcumin inhibited cell growth, increased apoptosis, reduced cell migration, downregulated BIRC5 expression and enhanced CDH1 (E-cadherin) in vitro and in vivo (Chen et al., 2016).

Treatment failure in colorectal cancer was previously associated to the presence of stem cells bearing a KRAS mutation, which, then, become resistant to chemotherapy. Treatment with Omega-3 fatty acid DHA promoted a reduction of cell viability, with caspase-3 activation mediated by a decrease in transcript and protein levels of BIRC5 and, moreover, an increase in MIR16-1 expression levels, suggesting that BIRC5 and microRNA-16-1 to be promising molecular targets of DHA (Sam et al., 2018).

## Endometrial cancer

In endometrial cancer, BIRC5 was identified to be critical for NEF2-driven progestin resistance. The authors also demonstrated that BIRC5 silencing enabled restoration of progestin sensitivity in NRF2-overexpressing RL-95-2 cells (Fan et al., 2017).

## Gastric cancer

Gastric adenocarcinoma patients undergoing gastrectomy were evaluated for the expression of markers with relevance for tumor progression and prognosis. Among them, 93.9 % of samples from gastric cancer patients presented nuclear sub-localization of BIRC5, which was associated with a poor prognosis (Lins et al., 2016). It has been demonstrated that BIRC5 upregulation increased VEGF expression in gastric cancer (Zhang et al., 2014). The authors also demonstrated that 51.3% of gastric carcinoma samples presented BIRC5 expression, which was located mainly in the cytoplasm of tumor cells, associated with lymph node metastasis and reduction of overall survival in the univariate analysis (Zhang et al., 2014).

BIRC5 knockdown using shRNA promoted an elevated sensitivity to radiation and chemotherapy using 5-FU, demonstrating that the modulation of BIRC5 levels may be an important adjuvant therapy for gastric cancer patients (Shen et al., 2012). In agreement, BIRC5 silencing mediated by siRNA increased apoptosis rates, inhibited cell proliferation in a cisplatin-resistant cell line (Li et al., 2014) and impaired cell migration in gastric cancer cells (Li et al., 2015).

## Head and neck squamous cell carcinoma

Hih levels of BIRC5 was observed in samples from head and neck squamous cell carcinoma patients, which was associated with poor survival outcomes and chemotherapy resistance (Zhang et al., 2015a) In head and neck squamous cell carcinoma cells, a treatment targeting BIRC5 by using YM155 increased apoptotic and autophagic cell deaths, suppressing pro-survival pathways (Zhang et al., 2015a).

Similarly, treatment with an aliphatic hydroxamate-based compound targeting BIRC5 reduced survivin levels through LKB1/AMPK/p38MAPK signaling, and further enhanced p63 phosphorylation and p21 activation (Yen et al., 2018).

## Hepatocellular carcinoma

In SMMC-7721 hepatocellular carcinoma cells, treatment with berbamine, a natural compound from Chinese medicine, promoted upregulation of p53 expression and downregulation of BIRC5, which further triggered mitochondria signaling pathway-mediated apoptosis (Cao et al., 2018).

## Kidney cancer

In renal cell carcinoma patients, high BIRC5 expression was associated with increased TNM stage and high Fuhrman grade, which indicates that BIRC5 may be a good prognosis predictor (Ma et al., 2017).

Furthermore, BIRC5 has been associated with tumor progression and chemoresistance to temsirolimus, an MTOR inhibitor. Strategies that abrogate survivin expression, such as shRNA-mediated BIRC5 silencing or pharmacological approach (YM155), reduced chemoresistance of renal cell carcinoma cells in vitro and in vivo (Carew et al., 2015).

Other signaling pathways seem to converge to the induction of BIRC5 expression in renal cell carcinoma.

For instance, combined treatment between the histone deacetylase (HDAC) inhibitor OBP-801 and the phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002 synergistically inhibited cell growth and induced apoptosis in renal cell carcinoma through BIRC5 downregulation (Yamada et al., 2013).

## Leukemia

In chronic myeloid leukemia, the oncogenic signaling induced byBCR/ ABL1 leads to BIRC5 upregulation by activating the JAK2/STAT3 pathway.

Moreover, BIRC5 silencing promoted pronounced cytotoxic effect in both imatinib-sensitive and -resistant chronic myeloid leukemia cell lines, a similar effect to that observed after treatment with

shepherdin, a cell-permeable peptidomimetic compound that downregulates BIRC5. These findings indicate that survivin may be a target in BIRC5-overexpressing leukemias (Stella et al., 2013). The combined use of C82 (a Wnt/β-catenin signaling modulator) and nilotinib in chronic myeloid leukemia progenitor cells inhibited the expression of CD44, MYC, BIRC5, p-CRKL and p-STAT5 (Zhou et al., 2017)

In acute myeloid leukemia, BIRC5 overexpression is involved in drug resistance of leukemia stem cells, regulated by the ERK/MSK/Sp1/MYC axis (Zhang et al., 2015b). Interestingly, BIRC5 depletion, by siRNA, reduced cell proliferation, induced apoptosis, and synergistically enhanced cytotoxicity of etoposide in acute myeloid leukemia cells (Karami et al., 2013). Other molecular signaling that has been involved in acute myeloid leukemia resistance is the expression of MUC1 (MUC1-C), an oncoprotein critical for the onset of tumorigenesis, which is overexpressed in acute myeloid leukemia blasts and leukemia stem cells. It has been demonstrated that targeting MUC1-C reduced BIRC5 levels and increased sensitivity to cytarabine, indicating that BIRC5 is involved in multiple signaling pathways required for survival in leukemia cells (Stroopinsky et al., 2018).

Acute lymphoblastic leukemia (ALL) patients also presented elevated levels of BIRC5 and VEGF, especially prior to treatment with an association of idarubicin, cytosine arabinoside and etoposide. Nevertheless, those levels decreased after treatment (Yang et al., 2013). In children diagnosed with acute lymphoblastic leukemia, BIRC5 expression was higher compared to healthy donors. The same group of patients was monitored during the entire treatment period and those who went in to complete remission of the disease presented decreased levels of BIRC5, compared to diagnosis sample. In contrast, BIRC5 protein levels were elevated in non-survived ALL patients (Yahya et al., 2012). In acute lymphoblastic leukemia primary samples and cell lines, treatment with YM155 exhibited elevated cytotoxicity by induction of DNA damage, leading to phosphorylation of CHEK2 and H2AFX and promoting suppression of BIRC5 expression (Chang et al., 2015).

It is well accepted that leukemia stem cells contribute to a reduced treatment efficacy and also to chemoresistance. The natural product curcumin decreased BIRC5 levels in leukemia stem cell-like KG1a in a combined treatment with busulfan, which may overcome such chemoresistant of leukemia stem cells (Weng et al., 2015).

Furthermore, Li and colleagues (Li et al., 2018) observed an association between the presence of C allele of BIRC5 polymorphism rs9904341, but not of rs8073069, and an increased risk of acute leukemia development in a cohort including 182 childhood acute leukemia patients and 200 controls.

## Liver cancer

In samples from hepatocarcinoma patients, 55.4% of tumor tissues were positive for BIRC5 expression, which was higher when compared to non-tumor adjacent tissues (2%). Additionally, BIRC5 expression has been directly correlated with unfavorable clinical staging and tumor score, and the presence of extrahepatic metastasis. The authors also demonstrated a positive correlation between BIRC5 and VEGF expression, implying that besides avoiding apoptosis, BIRC5 may induces angiogenesis contribute to tumor dissemination (Tian et al., 2018).

## Lung cancer

A meta-analysis study including 3,206 non-small cells lung cancer (NSCLC) patients and 816 normal controls, BIRC5 was found to be overexpressed in tumor samples and strongly correlated with histological differentiation, tumor-node-metastasis stage and lymph node metastasis, which indicates that BIRC5 may be a tumor progression marker for such cancer type (Duan et al., 2016). Another study indicated that BIRC5 may be involved in chemoresistance of NSCLC cells (Hu et al., 2016). Additionally, it was demonstrated that the GC+CC genotypes in the promoter region (-31) of the BIRC5 gene (polymorphism rs9904341) were significantly associated with EGFR mutations in a cohort of 360 lung cancer patients (Liu et al., 2016).

Recently, BIRC5 was identified as a target of MIR195, a microRNA that induced apoptosis and senescence in NSCLC cells (Yu et al., 2018). A combined therapy using the natural product resveratrol and the epidermal growth factor receptor (EGFR) inhibitor erlotinib promoted an increase in cell death mediated by BIRC5 depletion in NSCLC cells (Nie et al., 2015). Similarly, depletion of BIRC5 induced by treatment with YM155 increased the sensitivity of such cells to radiation (Hu et al., 2015).

Treatment with the natural product fisetin also increased sensitivity to cisplatin in cisplatin-resistant NSCLC cells by modulation of MAPK/BIRC5/Caspase axis (Zhuo et al., 2015).

Lung cancer stem cells were more sensitive to FL118, a BIRC5 inhibitor, than cisplatin. Additionally, FL118 downregulated cancer stem cell related markers, which may improve drug-sensitivity in this kind of tumor cells (Wang et al., 2017c).

## Lymphoma

In non-Hodgkin lymphoma, specifically the aggressive subtype extranodal natural killer/T-cell lymphoma, which is frequently associated with resistance to anthracyclines, presence of BIRC5

serum levels were detected in approximately 25% of patients, which is associated with advanced stages of the disease. In addition, the percentage of lymphoma cells that demonstrated BIRC5 nuclear localization was significantly associated with BIRC5 serum concentration (Kim et al., 2015).

BIRC5 expression was positive in 40% of lymph node biopsy of diffuse large B-cell lymphoma patients. Such observation correlated with unfavorable factors for therapy response and predicted shorter survival outcomes (Markovic et al., 2012). A meta-analysis, including 17 studies and 1,352 diffuse large B-cell lymphoma patients, found positive BIRC5 expression to be associated with advanced clinical stages and reduced overall survival (Zhang et al., 2015c).

The combinatory use of bendamustine and rituximab associated with BIRC5 inhibitor, YM155, presented potentiating effects on induction of cell death by triggering DNA damage and cell cycle arrest in lymphoma cells, and, moreover, reduced tumor size and metastatic capacity in diffuse large B-cell lymphoma xenograft murine models (Kaneko et al., 2014). A combined treatment of rituximab and YM155 was shown to reduce tumor growth more effectively than monotherapy (Kita et al., 2012). In B and T cell lymphoma cells, BIRC5 abrogation using the non-toxic tellurium compound, AS101, has overcome chemoresistance, sensitizing these cells to paclitaxel (Danoch et al., 2015). BIRC5 expression presented anti-apoptotic functions and is regulated by NF-κB and PI3K/AKT signaling pathways in nasal NK/T-cell lymphoma cells (Sun et al., 2015).

## Malignant pleural mesothelioma

In two independent cohorts of malignant pleural mesothelioma patients, nuclear BIRC5 expression in both, pre- and post-chemotherapy tissues, was associated with shorter freedom from recurrence and overall survival, indicating that BIRC5 expression may be a prognostic factor for poor clinical outcomes in this cancer type (Meerang et al., 2016).

## Melanoma

BIRC5 expression was previously demonstrated in melanoma and melanocytic nevus, which demonstrated all nevi, regardless of histologic type, expressed detectable levels of BIRC5 (Yan et al., 2006). Additionally, a cytoplasmic staining of BIRC5 was evidenced in dysplastic nevi (Florell et al., 2005). In normal melanocytes, it was demonstrated that p53 and RB1 are required to repress BIRC5 expression. A role for E2F2 in the negative regulation of BIRC5 expression was also pointed out (Raj et al., 2008). Increased BIRC5 expression was observed in vivo in melanocytes that were more resistant to UV-induced apoptosis, which was further associated to lower rates of spontaneous apoptosis, earlier melanocytic tumor development and increased tendency for lymph node and lung metastasis (Thomas et al., 2007). Furthermore, BIRC5 overexpression in melanocytes activated the AKT and MAPK signaling pathways, acquiring a more invasive phenotype, and demonstrating the involvement of BIRC5 on the onset and progression of melanoma (McKenzie et al., 2013).

In melanoma cells, BIRC5 was associated to enhanced AKT and MAPK signaling dependent migration and invasion, as well as to the upregulation of ITGA5 (α5 integrin) (McKenzie et al., 2010). BIRC5 silencing through RNA interference promoted cell cycle arrest and reduced cell proliferation and metastasis in vivo and in vitro in melanoma models. Moreover, as observed for other tumor types, BIRC5 inhibition led to increased sensitivity to chemotherapy in melanoma cells (Kedinger et al., 2013). In another study, a proposed strategy to overcome chemoresistance and to promote melanoma cell death was the combination of vemurafenib and Nutlin-3, whose synergism was responsible for BIRC5 depletion and apoptosis induction (Ji et al., 2013).

Pharmacological suppression of BIRC5 expression, using YM155, increased apoptosis induction and tumor regression in melanoma xenograft models. In the same study, combined treatment of YM155 and docetaxel presented potentiating effects in induction of apoptosis compared to monotherapy, corroborating the notion that targeting BIRC5 may be an interesting approach in melanoma management (Yamanaka et al., 2011). Similar results were obtained using natural compounds extracted from plants that target BIRC5 through β-catenin and STAT3 suppression (Habibie et al., 2014).

Another alternative approach for targeting BIRC5 was the generation of recombinant fusion proteins containing the TAT protein transduction domain and either wild-type survivin (TAT-Surv-WT) or a dominant- negative mutant (TAT-Surv-T34A). The mutant promoted in vitro cell death through apoptosis and DNA fragmentation in melanoma cells. In vivo injections of such mutant in melanoma xenograft mice increased apoptosis, induced aberrant nuclei formation and impaired tumor growth (Yan et al., 2006).

BIRC5 mRNA was detected in 98% of samples from metastatic melanoma patients. High BIRC5 mRNA levels were significantly associated with poor overall survival (Takeuchi et al., 2005).

## Multiple myeloma

BIRC5 expression was positive in 35% of samples from newly diagnosed multiple myeloma patients, but no association with clinical and laboratorial characteristics, treatment response and survival outcomes was found (Zeng et al., 2014). On the other hand, Yang and colleagues (Yang et al., 2016b), in a

study that evaluated the efficacy of a combination treatment with fludarabine, vincristine, epirubicin, dexamethasone and thalidomide (FVADT) chemotherapy regimen for refractory multiple myeloma patients, reported that complete remission and efficacy rates were significantly lower in the BIRC5-positive group, when compared with the BIRC5-negative group.

## Myxoid liposarcoma

Using high-throughput drug screen and myxoid liposarcoma cell lines, BIRC5 has been identified as a relevant protein important for cell survival (de Graaff et al., 2017).

## Oral squamous cell carcinoma

Elevated BIRC5 mRNA expression was observed in samples from oral squamous cell carcinoma patients compared to peritumoral or normal tissues (Li et al., 2012). Still, such increase was shown to be insufficient to drive tumor progression in oral squamous cell carcinoma, however nuclear expression of BIRC5 was correlated with tumor stage and differentiation grade (Liu et al., 2017). Additionally, the authors suggested that nuclear localization of BIRC5 has been due to the acetylation at K129 in the protein C-terminal region (Liu et al., 2017). In oral squamous cell carcinoma cells, treatment with YM155 reduced BIRC5 levels and increased apoptosis rates (Yan and Su, 2017).

## Ovarian cancer

High BIRC5 levels correlate with advanced stage, metastasis and poor disease-free survival in ovarian cancer (Aune et al., 2011; No et al., 2011). Moreover, BIRC5 serum levels were significantly higher, while DIABLO (Smac) levels were significantly lower in patients with serous ovarian carcinoma when compared to healthy controls (Dobrzycka et al., 2015).

The association of nuclear and cytoplasmic BIRC5 expression and prognosis remains controversial in ovarian cancer. The evaluation of BIRC5 expression in patients treated with taxane and platinum agents concluded that, in this treatment regimen, higher nuclear BIRC5 expression was associated with reduced risk of disease recurrence and death (Felisiak-Golabek et al., 2011). By contrast, another study reported that nuclear BIRC5 was significantly associated with chemoresistance to taxane-based chemotherapy, predicting poor progression-free survival (Du et al., 2015). Immunohistochemistry analysis revealed that BIRC5 expression presented a positive correlation with FIGO stage in epithelial ovarian cancer, benign epithelial ovarian tumor tissue and borderline ovarian tumor tissues (Ju et al., 2016).

BIRC5 splices variants were also correlated to the development of ovarian cancer and resistance to chemotherapy. Taxane-resistant ovarian cancer cells expressed higher BIRC5 mRNA levels than their taxane-sensitive counterparts. Survivin-2B expression was significantly higher in taxane-resistant cells, when compared to sensitive cells (Vivas-Mejia et al., 2011).

YM155 treatment induced BIRC5 downregulation, cell growth inhibition, cell cycle arrest, reactive oxygen species formation and apoptosis, and enhanced docetaxel efficacy in ovarian cancer cell lines (Hou et al., 2018). In agreement, in ovarian cancer cells, BIRC5 knockdown enhanced cisplatin sensitivity in resistant cancer cells, inducing apoptosis and inhibiting the invasive process through downregulation of MMP2 (Jiang et al., 2013).

## Pancreatic cancer

In a cohort of 51 pancreatic adenocarcinoma patients, BIRC5 expression was found in 49% of samples and was associated with poor survival outcomes (Contis et al., 2018). Similar results were reported by Zhou and colleagues (Zhou et al., 2018), who described that nuclear BIRC5 was higher in tumor compared to non-tumor pancreatic tissues, and a high nuclear BIRC5 expression was an independent predictor of disease-specific survival in ductal pancreatic adenocarcinoma patients. In pancreatic cancer models, FL118, a BIRC5 inhibitor, reduced cell viability, including for stem cell like and cisplatin-resistant cells, and decreased xenograft tumor growth and metastasis (Ling et al., 2018).

## Prostate cancer

BIRC5 levels was not detected in normal tissues, slightly detected in benign prostate hyperplasia tissues and considerably higher in prostate adenocarcinoma, which was positively correlated with higher tumor stage (Eslami et al., 2016). In agreement, increased BIRC5 levels were also associated with poor survival outcomes in prostate cancer patients (Xu et al., 2015).

In a cohort including 157 prostate cancer patients and 145 controls, genetic polymorphisms c.-31G>C (rs9904341), c.454G>A (rs2071214), and c.*148T>C (rs1042489) of BIRC5 were associated with risk for prostate cancer development (Karimian et al., 2018).

Treatment with BIRC5 inhibitor (YM155) inhibited cell growth, cell migration and invasion in prostate cancer cells (Xu et al., 2015). Overexpression of miR-494 (a microRNA targeting BIRC5) and/or BIRC5 silencing using shRNA attenuated cell growth in vitro and in vivo (Zhu et al., 2016). Moreover, treatment of prostate cancer cells with a selective inhibitor of nuclear export, KPT-330, inhibited proliferation and promoted apoptosis of tumor cells, by increasing protein degradation of exportin XPO1, BIRC5 and CCND1, further leading to cell cycle arrest and apoptosis (Gravina et al., 2015). Natural products, such as the triterpenoid

pristimerin, demonstrated that BIRC5 levels may modulate therapeutic responses, once BIRC5-overexpressing prostate cancer cells became resistant to pristimerin (Liu et al., 2014).

### *Salivary adenoid cystic carcinoma*

In SACC-83 salivary adenoid cystic carcinoma cells, treatment with simvastatin reduced cell viability and induced apoptosis by decreasing BIRC5 levels (Cai et al., 2018).

### *Thyroid cancer*

Nicotinamide phosphorybosiltransferase (NAMPT), a marker for thyroid cancer that is positively associated with tumor stage and metastasis, presented a positive correlation with BIRC5 (survivin) and survivin splice variant º, but not with survivin-2B, expressions, reinforcing that survivin and its variant ΔEx3 are associated with poor prognosis and advanced stage cancer (Sawicka-Gutaj et al., 2015).

### *Urinary tract cancer*

In SK-NEP-1 Wilms tumor cells, YM155 treatment reduced cell proliferation, induced apoptosis and inhibited growth of xenograft tumors. Interestingly, YM155 treatment promoted an elevation in levels of other BIRC-related genes, such as BIRC3 and BIRC8, suggesting that the regulation of cell death induced by BIRC5 suppression is highly orchestrated with other members of the IAP family (Tao et al., 2012).

## To be noted

**Pharmacological Advances for BIRC5 inhibition**

YM155, a small-molecule BIRC5 inhibitor, was developed in 2007 and tested in multiple cancer models. YM155 caused a concentration-dependent cytotoxic effect with $IC_{50}$ values reaching nanomolar concentrations (Nakahara et al., 2007; Rauch et al., 2014). The mechanism of action for YM155 involves a selective inhibition of BIRC5 promoter activity by disrupting Sp1 interaction in a specific region of the BIRC5 core promoter. Such repression occurs in a cell cycle-independent manner (Cheng et al., 2012).

A novel survivin inhibitor developed in 2012, FL118, presents structural similarities to irinotecan. Such molecule selectively inhibits survivin promoter activity and gene expression in a TP53 status-independent manner.

Additionally, it promotes the inhibition of three additional cancer-associated survival genes (MCL1, BIRC4 and BIRC3) (Ling et al., 2012). FL118 was able to suppress BIRC5 expression in cancer stem cells in a lung cancer model (Wang et al., 2017c), which are known to be a cell population that presents chemoresistance and are responsible for disease recurrence in multiple type of cancer (Zhao, 2016).

**Vaccines against BIRC5**

Survivin-2B80-88 (AYACNTSTL) is an antigenic peptide that can be recognized by CD8+ cells and demonstrated promising results as a potent immunogenic cancer vaccine (Idenoue et al., 2005). By using an HLA-A24/survivin-2B80-88 tetramer, the number of cytotoxic T-lymphocytes precursors in peripheral blood mononuclear cells of HLA-A24+ cancer patients was increased. Interestingly, cytotoxic cells positive for this peptide were found among peripheral blood mononuclear cells obtained from 100% of patients with breast cancers (n=7), 83% with colorectal cancers (n=7) and 57% with gastric cancers (n=7) (Idenoue et al., 2005).

Dendritic cells vaccines using recombinant BIRC5 were tested in hormone refractory prostate cancer patients and results revealed cellular response, disease stabilization, partial tumor remission and no adverse events (Xi et al., 2015).

Using the DepoVax platform, a BIRC5 vaccine was developed (DPX-Survivac) and produced antigen-specific immune responses in ovarian cancer patients. Of note, 12 out of 18 ovarian patients remained without clinical progression after a 6-month treatment (Berinstein et al., 2015).

A study using vaccination with a long BIRC5 peptide demonstrated a BIRC5-specific CD8-mediated tumor cell lysis and, more importantly, the presence of circulating anti-BIRC5 antibodies was found in both, murine glioblastoma models and human glioblastoma patients following vaccination. The same vaccine showed promising results in GL261 glioma and B16 melanoma murine models (Fenstermaker et al., 2018).

**Gene Therapy targeting BIRC5**

Gene therapy has already been used as an approach for inhibiting the expression of BIRC5 and to improve cell death induction in cancer. A combined gene therapy using BIRC5 siRNA and the fusion suicide gene yCDglyTK system displayed a relevant antitumor effect, inducing apoptosis more efficiently and eradicating colon cancer cells. Furthermore, this therapeutic system was able to inhibit the migration of colon cancer cells in vitro (Ye et al., 2017).

**Pharmacological approaches**

| Drug | Clade | Cancer type | References |
|---|---|---|---|
| YM155 | Small-molecule survivin inhibitor | Multiple cancer types | Cheng et al., 2014; Jane et al., 2013; Kita et al., 2012; Lai et al., 2012 |

| | | | |
|---|---|---|---|
| FL118 | Small-molecule survivin inhibitor | Cancer Stem Cell | Wang et al., 2017 |
| | **Vaccines** | | |
| **Vaccine** | **Clade** | **Cancer Type** | **References** |
| Survivin-2B80-88 | Antigenic peptide | Breast cancer; Gastric cancer; Colorectal cancer | Idonoue et al., 2005 |
| Dendritic Cell Vaccines | Dendritic cells vaccines using recombinant BIRC5 | Hormone refractory prostate cancer patients | Xi et al., 2015 |
| DPX-Survivac | BIRC 5 vaccine developed based on DepoVax platform | Ovarian cancer | Berinstein et al., 2015 |
| SurVaxM | Long BIRC5 peptide | Gliobastoma | Fernstermarker et al., 2018 |
| | **Gene Therapy** | | |
| **Strategy** | | **Cancer Type** | **References** |
| Suicide gene yCDglyTK combined with BIRC5 siRNA | | Colon cancer cells | Ye et al., 2017 |
| Heparin-polyethyleneimine (HPEI) nanoparticles to deliver a dominant-negative human BIRC5 T34A (hs-T34A) | | Ovarian carcinoma | Luo et al.,2016 |
| Packaging RNA (pRNA) of bacteriophage phi29 DNA-packaging motor to carry BIRC 5 and methallotionein siRNA | | Ovarian carcinoma | Tarapore et al., 2011 |
| Adeno-associated virus (aaV)-mediated the dominant-negative human BIRC5 T34A (raaV-Sur- Mut(T34a) | | Gastric cancer | Dang et al., 2015 |
| | **Nanotechnology** | | |
| **Strategy of use** | **Nanoparticle** | **Cancer Type** | **References** |
| | Fe3O4 core covered respectively by polyacrylate (PA) and polyethyleneimine (PEI) layer (Fe3O4-PA-PEI) | Breast cancer | Arami et al., 2016 |
| Nanoparticles for siRNA delivery | Magnetic nanoparticles containing polyethyleneglycol-lactate polymer (PEG-LAC), chitosan, and polyethyleneimine (PEI) | Breast cancer and Leukemia | Arami et al., 2017 |
| | Poly(ethylene glycol)-modified chitosan (PEG-CS) | Murine breast cancer | Sun et al., 2016 |
| | NDCONH(CH2)2NH-VDGR/survivin | Breast cancer | Bi et al., 2016 |
| Nanoparticles for shRNA delivery | Monomethoxypolyethylene glycol-chitosan (mPEG-CS) | Prostate cancer | Yang et al., 2015 |
| Nanoparticles for combinatory treatment | Nanoparticles were also developed for co-delivery of siRNA targeting BIRC5 and paclitaxel | Murine cancer models | Jin et al., 2018; Salzano et al., 2015 |

**Table 2.** Summary of BIRC5 targeting strategies in cancer.

Gene therapy using degradable heparin-polyethyleneimine (HPEI) nanoparticles to deliver a dominant-negative human BIRC5 T34A (hs-T34A) gene was also used in ovarian cancer with promising results. HPEI nanoparticles effectively delivered the hs-T34A into ovarian carcinoma cells with low systemic cytotoxicity. Additionally, intraperitoneal administration of HPEI/hs-T34A complexes inhibited tumor growth in ovarian cancer xenograft murine model (Luo et al., 2016). The use of packaging RNA (pRNA) of bacteriophage phi29 DNA-packaging motor to carry siRNA for combined BIRC5 and metallothionein silencing presented a stronger effect on reducing cell proliferation and aggressiveness in ovarian tumor cell lines than either one applied alone (Tarapore et al., 2011).

Adeno-associated virus (aaV)-mediated the dominant-negative human BIRC5 T34A (raaV-Sur-Mut(T34a)) delivery inhibited cell proliferation, induced apoptosis and sensitized gastric cancer cells

to 5-FU in vitro and impaired tumor growth in vivo (Dang et al., 2015).

**Nanotechonology for BIRC5 depletion**

Several nanotechnology-based systems were developed to improve the delivery of siRNA or shRNA targeting BIRC5 in cancer cells, including a $Fe_3O_4$ core covered respectively by a polyacrylate (PA) or polyethyleneimine (PEI) layer ($Fe_3O_4$-PA-PEI) (Arami et al., 2016). Moreover, magnetic nanoparticles containing polyethyleneglycol-lactate polymer (PEG-LAC) have also been used for such means, as well as other systems, like chitosan and polyethyleneimine (PEI) (Arami et al., 2017), poly(ethylene glycol)-modified chitosan (PEG-CS) (Sun et al., 2016), $NDCONH(CH_2)_2NH$-VDGR/survivin (Bi et al., 2016) and monomethoxypolyethylene glycol-chitosan (mPEG-CS) (Yang et al., 2016a). These systems have been shown to inhibit expression of BIRC5, increase apoptosis, reduce cell proliferation and metastasis, and to shrink tumor size in multiple cancer models. Nanoparticles were also developed for co-delivery of siRNA targeting BIRC5 and paclitaxel, which constrained tumor growth, prolonged survival and augmented anticancer properties of paclitaxel in murine cancer models (Jin et al., 2018; Salzano et al., 2015).

A summary of approaches to BIRC5 targeting in cancer is described in Table 2.

**Funding:** Process numbers: 2017/09022-8 and 2015/17177-6, Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)

# References

Adida C, Crotty PL, McGrath J, Berrebi D, Diebold J, Altieri DC. Developmentally regulated expression of the novel cancer anti-apoptosis gene survivin in human and mouse differentiation. Am J Pathol. 1998 Jan;152(1):43-9

AlShamaileh H, Wang T, Xiang D, Yin W, Tran PH, Barrero RA, Zhang PZ, Li Y, Kong L, Liu K, Zhou SF, Hou Y, Shigdar S, Duan W. Aptamer-mediated survivin RNAi enables 5-fluorouracil to eliminate colorectal cancer stem cells. Sci Rep. 2017 Jul 19;7(1):5898

Altieri DC. Targeting survivin in cancer. Cancer Lett. 2013 May 28;332(2):225-8

Ambrosini G, Adida C, Altieri DC. A novel anti-apoptosis gene, survivin, expressed in cancer and lymphoma. Nat Med. 1997 Aug;3(8):917-21

Arami S, Mahdavi M, Rashidi MR, Fathi M, Hejazi MS, Samadi N. Novel polyacrylate-based cationic nanoparticles for survivin siRNA delivery combined with mitoxantrone for treatment of breast cancer Biologicals 2016

Nov;44(6):487-496

Arami S, Rashidi MR, Mahdavi M, Fathi M, Entezami AA. Synthesis and characterization of Fe(3)O(4)-PEG-LAC-chitosan-PEI nanoparticle as a survivin siRNA delivery system Hum Exp Toxicol 2017 Mar;36(3):227-237

Aune G, Stunes AK, Tingulstad S, Salvesen O, Syversen U, Torp SH. The proliferation markers Ki-67/MIB-1, phosphohistone H3, and survivin may contribute in the identification of aggressive ovarian carcinomas Int J Clin Exp Pathol 2011 Jun 20;4(5):444-53

Azuhata T, Scott D, Takamizawa S, Wen J, Davidoff A, Fukuzawa M, Sandler A. The inhibitor of apoptosis protein survivin is associated with high-risk behavior of neuroblastoma J Pediatr Surg 2001 Dec;36(12):1785-91

Bae IS, Kim CH, Kim JM, Cheong JH, Ryu JI, Han MH. Correlation of survivin and B-cell lymphoma 2 expression with pathological malignancy and anti-apoptotic properties of glial cell tumors Biomed Rep 2017 Apr;6(4):396-400

Berinstein NL, Karkada M, Oza AM, Odunsi K, Villella JA, Nemunaitis JJ, Morse MA, Pejovic T, Bentley J, Buyse M, Nigam R, Weir GM, MacDonald LD, Quinton T, Rajagopalan R, Sharp K, Penwell A, Sammatur L, Burzykowski T, Stanford MM, Mansour M. Survivin-targeted immunotherapy drives robust polyfunctional T cell generation and differentiation in advanced ovarian cancer patients Oncoimmunology 2015 May 7;4(8):e1026529

Bi Y, Zhang Y, Cui C, Ren L, Jiang X. Gene-silencing effects of anti-survivin siRNA delivered by RGDV-functionalized nanodiamond carrier in the breast carcinoma cell line MCF-7 Int J Nanomedicine 2016 Nov 4;11:5771-5787

Brun SN, Markant SL, Esparza LA, Garcia G, Terry D, Huang JM, Pavlyukov MS, Li XN, Grant GA, Crawford JR, Levy ML, Conway EM, Smith LH, Nakano I, Berezov A, Greene MI, Wang Q, Wechsler-Reya RJ. Survivin as a therapeutic target in Sonic hedgehog-driven medulloblastoma Oncogene 2015 Jul;34(29):3770-9

Budhidarmo R, Day CL. IAPs: Modular regulators of cell signalling Semin Cell Dev Biol 2015 Mar;39:80-90

Budman DR, Calabro A, Rosen L, Lesser M. Identification of unique synergistic drug combinations associated with downexpression of survivin in a preclinical breast cancer model system Anticancer Drugs 2012 Mar;23(3):272-9

Cai WY, Zhuang Y, Yan F, Li T, Song WT, Sun JH. Effect of survivin downregulation by simvastatin on the growth and invasion of salivary adenoid cystic carcinoma Mol Med Rep 2018 Aug;18(2):1939-1946

Cai X, Ma S, Gu M, Zu C, Qu W, Zheng X. Survivin regulates the expression of VEGF-C in lymphatic metastasis of breast cancer Diagn Pathol 2012 May 18;7:52

Caldas H, Jiang Y, Holloway MP, Fangusaro J, Mahotka C, Conway EM, Altura RA. Survivin splice variants regulate the balance between proliferation and cell death Oncogene 2005 Mar 17;24(12):1994-2007

Cao Y, Cao J, Yu B, Wang S, Liu L, Tao L, Sun W. Berbamine induces SMMC-7721 cell apoptosis via upregulating p53, downregulating survivin expression and activating mitochondria signaling pathway Exp Ther Med 2018 Feb;15(2):1894-1901

Carew JS, Espitia CM, Zhao W, Mita MM, Mita AC, Nawrocki ST. Targeting Survivin Inhibits Renal Cell Carcinoma Progression and Enhances the Activity of Temsirolimus Mol Cancer Ther 2015 Jun;14(6):1404-13

Chade MC, Piato S, Galvão MAL, Aldrighi JM, Negrini R, Mateus EF, Medeiros EM. Evaluation of survivin immunoexpression in the differentiation of high- and low-grade breast ductal carcinoma in situ Einstein (Sao Paulo) 2018;16(1):eAO4065

Chang BH, Johnson K, LaTocha D, Rowley JS, Bryant J, Burke R, Smith RL, Loriaux M, Müschen M, Mullighan C, Druker BJ, Tyner JW. YM155 potently kills acute lymphoblastic leukemia cells through activation of the DNA damage pathway J Hematol Oncol 2015 Apr 22;8:39

Chantalat L, Skoufias DA, Kleman JP, Jung B, Dideberg O, Margolis RL. Crystal structure of human survivin reveals a bow tie-shaped dimer with two unusual alpha-helical extensions Mol Cell 2000 Jul;6(1):183-9

Chen D, Dai F, Chen Z, Wang S, Cheng X, Sheng Q, Lin J, Chen W. Dimethoxy Curcumin Induces Apoptosis by Suppressing Survivin and Inhibits Invasion by Enhancing E-Cadherin in Colon Cancer Cells Med Sci Monit 2016 Sep 11;22:3215-22

Chen JH, Chen KY, Ma HI, Yu CP, Nieh S, Lee HS, Jin JS. Cortactin, fascin and survivin expression associated with clinicopathological parameters in brain gliosarcoma Chin J Physiol 2010 Aug 31;53(4):234-44

Cheng KY, Wang ZL, Gu QY, Hao M. Survivin Overexpression Is Associated with Aggressive Clinicopathological Features in Cervical Carcinoma: A Meta-Analysis PLoS One 2016 Oct 20;11(10):e0165117

Cheng Q, Ling X, Haller A, Nakahara T, Yamanaka K, Kita A, Koutoku H, Takeuchi M, Brattain MG, Li F. Suppression of survivin promoter activity by YM155 involves disruption of Sp1-DNA interaction in the survivin core promoter Int J Biochem Mol Biol 2012;3(2):179-97

Cheng SM, Chang YC, Liu CY, Lee JY, Chan HH, Kuo CW, Lin KY, Tsai SL, Chen SH, Li CF, Leung E, Kanwar JR, Huang CC, Chang JY, Cheung CH. YM155 down-regulates survivin and XIAP, modulates autophagy and induces autophagy-dependent DNA damage in breast cancer cells Br J Pharmacol 2015 Jan;172(1):214-34

Choi JY, Yoon H, Na G, Choi YJ, Shin CM, Park YS, Kim N, Lee DH. Evaluation of the Expression of the Inhibitor of Apoptosis Protein Family and Human Telomerase Reverse Transcriptase in Patients With Advanced Colorectal Adenoma J Cancer Prev 2017 Jun;22(2):98-102

Contis J, Lykoudis PM, Goula K, Karandrea D, Kondi-Pafiti A. Survivin expression as an independent predictor of overall survival in pancreatic adenocarcinoma J Cancer Res Ther 2018 Sep;14(Supplement):S719-S723

Coumar MS, Tsai FY, Kanwar JR, Sarvagalla S, Cheung CH. Treat cancers by targeting survivin: just a dream or future reality? Cancer Treat Rev 2013 Nov;39(7):802-11 doi: 10

Dahan P, Martinez Gala J, Delmas C, Monferran S, Malric L, Zentkowski D, Lubrano V, Toulas C, Cohen-Jonathan Moyal E, Lemarie A. Ionizing radiations sustain glioblastoma cell dedifferentiation to a stem-like phenotype through survivin: possible involvement in radioresistance Cell Death Dis 2014 Nov 27;5:e1543

Dang SC, Feng S, Wang PJ, Cui L, Qu JG, Zhang JX. Overexpression of Survivin mutant Thr34Ala induces apoptosis and inhibits gastric cancer growth Neoplasma 2015;62(1):81-7

Danoch H, Kalechman Y, Albeck M, Longo DL, Sredni B. Sensitizing B- and T- cell Lymphoma Cells to Paclitaxel/Abraxane-Induced Death by AS101 via Inhibition of the VLA-4-IL10-Survivin Axis Mol Cancer Res 2015 Mar;13(3):411-22

Dobrzycka B, Mackowiak-Matejczyk B, Terlikowska KM, Kulesza-Bronczyk B, Kinalski M, Terlikowski SJ. Prognostic significance of pretreatment VEGF, survivin, and Smac/DIABLO serum levels in patients with serous ovarian carcinoma Tumour Biol 2015 Jun;36(6):4157-65

Du J, Li B, Fang Y, Liu Y, Wang Y, Li J, Zhou W, Wang X. Overexpression of Class III β-tubulin, Sox2, and nuclear Survivin is predictive of taxane resistance in patients with stage III ovarian epithelial cancer BMC Cancer 2015 Jul 23;15:536

Duan L, Hu X, Jin Y, Liu R, You Q. Survivin protein expression is involved in the progression of non-small cell lung cancer in Asians: a meta-analysis BMC Cancer 2016 Apr 18;16:276

Eslami M, Khamechian T, Mazoochi T, Ehteram H, Sehat M, Alizargar J. Evaluation of survivin expression in prostate specimens of patients with prostate adenocarcinoma and benign prostate hyperplasia underwent transurethral resection of the prostate or prostatectomy Springerplus 2016 May 14;5:621

Fan R, Wang Y, Wang Y, Wei L, Zheng W. Mechanism of progestin resistance in endometrial precancer/cancer through Nrf2-survivin pathway Am J Transl Res 2017 Mar 15;9(3):1483-1491

Faversani A, Vaira V, Moro GP, Tosi D, Lopergolo A, Schultz DC, Rivadeneira D, Altieri DC, Bosari S. Survivin family proteins as novel molecular determinants of doxorubicin resistance in organotypic human breast tumors Breast Cancer Res 2014 May 30;16(3):R55

Felisiak-Golabek A, Rembiszewska A, Rzepecka IK, Szafron L, Madry R, Murawska M, Napiorkowski T, Sobiczewski P, Osuch B, Kupryjanczyk J; Polish Ovarian Cancer Study Group (POCSG). Nuclear survivin expression is a positive prognostic factor in taxane-platinum-treated ovarian cancer patients J Ovarian Res 2011 Nov 10;4(1):20

Fenstermaker RA, Figel SA, Qiu J, Barone TA, Dharma SS, Winograd EK, Galbo PM, Wiltsie LM, Ciesielski MJ. Survivin Monoclonal Antibodies Detect Survivin Cell Surface Expression and Inhibit Tumor Growth In Vivo Clin Cancer Res 2018 Jun 1;24(11):2642-2652

Fernández JG, Rodríguez DA, Valenzuela M, Calderon C, Urzúa U, Munroe D, Rosas C, Lemus D, Díaz N, Wright MC, Leyton L, Tapia JC, Quest AF. Survivin expression promotes VEGF-induced tumor angiogenesis via PI3K/Akt enhanced β-catenin/Tcf-Lef dependent transcription Mol Cancer 2014 Sep 9;13:209

Florell SR, Bowen AR, Hanks AN, Murphy KJ, Grossman D. Proliferation, apoptosis, and survivin expression in a spectrum of melanocytic nevi J Cutan Pathol 2005 Jan;32(1):45-9

Fortugno P, Beltrami E, Plescia J, Fontana J, Pradhan D, Marchisio PC, Sessa WC, Altieri DC. Regulation of survivin function by Hsp90 Proc Natl Acad Sci U S A 2003 Nov 25;100(24):13791-6

Garg H, Suri P, Gupta JC, Talwar GP, Dubey S. Survivin: a unique target for tumor therapy Cancer Cell Int 2016 Jun 23;16:49

Gholinejad Z, Kheiripour N, Nourbakhsh M, Ilbeigi D, Behroozfar K, Hesari Z, Golestani A, Shabani M, Einollahi N. Extracellular NAMPT/Visfatin induces proliferation through ERK1/2 and AKT and inhibits apoptosis in breast cancer cells Peptides 2017 Jun;92:9-15

Gravina GL, Mancini A, Sanita P, Vitale F, Marampon F, Ventura L, Landesman Y, McCauley D, Kauffman M, Shacham S, Festuccia C. KPT-330, a potent and selective exportin-1 (XPO-1) inhibitor, shows antitumor effects modulating the expression of cyclin D1 and survivin [corrected] in prostate cancer models BMC Cancer 2015 Dec 1;15:941

Gyrd-Hansen M, Meier P. IAPs: from caspase inhibitors to modulators of NF-kappaB, inflammation and cancer Nat Rev Cancer 2010 Aug;10(8):561-74

Habibie, Yokoyama S, Abdelhamed S, Awale S, Sakurai H, Hayakawa Y, Saiki I. Survivin suppression through STAT3/β-catenin is essential for resveratrol-induced melanoma apoptosis Int J Oncol 2014 Aug;45(2):895-901

Hamy AS, Bieche I, Lehmann-Che J, Scott V, Bertheau P, Guinebretière JM, Matthieu MC, Sigal-Zafrani B, Tembo O, Marty M, Asselain B, Spyratos F, de Cremoux P. BIRC5 (survivin): a pejorative prognostic marker in stage II/III breast cancer with no response to neoadjuvant chemotherapy Breast Cancer Res Treat 2016 Oct;159(3):499-511

He XJ, Zhang Q, Ma LP, Li N, Chang XH, Zhang YJ. Aberrant Alternative Polyadenylation is Responsible for Survivin Up-regulation in Ovarian Cancer Chin Med J (Engl) 2016 May 20;129(10):1140-6

Hou LJ, Huang XX, Xu LN, Zhang YY, Zhao N, Ou RY, Li WF, Zhang WJ, Jiang QW, Yang Y, Wei MN, Huang JR, Wang K, Yuan ML, Xing ZH, Shi Z, Yan XJ. YM155 enhances docetaxel efficacy in ovarian cancer Am J Transl Res 2018 Mar 15;10(3):696-708

Hu S, Fu S, Xu X, Chen L, Xu J, Li B, Qu Y, Yu H, Lu S, Li W. The mechanism of radiosensitization by YM155, a novel small molecule inhibitor of survivin expression, is associated with DNA damage repair Cell Physiol Biochem 2015;37(3):1219-30

Hu W, Jin P, Liu W. Periostin Contributes to Cisplatin Resistance in Human Non-Small Cell Lung Cancer A549 Cells via Activation of Stat3 and Akt and Upregulation of Survivin Cell Physiol Biochem 2016;38(3):1199-208

Idenoue S, Hirohashi Y, Torigoe T, Sato Y, Tamura Y, Hariu H, Yamamoto M, Kurotaki T, Tsuruma T, Asanuma H, Kanaseki T, Ikeda H, Kashiwagi K, Okazaki M, Sasaki K, Sato T, Ohmura T, Hata F, Yamaguchi K, Hirata K, Sato N. A potent immunogenic general cancer vaccine that targets survivin, an inhibitor of apoptosis proteins Clin Cancer Res 2005 Feb 15;11(4):1474-82

Islam A, Kageyama H, Takada N, Kawamoto T, Takayasu H, Isogai E, Ohira M, Hashizume K, Kobayashi H, Kaneko Y, Nakagawara A. High expression of Survivin, mapped to 17q25, is significantly associated with poor prognostic factors and promotes cell survival in human neuroblastoma Oncogene 2000 Feb 3;19(5):617-23

Jane EP, Premkumar DR, DiDomenico JD, Hu B, Cheng SY, Pollack IF. YM-155 potentiates the effect of ABT-737 in malignant human glioma cells via survivin and Mcl-1 downregulation in an EGFR-dependent context Mol Cancer Ther 2013 Mar;12(3):326-38

Ji Z, Kumar R, Taylor M, Rajadurai A, Marzuka-Alcalá A, Chen YE, Njauw CN, Flaherty K, Jönsson G, Tsao H. Vemurafenib synergizes with nutlin-3 to deplete survivin and suppresses melanoma viability and tumor growth Clin Cancer Res 2013 Aug 15;19(16):4383-91

Jiang G, Ren B, Xu L, Song S, Zhu C, Ye F. Survivin may enhance DNA double-strand break repair capability by up-regulating Ku70 in human KB cells Anticancer Res 2009 Jan;29(1):223-8

Jiang L, Luo RY, Yang J, Cheng YX. Knockdown of survivin contributes to antitumor activity in cisplatin-resistant ovarian cancer cells Mol Med Rep 2013 Feb;7(2):425-30

Jiao D, Zhang XD. Myricetin suppresses p21-activated kinase 1 in human breast cancer MCF-7 cells through downstream signaling of the β-catenin pathway Oncol Rep 2016 Jul;36(1):342-8

Jin M, Jin G, Kang L, Chen L, Gao Z, Huang W. Smart polymeric nanoparticles with pH-responsive and PEG-detachable properties for co-delivering paclitaxel and survivin siRNA to enhance antitumor outcomes Int J Nanomedicine 2018 Apr 20;13:2405-2426

Ju LL, Zhao CY, Ye KF, Yang H, Zhang J. Expression and clinical implication of Beclin1, HMGB1, p62, survivin, BRCA1 and ERCC1 in epithelial ovarian tumor tissues Eur Rev Med Pharmacol Sci 2016 May;20(10):1993-2003

Kaneko N, Mitsuoka K, Amino N, Yamanaka K, Kita A, Mori M, Miyoshi S, Kuromitsu S. Combination of YM155, a survivin suppressant, with bendamustine and rituximab: a new combination therapy to treat relapsed/refractory diffuse large B-cell lymphoma Clin Cancer Res 2014 Apr 1;20(7):1814-22

Karami H, Baradaran B, Esfahani A, Estiar MA, Naghavi-Behzad M, Sakhinia M, Sakhinia E. siRNA-mediated silencing of survivin inhibits proliferation and enhances etoposide chemosensitivity in acute myeloid leukemia cells Asian Pac J Cancer Prev 2013;14(12):7719-24

Karimian M, Aftabi Y, Mazoochi T, Babaei F, Khamechian T, Boojari H, Nikzad H. Survivin polymorphisms and susceptibility to prostate cancer: A genetic association study and an in silico analysis EXCLI J 2018 May 18;17:479-491

Kedinger V, Meulle A, Zounib O, Bonnet ME, Gossart JB, Benoit E, Messmer M, Shankaranarayanan P, Behr JP, Erbacher P, Bolcato-Bellemin AL. Sticky siRNAs targeting survivin and cyclin B1 exert an antitumoral effect on melanoma subcutaneous xenografts and lung metastases BMC Cancer 2013 Jul 9;13:338

Khan S, Bennit HF, Turay D, Perez M, Mirshahidi S, Yuan Y, Wall NR. Early diagnostic value of survivin and its alternative splice variants in breast cancer BMC Cancer 2014 Mar 12;14:176

Khan S, Jutzy JM, Aspe JR, McGregor DW, Neidigh JW, Wall NR. Survivin is released from cancer cells via exosomes Apoptosis 2011 Jan;16(1):1-12

Kim SJ, Hong M, Do IG, Lee SH, Ryu KJ, Yoo HY, Hong JY, Ko YH, Kim WS. Serum survivin and vascular endothelial growth factor in extranodal NK/T-cell lymphoma, nasal type: implications for a potential new prognostic indicator Haematologica 2015 Mar;100(3):e106-9

Kita A, Mitsuoka K, Kaneko N, Nakata M, Yamanaka K, Jitsuoka M, Miyoshi S, Noda A, Mori M, Nakahara T, Sasamata M. Sepantronium bromide (YM155) enhances response of human B-cell non-Hodgkin lymphoma to rituximab J Pharmacol Exp Ther 2012 Oct;343(1):178-83

Kreger BT, Johansen ER, Cerione RA, Antonyak MA. The Enrichment of Survivin in Exosomes from Breast Cancer Cells Treated with Paclitaxel Promotes Cell Survival and Chemoresistance Cancers (Basel) 2016 Dec 9;8(12)

LaCasse EC, Mahoney DJ, Cheung HH, Plenchette S, Baird S, Korneluk RG. IAP-targeted therapies for cancer Oncogene 2008 Oct 20;27(48):6252-75

Lai PC, Chen SH, Yang SH, Cheng CC, Chiu TH, Huang YT. Novel survivin inhibitor YM155 elicits cytotoxicity in glioblastoma cell lines with normal or deficiency DNA-dependent protein kinase activity Pediatr Neonatol 2012 Jun;53(3):199-204

Lee EY, Gong EY, Shin JS, Moon JH, Shim HJ, Kim SM, Lee S, Jeong J, Gong JH, Kim MJ, Lee DH, Park YS, Shin J, Hong SW, Kim YS, Jin DH. Human breast cancer cells display different sensitivities to ABT-263 based on the level of survivin Toxicol In Vitro 2018 Feb;46:229-236

Li F, Ambrosini G, Chu EY, Plescia J, Tognin S, Marchisio PC, Altieri DC. Control of apoptosis and mitotic spindle checkpoint by survivin Nature 1998 Dec 10;396(6711):580-4

Li SX, Chai L, Cai ZG, Jin LJ, Chen Y, Wu HR, Sun Z. Expression of survivin and caspase 3 in oral squamous cell carcinoma and peritumoral tissue Asian Pac J Cancer Prev 2012;13(10):5027-31

Li W, Lee MR, Choi E, Cho MY. Clinicopathologic Significance of Survivin Expression in Relation to CD133 Expression in Surgically Resected Stage II or III Colorectal Cancer J Pathol Transl Med 2017 Jan;51(1):17-23

Li WX, Li YK, Lin HT. Correlation between survivin polymorphism and acute leukemia of children Exp Ther Med 2018 Mar;15(3):2941-2945

Li Y, Zhou Y, Zheng J, Niu C, Liu B, Wang M, Fang H, Hou C. Downregulation of survivin inhibits proliferation and migration of human gastric carcinoma cells Int J Clin Exp Pathol 2015 Feb 1;8(2):1731-6

Li YH, Chen M, Zhang M, Zhang XQ, Zhang S, Yu CG, Xu ZM, Zou XP. Inhibitory effect of survivin-targeting small interfering RNA on gastric cancer cells Genet Mol Res 2014 Aug 28;13(3):6786-803

Ling X, Cao S, Cheng Q, Keefe JT, Rustum YM, Li F. A novel small molecule FL118 that selectively inhibits survivin, Mcl-1, XIAP and cIAP2 in a p53-independent manner, shows superior antitumor activity PLoS One 2012;7(9):e45571

Ling X, Wu W, Fan C, Xu C, Liao J, Rich LJ, Huang RY, Repasky EA, Wang X, Li F. An ABCG2 non-substrate anticancer agent FL118 targets drug-resistant cancer stem-like cells and overcomes treatment resistance of human pancreatic cancer J Exp Clin Cancer Res 2018 Oct 3;37(1):240

Lins RR, Oshima CT, Oliveira LA, Silva MS, Mader AM, Waisberg J. EXPRESSION OF E-CADHERIN AND WNT PATHWAY PROTEINS BETACATENIN, APC, TCF-4 AND SURVIVIN IN GASTRIC ADENOCARCINOMA: CLINICAL AND PATHOLOGICAL IMPLICATION Arq Bras Cir Dig 2016 Nov-Dec;29(4):227-231

Liu S, Shi L, Yang X, Ye D, Wang T, Dong C, Guo W, Liao Y, Song H, Xu D, Hu J, Zhang Z, Deng J. Nuclear survivin promoted by acetylation is associated with the aggressive phenotype of oral squamous cell carcinoma Cell Cycle 2017 May 3;16(9):894-902

Liu TC, Hsieh MJ, Wu WJ, Chou YE, Chiang WL, Yang SF, Su SC, Tsao TC. Association between survivin genetic polymorphisms and epidermal growth factor receptor mutation in non-small-cell lung cancer Int J Med Sci 2016 Nov 23;13(12):929-935

Liu YB, Gao X, Deeb D, Brigolin C, Zhang Y, Shaw J, Pindolia K, Gautam SC. Ubiquitin-proteasomal degradation of antiapoptotic survivin facilitates induction of apoptosis in prostate cancer cells by pristimerin Int J Oncol 2014 Oct;45(4):1735-41

Lopez J, Meier P. To fight or die - inhibitor of apoptosis proteins at the crossroad of innate immunity and death Curr Opin Cell Biol 2010 Dec;22(6):872-81

Luo L, Du T, Zhang J, Zhao W, Cheng H, Yang Y, Wu Y, Wang C, Men K, Gou M. Efficient inhibition of ovarian cancer by degradable nanoparticle-delivered survivin T34A gene Int J Nanomedicine 2016 Feb 2;11:501-12

Ma C, Lu B, Sun E. Clinicopathological and prognostic significance of survivin expression in renal cancer patients: a meta-analysis Postgrad Med J 2017 Apr;93(1098):186-192

Mak CS, Yung MM, Hui LM, Leung LL, Liang R, Chen K, Liu SS, Qin Y, Leung TH, Lee KF, Chan KK, Ngan HY, Chan DW. MicroRNA-141 enhances anoikis resistance in metastatic progression of ovarian cancer through targeting KLF12/Sp1/survivin axis Mol Cancer 2017 Jan 17;16(1):11

Markovic O, Marisavljevic D, Cemerikic-Martinovic V, Martinovic T, Filipovic B, Stanisavljevic D, Zivković R, Hajder J, Stanisavljevic N, Mihaljevic B. Survivin expression in patients with newly diagnosed nodal diffuse large B cell lymphoma (DLBCL) Med Oncol 2012 Dec;29(5):3515-21

McKenzie JA, Liu T, Jung JY, Jones BB, Ekiz HA, Welm AL, Grossman D. Survivin promotion of melanoma metastasis requires upregulation of α5 integrin Carcinogenesis 2013 Sep;34(9):2137-44

Meerang M, Bérard K, Friess M, Bitanihirwe BK, Soltermann A, Vrugt B, Felley-Bosco E, Bueno R, Richards WG, Seifert B, Stahel R, Weder W, Opitz I. Low Merlin expression and high Survivin labeling index are indicators for poor prognosis in patients with malignant pleural mesothelioma Mol Oncol 2016 Oct;10(8):1255-65

Nakahara T, Kita A, Yamanaka K, Mori M, Amino N, Takeuchi M, Tominaga F, Hatakeyama S, Kinoyama I, Matsuhisa A, Kudoh M, Sasamata M. YM155, a novel small-molecule survivin suppressant, induces regression of established human hormone-refractory prostate tumor xenografts Cancer Res 2007 Sep 1;67(17):8014-21

Nam K, Son SH, Oh S, Jeon D, Kim H, Noh DY, Kim S, Shin I. Binding of galectin-1 to integrin β1 potentiates drug resistance by promoting survivin expression in breast cancer cells Oncotarget 2017 May 30;8(22):35804-35823

Nie P, Hu W, Zhang T, Yang Y, Hou B, Zou Z. Synergistic Induction of Erlotinib-Mediated Apoptosis by Resveratrol in Human Non-Small-Cell Lung Cancer Cells by Down-Regulating Survivin and Up-Regulating PUMA Cell Physiol Biochem 2015;35(6):2255-71

No JH, Jeon YT, Kim YB, Song YS. Quantitative detection of serum survivin and its relationship with prognostic factors in ovarian cancer Gynecol Obstet Invest 2011;71(2):136-40

Nuncia-Cantarero M, Martinez-Canales S, Andrés-Pretel F, Santpere G, Ocaña A, Galan-Moya EM. Functional transcriptomic annotation and protein-protein interaction network analysis identify NEK2, BIRC5, and TOP2A as potential targets in obese patients with luminal A breast cancer Breast Cancer Res Treat 2018 Apr;168(3):613-623

Ou QJ, Wu XJ, Peng JH, Zhang RX, Lu ZH, Jiang W, Zhang L, Pan ZZ, Wan DS, Fang YJ. Endocrine therapy inhibits proliferation and migration, promotes apoptosis and suppresses survivin protein expression in colorectal cancer cells Mol Med Rep 2017 Nov;16(5):5769-5778

Panayotopoulou EG, Müller AK, Börries M, Busch H, Hu G, Lev S. Targeting of apoptotic pathways by SMAC or BH3 mimetics distinctly sensitizes paclitaxel-resistant triple negative breast cancer cells Oncotarget 2017 Jul 11;8(28):45088-45104

Parvani JG, Davuluri G, Wendt MK, Espinosa C, Tian M, Danielpour D, Sossey-Alaoui K, Schiemann WP. Deptor enhances triple-negative breast cancer metastasis and chemoresistance through coupling to survivin expression Neoplasia 2015 Mar;17(3):317-28

Pavlidou A, Dalamaga M, Kroupis C, Konstantoudakis G, Belimezi M, Athanasas G, Dimas K. Survivin isoforms and

clinicopathological characteristics in colorectal adenocarcinomas using real-time qPCR World J Gastroenterol 2011 Mar 28;17(12):1614-21

Peery RC, Liu JY, Zhang JT. Targeting survivin for therapeutic discovery: past, present, and future promises Drug Discov Today 2017 Oct;22(10):1466-1477

Premkumar DR, Jane EP, Pollack IF. Cucurbitacin-I inhibits Aurora kinase A, Aurora kinase B and survivin, induces defects in cell cycle progression and promotes ABT-737-induced cell death in a caspase-independent manner in malignant human glioma cells Cancer Biol Ther 2015;16(2):233-43

Rödel F, Sprenger T, Kaina B, Liersch T, Rödel C, Fulda S, Hehlgans S. Survivin as a prognostic/predictive marker and molecular target in cancer therapy Curr Med Chem 2012;19(22):3679-88

Raj D, Liu T, Samadashwily G, Li F, Grossman D. Survivin repression by p53, Rb and E2F2 in normal human melanocytes Carcinogenesis 2008 Jan;29(1):194-201

Rauch A, Hennig D, Schäfer C, Wirth M, Marx C, Heinzel T, Schneider G, Krämer OH. Survivin and YM155: how faithful is the liaison? Biochim Biophys Acta 2014 Apr;1845(2):202-20 doi: 10

Roy K, Kanwar RK, Krishnakumar S, Cheung CH, Kanwar JR. Competitive inhibition of survivin using a cell-permeable recombinant protein induces cancer-specific apoptosis in colon cancer model Int J Nanomedicine 2015 Feb 2;10:1019-43

Sah NK, Khan Z, Khan GJ, Bisen PS. Structural, functional and therapeutic biology of survivin Cancer Lett 2006 Dec 8;244(2):164-71

Sajid A, Manzoor Q, Iqbal M, Tyagi AK, Sarfraz RA, Sajid A. Pinus Roxburghii essential oil anticancer activity and chemical composition evaluation EXCLI J 2018 Mar 12;17:233-245

Salzano G, Navarro G, Trivedi MS, De Rosa G, Torchilin VP. Multifunctional Polymeric Micelles Co-loaded with Anti-Survivin siRNA and Paclitaxel Overcome Drug Resistance in an Animal Model of Ovarian Cancer Mol Cancer Ther 2015 Apr;14(4):1075-84

Sam MR, Tavakoli-Mehr M, Safaralizadeh R. Omega-3 fatty acid DHA modulates p53, survivin, and microRNA-16-1 expression in KRAS-mutant colorectal cancer stem-like cells Genes Nutr 2018 Apr 2;13:8

Sandler A, Scott D, Azuhata T, Takamizawa S, O'Dorisio S. The survivin:Fas ratio is predictive of recurrent disease in neuroblastoma J Pediatr Surg 2002 Mar;37(3):507-11

Sawicka-Gutaj N, Waligórska-Stachura J, Andrusiewicz M, Biczysko M, Sowiński J, Skrobisz J, Ruchańa M. Nicotinamide phosphorybosiltransferase overexpression in thyroid malignancies and its correlation with tumor stage and with survivin/survivin ΔEx3 expression Tumour Biol 2015 Sep;36(10):7859-63

Serrano-López J, Serrano J, Figueroa V, Torres-Gomez A, Tabares S, Casaño J, Fernandez-Escalada N, Sánchez-Garcia J. Cytoplasmic localization of wild-type survivin is associated with constitutive activation of the PI3K/Akt signaling pathway and represents a favorable prognostic factor in patients with acute myeloid leukemia Haematologica 2013 Dec;98(12):1877-85

Shankar SL, Mani S, O'Guin KN, Kandimalla ER, Agrawal S, Shafit-Zagardo B. Survivin inhibition induces human neural tumor cell death through caspase-independent and -dependent pathways J Neurochem 2001 Oct;79(2):426-36

Shen X, Zheng JY, Shi H, Zhang Z, Wang WZ. Survivin knockdown enhances gastric cancer cell sensitivity to radiation and chemotherapy in vitro and in nude mice Am J Med Sci 2012 Jul;344(1):52-8

Shi K, An J, Shan L, Jiang Q, Li F, Ci Y, Wu P, Duan J, Hui K, Yang Y, Xu C. Survivin-2B promotes autophagy by accumulating IKK alpha in the nucleus of selenite-treated NB4 cells Cell Death Dis 2014 Feb 20;5:e1071

Shintani M, Sangawa A, Yamao N, Kamoshida S. Immunohistochemical expression of nuclear and cytoplasmic survivin in gastrointestinal carcinoma Int J Clin Exp Pathol 2013 Nov 15;6(12):2919-27

Song Z, Yao X, Wu M. Direct interaction between survivin and Smac/DIABLO is essential for the anti-apoptotic activity of survivin during taxol-induced apoptosis J Biol Chem 2003 Jun 20;278(25):23130-40

Stauber RH, Mann W, Knauer SK. Nuclear and cytoplasmic survivin: molecular mechanism, prognostic, and therapeutic potential Cancer Res 2007 Jul 1;67(13):5999-6002

Stella S, Tirrò E, Conte E, Stagno F, Di Raimondo F, Manzella L, Vigneri P. Suppression of survivin induced by a BCR-ABL/JAK2/STAT3 pathway sensitizes imatinib-resistant CML cells to different cytotoxic drugs Mol Cancer Ther 2013 Jun;12(6):1085-98

Stroopinsky D, Rajabi H, Nahas M, Rosenblatt J, Rahimian M, Pyzer A, Tagde A, Kharbanda A, Jain S, Kufe T, Leaf RK, Anastasiadou E, Bar-Natan M, Orr S, Coll MD, Palmer K, Ephraim A, Cole L, Washington A, Kufe D, Avigan D. MUC1-C drives myeloid leukaemogenesis and resistance to treatment by a survivin-mediated mechanism J Cell Mol Med 2018 May 15

Sun L, Zhao Y, Shi H, Ma C, Wei L. LMP-1 induces survivin expression to inhibit cell apoptosis through the NF-κB and PI3K/Akt signaling pathways in nasal NK/T-cell lymphoma Oncol Rep 2015 May;33(5):2253-60

Sun P, Huang W, Jin M, Wang Q, Fan B, Kang L, Gao Z. Chitosan-based nanoparticles for survivin targeted siRNA delivery in breast tumor therapy and preventing its metastasis Int J Nanomedicine 2016 Sep 27;11:4931-4945

Szafer-Glusman E, Fuller MT, Giansanti MG. Role of Survivin in cytokinesis revealed by a separation-of-function allele Mol Biol Cell 2011 Oct;22(20):3779-90

Tajiri T, Tanaka S, Shono K, Kinoshita Y, Fujii Y, Suita S, Ihara K, Hara T. Quick quantitative analysis of gene dosages associated with prognosis in neuroblastoma Cancer Lett 2001 May 10;166(1):89-94

Takeuchi H, Morton DL, Elashoff D, Hoon DS. Survivin expression by metastatic melanoma predicts poor disease outcome in patients receiving adjuvant polyvalent vaccine Int J Cancer 2005 Dec 20;117(6):1032-8

Tang TK, Chiu SC, Lin CW, Su MJ, Liao MH. Induction of survivin inhibition, G/M cell cycle arrest and autophagic on cell death in human malignant glioblastoma cells Chin J Physiol 2015 Apr 30;58(2):95-103

Tao YF, Lu J, Du XJ, Sun LC, Zhao X, Peng L, Cao L, Xiao PF, Pang L, Wu D, Wang N, Feng X, Li YH, Ni J, Wang J, Pan J. Survivin selective inhibitor YM155 induce apoptosis in SK-NEP-1 Wilms tumor cells BMC Cancer 2012 Dec 26;12:619

Tarapore P, Shu Y, Guo P, Ho SM. Application of phi29 motor pRNA for targeted therapeutic delivery of siRNA

silencing metallothionein-IIA and survivin in ovarian cancers Mol Ther 2011 Feb;19(2):386-94

Thomas J, Liu T, Cotter MA, Florell SR, Robinette K, Hanks AN, Grossman D. Melanocyte expression of survivin promotes development and metastasis of UV-induced melanoma in HGF-transgenic mice Cancer Res 2007 Jun 1;67(11):5172-8

Tian QG, Wu YT, Liu Y, Zhang J, Song ZQ, Gao WF, Guo TK, He CH, Dai FR. Expressions and correlation analysis of HIF-1α, survivin and VEGF in patients with hepatocarcinoma Eur Rev Med Pharmacol Sci 2018 Jun;22(11):3378-3385

Tsuneki M, Kinjo T, Mori T, Yoshida A, Kuyama K, Ohira A, Miyagi T, Takahashi K, Kawai A, Chuman H, Yamazaki N, Masuzawa M, Arakawa H. Survivin: A novel marker and potential therapeutic target for human angiosarcoma Cancer Sci 2017 Nov;108(11):2295-2305

Verdecia MA, Huang H, Dutil E, Kaiser DA, Hunter T, Noel JP. Structure of the human anti-apoptotic protein survivin reveals a dimeric arrangement Nat Struct Biol 2000 Jul;7(7):602-8

Vivas-Mejia PE, Rodriguez-Aguayo C, Han HD, Shahzad MM, Valiyeva F, Shibayama M, Chavez-Reyes A, Sood AK, Lopez-Berestein G. Silencing survivin splice variant 2B leads to antitumor activity in taxane--resistant ovarian cancer Clin Cancer Res 2011 Jun 1;17(11):3716-26

Wang D, Jiao C, Zhu Y, Liang D, Zao M, Meng X, Gao J, He Y, Liu W, Hou J, Zhong Z, Cheng Z. Activation of CXCL12/CXCR4 renders colorectal cancer cells less sensitive to radiotherapy via up-regulating the expression of survivin Exp Biol Med (Maywood) 2017 Feb;242(4):429-435

Wang H, Li S, Luo X, Song Z, Long X, Zhu X. Knockdown of PARP6 or survivin promotes cell apoptosis and inhibits cell invasion of colorectal adenocarcinoma cells Oncol Rep 2017 Apr;37(4):2245-2251

Wang J, Liu Z, Zhang D, Liu R, Lin Q, Liu J, Yang Z, Ma Q, Sun D, Zhou X, Jiang G. FL118, a novel survivin inhibitor, wins the battle against drug-resistant and metastatic lung cancers through inhibition of cancer stem cell-like properties Am J Transl Res 2017 Aug 15;9(8):3676-3686

Wang Q, Chen Z, Diao X, Huang S. Induction of autophagy-dependent apoptosis by the survivin suppressant YM155 in prostate cancer cells Cancer Lett 2011 Mar 1;302(1):29-36

Wang S, Xu J, Zhang Q. Clinical significance of survivin and vascular endothelial growth factor mRNA detection in the peripheral whole blood of breast cancer patients Neoplasma 2016;63(1):133-40

Wang X, Qiu W, Zhang G, Xu S, Gao Q, Yang Z. MicroRNA-204 targets JAK2 in breast cancer and induces cell apoptosis through the STAT3/BCl-2/survivin pathway Int J Clin Exp Pathol 2015 May 1;8(5):5017-25

Weng G, Zeng Y, Huang J, Fan J, Guo K. Curcumin Enhanced Busulfan-Induced Apoptosis through Downregulating the Expression of Survivin in Leukemia Stem-Like KG1a Cells Biomed Res Int 2015;2015:630397

Xi HB, Wang GX, Fu B, Liu WP, Li Y. Survivin and PSMA Loaded Dendritic Cell Vaccine for the Treatment of Prostate Cancer Biol Pharm Bull 2015;38(6):827-35

Xu S, Adisetiyo H, Tamura S, Grande F, Garofalo A, Roy-Burman P, Neamati N. Dual inhibition of survivin and MAOA synergistically impairs growth of PTEN-negative prostate cancer Br J Cancer 2015 Jul 14;113(2):242-51

Yahya RS, Fouda MI, El-Baz HA, Mosa TE, Elmaksoud MD. Serum Survivin and TP53 Gene Expression in Children with Acute Lymphoblastic Leukemia Iran J Public Health 2012;41(1):37-44

Yamada T, Horinaka M, Shinnoh M, Yoshioka T, Miki T, Sakai T. A novel HDAC inhibitor OBP-801 and a PI3K inhibitor LY294002 synergistically induce apoptosis via the suppression of survivin and XIAP in renal cell carcinoma Int J Oncol 2013 Oct;43(4):1080-6

Yamanaka K, Nakahara T, Yamauchi T, Kita A, Takeuchi M, Kiyonaga F, Kaneko N, Sasamata M. Antitumor activity of YM155, a selective small-molecule survivin suppressant, alone and in combination with docetaxel in human malignant melanoma models Clin Cancer Res 2011 Aug 15;17(16):5423-31

Yan H, Thomas J, Liu T, Raj D, London N, Tandeski T, Leachman SA, Lee RM, Grossman D. Induction of melanoma cell apoptosis and inhibition of tumor growth using a cell-permeable Survivin antagonist Oncogene 2006 Nov 2;25(52):6968-74

Yan X, Su H. YM155 Down-Regulates Survivin and Induces P53 Up-Regulated Modulator of Apoptosis (PUMA)-Dependent in Oral Squamous Cell Carcinoma Cells Med Sci Monit 2017 Apr 24;23:1963-1972

Yang AQ, Wang PJ, Huang T, Zhou WL, Landman J. Effects of monomethoxypolyethylene glycol-chitosan nanoparticle-mediated dual silencing of livin and survivin genes in prostate cancer PC-3M cells Genet Mol Res 2016 Apr 4;15(2)

Yang H, Du X, Xi Y. Effects of survivin on FVADT chemotherapy for refractory multiple myeloma Exp Ther Med 2016 Aug;12(2):771-776

Yang M, Liu Y, Lu S, Wang Z, Wang R, Zi Y, Li J. Analysis of the expression levels of survivin and VEGF in patients with acute lymphoblastic leukemia Exp Ther Med 2013 Jan;5(1):305-307

Ye L, Yang Y, Ma XY, Li D, Xu ML, Tan P, Long LM, Wang HQ, Liu T, Guo YH. Construction of a novel vector expressing Survivin-shRNA and fusion suicide gene yCDglyTK and its application in inhibiting proliferation and migration of colon cancer cells Exp Ther Med 2017 Nov;14(5):4721-4728

Yen CS, Choy CS, Huang WJ, Huang SW, Lai PY, Yu MC, Shiue C, Hsu YF, Hsu MJ. A Novel Hydroxamate-Based Compound WMJ-J-09 Causes Head and Neck Squamous Cell Carcinoma Cell Death via LKB1-AMPK-p38MAPK-p63-Survivin Cascade Front Pharmacol 2018 Mar 1;9:167

Yu X, Zhang Y, Cavazos D, Ma X, Zhao Z, Du L, Pertsemlidis A. miR-195 targets cyclin D3 and survivin to modulate the tumorigenesis of non-small cell lung cancer Cell Death Dis 2018 Feb 7;9(2):193

Zeng W, Meng F, Liu Z, Mao X, Luo L, Zheng M, Qin S, Liu W, Zhou J, Sun H, Huang L. Bortezomib-based chemotherapy regimens can improve response in newly diagnosed multiple myeloma patients with bcl-2 and survivin overexpression Int J Clin Exp Pathol 2014 Jun 15;7(7):4239-46

Zhang J, Zhu Z, Sun Z, Sun X, Wang Z, Xu H. Survivin gene expression increases gastric cancer cell lymphatic metastasis by upregulating vascular endothelial growth factor-C expression levels Mol Med Rep 2014 Feb;9(2):600-6

Zhang L, Zhang W, Wang YF, Liu B, Zhang WF, Zhao YF, Kulkarni AB, Sun ZJ. Dual induction of apoptotic and autophagic cell death by targeting survivin in head neck

squamous cell carcinoma Cell Death Dis 2015 May 28;6:e1771

Zhang Y, Chen HX, Zhou SY, Wang SX, Zheng K, Xu DD, Liu YT, Wang XY, Wang X, Yan HZ, Zhang L, Liu QY, Chen WQ, Wang YF. Sp1 and c-Myc modulate drug resistance of leukemia stem cells by regulating survivin expression through the ERK-MSK MAPK signaling pathway Mol Cancer 2015 Mar 7;14:56

Zhang Y, Wang J, Sui X, Li Y, Lu K, Fang X, Jiang Y, Wang X. Prognostic and Clinicopathological Value of Survivin in Diffuse Large B-cell Lymphoma: A Meta-Analysis Medicine (Baltimore) 2015 Sep;94(36):e1432

Zhao J. Cancer stem cells and chemoresistance: The smartest survives the raid Pharmacol Ther 2016 Apr;160:145-58

Zheng WY, Kang YY, Li LF, Xu YX, Ma XY. Levels of effectiveness of gene therapies targeting survivin and its splice variants in human breast cancer cells Drug Discov Ther 2011 Dec;5(6):293-8

Zhou H, Mak PY, Mu H, Mak DH, Zeng Z, Cortes J, Liu Q, Andreeff M, Carter BZ. Combined inhibition of β-catenin and Bcr-Abl synergistically targets tyrosine kinase inhibitor-resistant blast crisis chronic myeloid leukemia blasts and progenitors in vitro and in vivo Leukemia 2017 Oct;31(10):2065-2074

Zhou L, Lu J, Liang ZY, Zhou WX, Yuan D, Li BQ, You L, Guo JC, Zhao YP. High nuclear Survivin expression as a poor prognostic marker in pancreatic ductal adenocarcinoma J Surg Oncol 2018 Dec;118(7):1115-1121

Zhu J, Sun C, Wang L, Xu M, Zang Y, Zhou Y, Liu X, Tao W, Xue B, Shan Y, Yang D. Targeting survivin using a combination of miR494 and survivin shRNA has synergistic effects on the suppression of prostate cancer growth Mol Med Rep 2016 Feb;13(2):1602-10

Zhuo W, Zhang L, Zhu Y, Zhu B, Chen Z. Fisetin, a dietary bioflavonoid, reverses acquired Cisplatin-resistance of lung adenocarcinoma cells through MAPK/Survivin/Caspase pathway Am J Transl Res 2015 Oct 15;7(10):2045-52

de Almagro MC, Vucic D. The inhibitor of apoptosis (IAP) proteins are critical regulators of signaling pathways and targets for anti-cancer therapy Exp Oncol 2012 Oct;34(3):200-11

de Graaff MA, Malu S, Guardiola I, Kruisselbrink AB, de Jong Y, Corver WE, Gelderblom H, Hwu P, Nielsen TO, Lazar AJ, Somaiah N, Bovée JVMG. High-Throughput Screening of Myxoid Liposarcoma Cell Lines: Survivin Is Essential for Tumor Growth Transl Oncol 2017 Aug;10(4):546-554

*This article should be referenced as such:*

Branco PC, Jimenez PC, Machado-Neto JA, Costa-Lotufo LV. BIRC5 (baculoviral IAP repeat containing 5). Atlas Genet Cytogenet Oncol Haematol. 2019; 23(7):168-186.