Trace of survivin in cancer

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Survivin is one of the most cancer-specific proteins overexpressed in almost all malignancies, but is nearly undetectable in most normal tissues in adults. Functionally, as a member of the inhibitor of apoptosis family, survivin has been shown to inhibit apoptosis and increase proliferation. The antiapoptotic function of survivin seems to be related to its ability to inhibit caspases directly or indirectly. Furthermore, the role of survivin in cell cycle division control is related to its role in the chromosomal passenger complex. Consistent with its determining role in these processes, survivin plays a crucial role in cancer progression and cancer cell resistance to anticancer drugs and ionizing radiation. On the basis of these findings, recently survivin has been investigated intensively as an ideal tumor biomarker. Thus, multiple molecular approaches such as use of the RNA interfering technique, antisense oligonucleotides, ribozyme, and small molecule inhibitors have been used to downregulate survivin regulation and inhibit its biological function consequently. In this review, all these approaches are explained and other compounds that induced apoptosis in different cell lines through survivin inhibition are also reported.

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Keywords: cancer, chromosomal passenger complex, inhibitor of apoptosis family, survivin

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Introduction

Survivin, the unique member of the inhibitor of apoptosis (IAP) family, plays a major role both in the cell division process and in the inhibition of apoptosis (Mita *et al*., 2008). Survivin serves its regulatory function in cell division through its role in the chromosomal passenger complex (CPC), which regulates microtubule dynamics, stability, and mitotic progression (Giodini *et al*., 2002), and serves its antiapoptotic function through interaction with multiple proteins such as hepatitis B X-interacting protein, X-linked inhibitor of apoptosis (XIAP), and second mitochondrial-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low Pi (Smac/DIABLO), which inhibits caspase activation (Peery *et al*., 2017). Survivin overexpression has been detected in a wide variety of malignancies, which results in cell-cycle checkpoints bypasses and promotion of aberrant progression of transformed cells, unlike its minimal expression in normal healthy tissues (Ryan *et al*., 2009). Survivin overexpression is correlated with adverse consequences including tumor aggressiveness, cancer relapse, therapy resistances (such as radiation therapy and chemotherapy), and poor clinical outcome (Li *et al*., 1998). Therefore, anticancer strategies have currently focused on survivin status both as a cancer biomarker and as a potential target for designing new approaches for cancer treatment. In this review, we introduce recently investigated survivin-targeted approaches besides different drugs and compounds that induced apoptosis in cancer cell lines through survivin downregulation. It is noteworthy, however, that survivin structure and physiological function are briefly reviewed.

Survivin structure

The IAPs is one of the well-known apoptosis inhibitor families consisting of several proteins such as NIAP, XIAP, Cellular inhibitor of apoptosis protein-1, cellular inhibitor of apoptosis protein-2, ILP2, livin, baculovirus inhibitor repeat (BIR)-repeat-containing ubiquitin-conjugating enzyme, and survivin (Jaiswal *et al*., 2015). All family members are characterized by a common motif in their structure called the BIR domain with a length of 70–80 amino acid (LaCasse *et al*., 1998). Survivin is the smallest member of this family, encoded by the baculoviral IAP repeat-containing 5 gene, consisting of four main exons and localized in the telomeric region of chromosome 17 (McKenzie and Grossman, 2012). Along with its major transcript (baculoviral IAP repeat-containing 5, survivin), which codes the wild-type protein 142 amino acids in length, alternative splicing generates four more splice variants coding survivin 2a, 2B, 3B, and ΔEx3, which serve different cell functions (Li, 2005). Survivin contains one single BIR domain in the N-terminal region and one coiled–coil motif in the C-terminal region. The BIR domain is critical for antiapoptotic function, whereas the coiled–coil motif is considered to interact with microtubules that are involved in cell division process (Wheatley and McNeish, 2005). X-ray crystallography showed that survivin structure forms a bow tie-shaped dimer.

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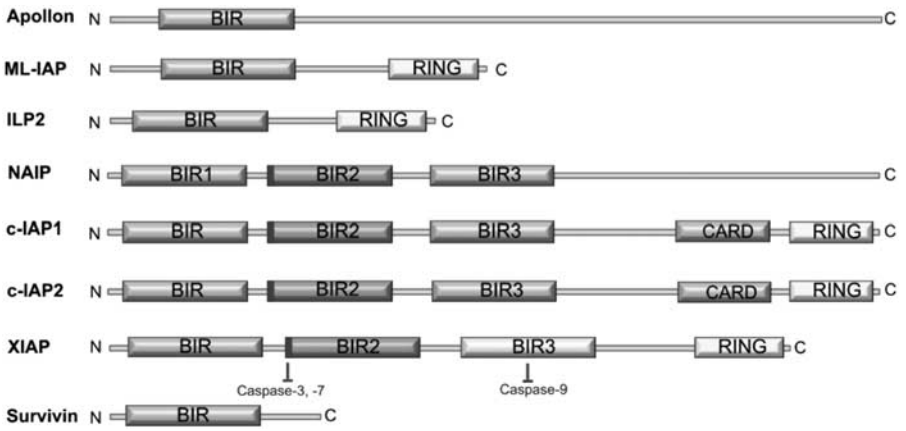
Fig. 1



Structures of IAP protein family members. The IAP family consists of eight antiapoptosis protein including NIAP/BIRC1, c-IAP1/BIRC2, c-IAP2/BIRC3, XIAP/BIRC4, Survivin/BIRC5, Apollon (BRUCE)/BIRC6, Livin/BIRC7, and ILP2/BIRC8. Survivin with only one BIR domain is the smallest member of this family. The caspase-inhibitory function of XIAP, NAIP, c-IAP1, and c-IAP2 is associated with a conserved linker peptide (shown in dark grey) that precedes the BIR2 of these proteins. This peptide inhibits caspase-3 and caspase-3. In addition, in XIAP, the BIR3 domain is responsible for inhibiting caspase-9 (Mobahat *et al*., 2014). BIR, baculovirus inhibitor repeat; BRUCE, BIR-repeat-containing ubiquitin-conjugating enzyme; CARD, caspase activation and recruitment domain; c-IAP, cellular inhibitor of apoptosis protein; IAP, inhibitor of apoptosis; ILP, IAP-like protein 2; NAIP, neuronal apoptosis inhibitor protein; XIAP, X-linked inhibitor of apoptosis.

There is also one zinc finger in its structure formed by four Zn^{2+}-binding residues including Cys-60, Cys-57, Cys-84, and His-77 that retain survivin integrity (Chantalat *et al*., 2000). Survivin is also distinguished from the other IAP family members by the lack of caspase activation and recruitment domain and RING finger (really interesting gene) motifs (Deveraux and Reed, 1999). Figure 1 shows the different members of the IAP protein family with diverse domains and lengths.

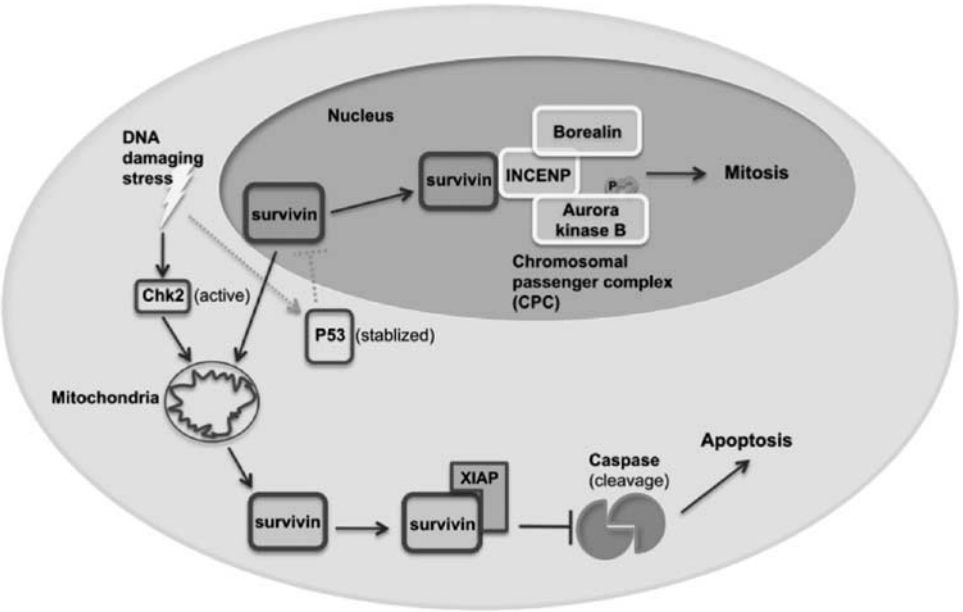
Role of survivin in cell apoptosis

Before explaining the apoptosis-inhibitory role of survivin, the apoptosis process is briefly mentioned. Apoptosis is described by a series of coordinated events called 'programmed cell death' to maintain tissue homeostasis and protect the cell against particular triggers and conditions such as cell-cycle arrest, irradiation exposure, and drugs (such as chemotherapy agents) that cause DNA damage and cell infection (Elmore, 2007). Apoptosis has through two intrinsic and extrinsic pathways. In both pathways, the activation of caspases (cysteine aspartate proteases) is essential. The active caspase gives rise to cell death through disruption of the essential cellular proteins such as nuclear lamina and cytoskeleton, activation of the caspase-activated domain, and cellular systems deregulation such as DNA repair (Turk *et al*., 2000). In the intrinsic pathway, after cell exposure to a wide range of stimuli such as UV irradiation, chemotherapy agents, and p53 activation, cytochrome C is released from the mitochondria and binds to apoptotic protease activating factor 1 and caspase-9 to form the apoptosome complex, which leads to caspase-9 activation (Acehan *et al*., 2002). The active form of caspase-9 activates caspase-7 and caspase-3 by cleavage of their prodomains, all finally resulting in cell death (Wheatley and McNeish, 2005). The extrinsic pathway is initiated after binding of death ligands such as TNF-related apoptosis-inducing ligand and FasL to their relative receptors, which leads to oligomerization of the receptor and recruits Fas-associated death domain, which is an adaptor protein. Binding of the death-inducing domain of Fas-associated death domain with the death-inducing domain of procaspase-8 and procaspase-10 promotes caspase activation to activate effector caspase-3, caspase-6, and caspase-7, which finally leads to cell death (Donepudi *et al*., 2003). As survivin lacks caspase activation and the recruitment domain, it cannot bind to caspase directly; therefore, survivin inhibits apoptosis through interaction with the XIAP, which increases XIAP stability to inhibit caspase-9 activation. Furthermore, survivin interacts with hepatitis B X-interacting protein and suppresses caspase-9 activation through blocking apoptotic protease activating factor 1 recruitment to the apoptosome (Marusawa *et al*., 2003). However, Survivin interacts with Smac/DIABLO (Sun *et al*., 2005). Smac/DIABLO is a protein released from the mitochondria after cell exposure to stimuli, which suppresses the apoptosis-inhibitory function of IAP by directly binding to them (Du *et al*., 2000). Survivin–Smac interaction neutralizes the effect of Smac/DIABLO on other IAPs, prevents XIAP inhibition by sequestering Smac/DIABLO, and enhances caspase-9-mediated cell apoptosis (McKenzie and Grossman, 2012; Jaiswal *et al*., 2015) (Fig. 2).

Role of survivin in the cell division process

Survivin expression is high during G_2/M phases of the cell-cycle, whereas a rapid decrease occurs in the G_1 phase. Its expression level is controlled by two cell cycle-dependent

Fig. 2



Survivin contribution toward the cell division process and inhibition of apoptosis. Survivin participates in cell cycle progression and mitosis through its role in the chromosomal passenger complex (CPC), which acts as a key regulator of chromosome segregation and cytokinesis. Survivin regulate the localization of the enzymatic component (Aurora kinase B) toward kinetochores in association with two other CPC complex components: borealin and inner centromere protein antigen (INCENP). During mitosis, aurora kinase B provides correct chromosomal alignment, segregation, and cytokinesis thorough its auto-phosphorylation upon recruitment to the CPC complex. After DNA-damaging stress, activation of checkpoint kinase 2 (Chk2) leads to the rapid release of survivin from the mitochondria, which inhibits cell death and promotes cancer cell survival. Furthermore, stabilization of wild-type p53 is another result of DNA damage which represses the survivin transcription and assisting to balance this pathway (Mobahat *et al.*, 2014). XIAP, X-linked inhibitor of apoptosis.

element and cell cycle gene homology region within the survivin gene promoter (Khan *et al.*, 2017). Survivin plays an important role in cell cycle progression toward successful mitosis through CPC formation; also, the role of survivin in cell division is accompanied by its localization in the centrosome, spindle microtubules, and spindle poles (Giodini *et al.*, 2002). Survivin dysfunction leads to cell-cycle defects including impairment of cytokinesis, centrosome dysregulation, and formation of multinucleated cells (Li *et al.*, 1999). Although overexpression of survivin as a part of this complex has an impact on microtubule stability through regulation of the growth rate and microtubule-associated proteins recruitment, which are regulatory elements in the organization of cytoskeleton (Giodini *et al.*, 2002), the CPC maintains the genomic stability through contributing in several cell division phases. In the prophase, CPC contributes toward chromosome structure regulation and cohesion elimination from chromosomal arms. In the anaphase, the CPC provides proper chromosomal arm shortening. In the metaphase, CPC plays a role in microtubule formation, stability, dynamics, and microtubule–kinetochore attachment as well as spindle assembly checkpoint activation and, in cytokinesis, CPC averts tetraploidization through controlling the division of the cytoplasm (van der Waal *et al.*, 2012). The other CPC components are inner centromere protein, borealin and the enzymatic core, and Aurora B kinase (van der Waal *et al.*, 2012). The localizations of inner centromere protein antigen, Aurora B kinase, Borealin, and survivin are all mutually dependent on each other. However, survivin plays all substrate, regulator, and adaptor roles related to Aurora B kinase. Thus, it stimulates kinase activity and regulates RasGAP in RAS signaling as an inhibitor of the kinase activity in a complex with survivin (Wheatley and McNeish, 2005). Furthermore, survivin in the CPC promotes the movement of complex from the inner centromere to the midbody during prometaphase progression to cytokinesis (Jeyaprakash *et al.*, 2007).

Survivin expression in cancer and therapeutic strategies

Survivin plays a conspicuous role in regulating apoptosis during the embryogenesis in which its expression leads to developing the proper phenotype of several human fetal tissues such as kidney, liver, gastrointestinal tract, brain and lung (Adida *et al.*, 1998). Whereas its expression is almost undetectable in finally differentiated healthy tissues (Ambrosini *et al.*, 1997). Survivin overexpression has been detected in most cancers, enables cancer cells to avoid apoptosis, and increases cell proliferation, tumor aggressiveness, cancer relapse, and chemotherapy resistance (Li *et al.*, 1998). In a cancer-screening program, the National Cancer Institute found survivin expression in all 60 human cancer lines. The highest survivin level for

breast and lung cancer and the lowest level for renal cancer were reported (Kusner *et al*., 2014; Ue *et al*., 2014). Thus, survivin is considered a molecular target in cancer diagnosis and cancer therapy. Different strategies have been applied to reduce survivin expression and even sensitize cancer cells to anticancer drugs. Therefore, utilizing the RNA interfering mechanism, antisense oligonucleotides, ribozyme approach, and other inhibitors of survivin are described below.

RNA-interfering survivin knockdown

The regulatory mechanism of RNAi (RNA interference) uses synthetic short RNAs duplex, which inhibits specific gene expression. Since the discovery of RNAi, many attentions have been attracted on its possible therapeutic application. Researchers have used small interfering RNA (siRNA) and short hairpin RNA to knock down survivin expression (Ambrosini *et al*., 1997; Pennati *et al*., 2007). Carvalho *et al*. (2003) first applied RNAi to suppress Survivin expression in HeLa cells, which resulted in cell accumulation in the prometaphase with delayed mitosis and misaligned chromosomes. It has been shown in several studies that the use of survivin-targeted siRNA or a vector coding for short hairpin RNA could reduce cell viability through activation of caspase-3 and caspase-7 at high levels and induces cell apoptosis subsequently (Nakao *et al*., 2006; Arami *et al*., 2017; Huang *et al*., 2017; Liu *et al*., 2017; Wang *et al*., 2017a; Ye *et al*., 2017). However, greater therapeutic effects may be achieved if the survivin-silencing strategy is combined with chemotherapy agents such as vinblastine (Trabulo *et al*., 2011), doxorubicin (Trabulo *et al*., 2011; Li *et al*., 2017), vincristine (Jiang *et al*., 2006), 5-fluorouracil (AlShamaileh *et al*., 2017), and paclitaxel (PXL) (Chen *et al*., 2017; Gu *et al*., 2017) because of the enhanced cell susceptibility to these treatments after survivin downregulation. In another study, survivin interference in HeLa cells not only inhibited cell proliferation but also enhanced radiosensitivity (Song *et al*., 2008).

Antisense oligonucleotide

Short single-strand DNA or RNA with a length of 13–20 bases, complementary to a single strand RNA, blocks specific gene expression and the protein products are subsequently known as antisense oligonucleotides (ASOs). Binding of ASOs with its target mRNA recruits RNase H, which recognizes and cleaves the RNA strand within the ASO–mRNA complex (Biroccio *et al*., 2003). ASOs are delivered to cells as chemically synthesized agents or through the ASO-expressing vectors. ASO-based survivin downregulation reduces cell proliferation, induces caspase-dependent cell apoptosis, and inhibits the tumor growth rate (Ansell *et al*., 2004; Fuessel *et al*., 2004; Sharma *et al*., 2005; Du *et al*., 2006). In another study by Sharma *et al*. (2005) ASOs sensitizes head and neck squamous cell carcinomas cells to cisplatin and etoposide as chemotherapy drugs, which leads to lower dose consumption of chemotherapy agents. Two common ASOs are described here: LY2181308 and SPC3042. LY2181308 is a 2′-O-methoxymethyl modified antisense oligonucleotide developed by Eli Lilly (ISIS 23722; Eli Lilly and Co. and ISIS Pharmaceuticals Inc.), used in both SW480 colorectal SW40 xenograft model to investigate whether the survivin attenuation by LY2181308 enhances radiation responses. LY2181308 effectively radiosensitized colorectal cancer cells in both SW40 cell culture and xenograft model (Rodel *et al*., 2008). Successful preclinical outcomes led to clinical testing of this antisense oligonucleotide. In patients with acute myeloid leukemia, LY2181308 inhibited survivin expression and more synergistic effects were also achieved after combining LY2181308 with cytarabine and idarubicin (Erba *et al*., 2013). The results of the LY2181308 application on patients with advanced solid tumors were not promising, neither when LY2181308 used alone in a phase I trial (Tanioka *et al*., 2011) nor in combination with other agents such as docetaxel/prednisone in phase II trial (Wiechno *et al*., 2014), which shows the limited potential of this strategy for aggressive solid tumor treatment. Because of the low stability and efficient neutralization of target mRNA by ASOs, Fisker *et al*. (2007) designed SPC3042 with higher stability that is presented as a locked nucleic acid-modified ASO. SPC3042 was found to be more efficient for survivin inhibition, and also enhanced the response of prostate cancer cells to taxol.

Ribozyme approach

Ribozymes are small RNA molecules that cleave RNA targets by their specific endonucleolytic activity. In particular, hammerhead ribozyme has a conserved catalytic core that cleaves the RNA target at the 3′ end of NHH triplet at the second H position, whereas N can be any nucleotide and H is any nucleotide, except guanidine (Wang *et al*., 2007). It has been discovered in multiple studies that ribozyme-mediated survivin downregulation inhibits the antiapoptotic function of survivin (Choi *et al*., 2003), and increases both spontaneous and drug-induced apoptosis, with a reduction in the tumorigenic potential of cancer cells (Pennati *et al*., 2004a). Pennati *et al*. (2003) used the pRC/CMV vector coding for a ribozyme sequence; the CUA110 triplet in the survivin mRNA was targeted by indicated ribozyme, and more cell susceptibility to gamma radiation and radiation-induced apoptosis in human melanoma cells was detected. In another In another study by this author, two active (RZ/survivin) and mutant (mutRZ/survivin) form of hammerhead ribozyme were generated and transfected to the JR8 human melanoma cell line to downregulate the survivin expression. The RZ/survivin targets the 3' end of GUC294 triplet in the exon 3 of survivin mRNA while the mutRZ/survivin carries a mutation in the catalytic core. The significant survivin downregulation was observed in the JR8-RZ/survivin cells. Furthermore, in the xenograft model, compared to the JR8-mutRZ/survivin cells, the JR8-RZ/survivin cells showed more

Table 1 List of compounds in cancer prevention with different substances led to the downregulation of survivin expression

Compound name	Type of compound	Cancer type	Function and effects	References
Berberine	Isoquinoline alkaloid (botanical drug)	Human eryhromyeloblastoid leukemia cell line (K562)	Suppression of survivin and iNOS through inhibition of NF-κB expression Antiproliferative, anti-inflammatory, and cytotoxic effect Apoptosis induction by survivin downregulation	Pazhang *et al.* (2011)
Dihydromyricetin	Natural flavonoid	Ovarian cancer cell line (A2780)	P-53-mediated survivin downregulation Suppress cell proliferation Cell sensitizing to both PXL and DOX Apoptosis induction	Xu *et al.* (2017)
Celecoxib and dimethyl-celecoxib	Coxib	Most cell lines including the colon carcinoma and the glioblastoma cell line	Survivin downregulation through inhibition of its promoter activity Glioma cell chemosensitizing to irinotecan (CPT-11) as an anticancer agent inhibiting tumor growth Apoptosis induction	Pyrko *et al.* (2006)
Epigallocatechin-3-gallate	Polyphenol (derived from green tea)	Gastric cancer cell lines (NUGC-3, MKN-1)	Inhibiting survivin expression through P73 activation Suppressing cell growth by inhibiting NF-κB, AKT signaling, p53 and p73 activation Apoptosis induction	Onoda *et al.* (2011)
Fasaplysin	Planar, aromatic compound derived from murine sponge, a CDK4 inhibitor	Lung cancer cells	Apoptosis induction through survivin and HIF-α downregulation and inhibition of VEGFR2 and TRKA	Oh *et al.* (2017)
Morusin	Natural compound derived from the root bark of *Morus alba* (white mulberry)	Breast cancer cell line (MCF-7, MDA-MB)	Survivin downregulation Inducing proapoptotic protein BAX Anticancer effect by inhibiting NF-κB pathway and STAT-3, which leads to cell apoptosis	Kang *et al.* (2017)
Olanzapine	Atypical antipsychotic, thienobenzodiazepine	Lung and pancreatic CSCs including A549 CSLC, PANC-1 CSLC	Survivin downregulation Sensitizing A549 CSLC to gemcitabine, as a chemotherapeutic agent	Sanomachi *et al.* (2017)
Aripiprazole	Atypical antipsychotic, partial dopamine antagonist	Lung and pancreatic CSCs	Survivin downregulation Cell sensitizing to 5-FU, gemcitabine, and cisplatin Growth-inhibitory effect Induce CSCs differentiation to non-CSCs	Suzuki *et al.* (2016)
Aspirin (acetylsalicylic acid)	NSAID	Gastric carcinoma cells	Survivin downregulation through inducing survivin pro easomal degradation and inhibition of E2-F-1 binding to the survivin promoter Inhibition of cell proliferation and TRAIL-induced apoptosis promotion because of survivin reduction	Lu *et al.* (2008); Yoo and Lee (2007); Yang *et al.* (2011)
Dequelin	Rotenoid derived from *Mundulea sericea*	T-cell leukemia cell line (KUT-1, MT-2)	Inhibition of HSP90, which promotes ubiquitin-mediated survivin degradation Inhibition of STAT-3 phosphorylation Decreasing cell proliferation Apoptosis induction	Ito *et al.* (2010)
IFN-γ and dehydroxymethyl-epoxyquinomicin	IFNs DHMEQ: NF-κB inhibitor	Renal cell carcinoma (KU19-20)	Survivin downregulation through inhibition of NF-κB IFN-γ and DHMEQ showed a synergistic effect on inhibition of cell proliferation	Sato *et al.* (2006)
Quercetin	Flavonoid	SW480 colon cancer	Antitumor activity through downregulation of survivin, cyclin D1, and the Wnt/B-catenin pathway Decreasing cell viability Inducing cell-cycle arrest and apoptosis	Shan *et al.* (2009)
Sorafenib	Multikinase inhibitor	Non-small-cell lung cancer (H1299, A549)	Downregulation of survivin through Redd1-induced inhibition of mTOR Cell sensitizing to TRAIL-induced apoptosis	Kim *et al.* (2011)
Tamoxifen	Nonsteroidal antiestrogen	Hepatocellular carcinoma cell line (Hep G2)	Reducing cell proliferation at a concentration of ≥ 10 μmol/l Cytocide effect and apoptosis induction because of survivin downregulation	Guo *et al.* (2009)

CSC, cancer stem cell; DHMEQ, dehydroxymethyl-epoxyquinomicin; DOX, doxorubicin; 5-FU, 5-fluorouracil; HSP90, heat shock protein 90; IFN, interferon; iNOS, inducible nitric oxide synthase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PXL, paclitaxel; Redd1, regulated in development and DNA damage responses; STAT, signal transducer and activator of transcription 3; TRIAL, TNF-related apoptosis-inducing ligand.

sensitivity to the topotecan as inhibitor of topoisomerase-1 (Pennati *et al*., 2004b). Thus, these studies used a ribozyme-mediated survivin inhibition approach to achieve more radiosensitization and chemosensitization in cancer cells. Along with the beneficial effects of ribozymes, a few major problems including RNA degradation, misfolding, and improper cell trafficking have hindered the therapeutic application of ribozymes in medicine. In an attempt to circumvent this, Liu *et al*. (2007) designed a chimeric pRNA/ribozyme in which the motor pRNA from bacteriophage phi29 was used as ribozyme carrier. The motor pRNA molecule comprises of an interlocking loop domain and a 5′/3′ helical domain with independent folding. After the ribozyme connection to the helical domain, the pRNA/ribozyme chimer recognizes into a circularly permuted form with relocated 5′/3′ ends. Finally, the chimeric pRNA/ribozyme with proper folding and increased stability leads to effective silencing of survivin gene at both RNA and protein level.

Survivin inhibitors

YM155 (sepantronium bromide) is the first and most recognized inhibitor of survivin, which binds directly to the survivin promoter and suppresses its transactivation (Nitta *et al*., 2017). As the basal expression of survivin is related to binding of specificity protein 1 (SP1) to the GC-rich region of the survivin promoter (Li and Altieri, 1999), inhibition of survivin transcription through disruption of the SP1–DNA interaction by YM155 was also reported by Cheng *et al*. (2012). The ability of YM155 to induce tumor regression in multiple xenograft models of cancer was proved (Nakahara *et al*., 2007; Kita *et al*., 2011; Yamanaka *et al*., 2011); furthermore, in comparison with monotherapy, YM155 combination with platinum compounds (cisplatin and carboplatin) (Iwasa *et al*., 2010) and docetaxel (Nakahara *et al*., 2011; Yamanaka *et al*., 2011) was found to be superior. As heat shock protein 90 (HSP90) protects ubiquitin-mediated survivin degradation in the G1 phase, the second survivin inhibitor focuses on the survivin–HSP90 interaction. Shepherdin antagonizes HSP90–survivin binding, and also acts as a global HSP90 inhibitor by competition with ATP, which leads to apoptosis, and inhibited the growth of the xenograft model of prostate and breast cancer (Plescia *et al*., 2005). Tetrameprocol [meso-tetra-O-methyl nordihyroguaiaretic acid (M4N)], also known as EM-1421, is another molecules that prevents SP1-dependent survivin transcription, which induces growth arrest and cell apoptosis in transformed cells (Chang *et al*., 2004). Felix *et al*. (2013) also proposed SF002-96-1 as a new survivin inhibitor. SF002-96-1 is a drimane sesquiterpene lactone isolated from *Aspergillus* species, which decreased survivin mRNA and protein levels by preventing the binding of transcriptional factors signal transducer and activator of transcription 3 and nuclear factor κ-light-chain-enhancer of activated B cells to the survivin promoter and triggered apoptosis subsequently. FL118 is another substance used in the treatment of lung cancer stem cells (CSCs) by Wang *et al*. (2017b). FL118 treatment led to a reduction in survivin in CSCs, downregulation of CSCs markers (such as ABCG2 and Oct4) and drug-resistance associated proteins (such as P-glycoprotein), and decreased the invasive ability of CSCs. These results suggest that FL118 could be useful in the phenotype alteration of CSCs and improvement of drug sensitivity in tumor cells. GDP366 is also another compound that acts by decreasing the survivin mRNA and protein and affects P53 and P21 levels too. GDP366 is responsible for polyploidy, chromosomal instability, and cellular senescence through inhibition of the telomerase activity (Shi *et al*., 2010). Among the many identified anticancer drugs, PXL has been introduced as an effective drug on survivin. PXL is a first-line anticancer drug with inhibitory effects on cancer cell proliferation, invasion, and migration (Terzis *et al*., 1997). Moreover, PXL is a mitotic inhibitor and stabilizes the microtubule structure through excitron protein synthesis, which binds to microtubules and prevents its depolymerization (Gu *et al*., 2017). It is noteworthy that one of the drawbacks in the cancer treatment regimen is tumor cell drug resistance; to circumvent this, researchers used combined therapy, which involves the application of both siRNA-targeted survivin and PXL as a chemotherapy agent in the treatment of multiple cancer cells. Chen *et al*. (2017) designed a liposome-based nanosystem for siRNA and PXL codelivery to breast cancer cells. Survivin downregulation sensitized cells to PXL and inhibited their growth and metastasis potential. In other studies, survivin reduction by siRNA facilitated PLX-induced apoptosis and reversed drug resistance similarly (Kar *et al*., 2015; Salzano *et al*., 2015; Gu *et al*., 2017). However, other compounds with a specific role in cancer prevention by downregulation of the survivin expression are also listed in Table 1.

Conclusion

Nowadays, the specific goal in cancer therapy is to identify how to induce cancer cell death or make the cells more sensitive to anticancer drugs, chemotherapy, and radiotherapy. Survivin, a unique member of the IAP family, prevents cell apoptosis by inhibiting caspase function. However, its role in cell-cycle progression and cell division has also been identified. Survivin has an aberrant expression in cancer cells, which leads to tumor progression, a poor prognosis, and therapeutic resistance in these cells. In terms of the difference between normal and cancer tissues in survivin expression, which can act as a tumor biomarker, researches have focused on targeting the survivin expression using multiple approaches mentioned above. In addition, survivin measurement can be useful in cancer diagnosis, prognosis, and predicting likely resistance or response to therapeutic approaches. According to previous studies in cancer prevention with a focus on survivin expression, evidences show that inhibition of survivin may lead to spontaneous apoptosis,

which is also consistent with more cell sensitivity to therapeutic approaches. Finally, survivin may be valuable in both cancer treatment and cancer prevention.

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Conflicts of interest

There are no conflicts of interest.

References

Acehan D, Jiang X, Morgan DG, Heuser JE, Wang X, Akey CW (2002). Three-dimensional structure of the apoptosome: implications for assembly, procaspase-9 binding, and activation. *Mol Cell* **9**:423–432.

Adida C, Crotty PL, McGrath J, Berrebi D, Diebold J, Altieri DC (1998). Developmentally regulated expression of the novel cancer anti-apoptosis gene survivin in human and mouse differentiation. *Am J Pathol* **152**:43–49.

AlShamaileh H, Wang T, Xiang D, Yin W, Tran PH, Barrero RA, *et al.* (2017). Aptamer-mediated survivin RNAi enables 5-fluorouracil to eliminate colorectal cancer stem cells. *Sci Rep* **7**:5898.

Ambrosini G, Adida C, Altieri DC (1997). A novel anti-apoptosis gene, survivin, expressed in cancer and lymphoma. *Nat Med* **3**:917–921.

Ansell SM, Arendt BK, Grote DM, Jelinek DF, Novak AJ, Wellik LE, *et al.* (2004). Inhibition of survivin expression suppresses the growth of aggressive non-Hodgkin's lymphoma. *Leukemia* **18**:616–623.

Arami S, Mahdavi M, Rashidi MR, Yekta R, Rahnamay M, Molavi L, *et al.* (2017). Apoptosis induction activity and molecular docking studies of survivin siRNA carried by Fe3O4-PEG-LAC-chitosan-PEI nanoparticles in MCF-7 human breast cancer cells. *J Pharm Biomed Anal* **142**:145–154.

Biroccio A, Leonetti C, Zupi G (2003). The future of antisense therapy: combination with anticancer treatments. *Oncogene* **22**:6579–6588.

Carvalho A, Carmena M, Sambade C, Earnshaw WC, Wheatley SP (2003). Survivin is required for stable checkpoint activation in taxol-treated HeLa cells. *J Cell Sci* **116**:2987–2998.

Chang CC, Heller JD, Kuo J, Huang RC (2004). Tetra-O-methyl nordihydroguaiaretic acid induces growth arrest and cellular apoptosis by inhibiting Cdc2 and survivin expression. *Proc Natl Acad Sci USA* **101**:13239–13244.

Chantalat L, Skoufias DA, Kleman JP, Jung B, Dideberg O, Margolis RL (2000). Crystal structure of human survivin reveals a bow tie-shaped dimer with two unusual alpha-helical extensions. *Mol Cell* **6**:183–189.

Chen X, Zhang Y, Tang C, Tian C, Sun Q, Su Z, *et al.* (2017). Co-delivery of paclitaxel and anti-survivin siRNA via redox-sensitive oligopeptide liposomes for the synergistic treatment of breast cancer and metastasis. *Int J Pharm* **529**:102–115.

Cheng Q, Ling X, Haller A, Nakahara T, Yamanaka K, Kita A, *et al.* (2012). Suppression of survivin promoter activity by YM155 involves disruption of Sp1-DNA interaction in the survivin core promoter. *Int J Biochem Mol Biol* **3**:179–197.

Choi KS, Lee TH, Jung MH (2003). Ribozyme-mediated cleavage of the human survivin mRNA and inhibition of antiapoptotic function of survivin in MCF-7 cells. *Cancer Gene Ther* **10**:87–95.

Deveraux QL, Reed JC (1999). IAP family proteins – suppressors of apoptosis. *Genes Dev* **13**:239–252.

Donepudi M, Mac Sweeney A, Briand C, Grutter MG (2003). Insights into the regulatory mechanism for caspase-8 activation. *Mol Cell* **11**:543–549.

Du C, Fang M, Li Y, Li L, Wang X (2000). Smac, a mitochondrial protein that promotes cytochrome c-dependent caspase activation by eliminating IAP inhibition. *Cell* **102**:33–42.

Du ZX, Zhang HY, Gao DX, Wang HQ, Li YJ, Liu GL (2006). Antisurvivin oligonucleotides inhibit growth and induce apoptosis in human medullary thyroid carcinoma cells. *Exp Mol Med* **38**:230–240.

Elmore S (2007). Apoptosis: a review of programmed cell death. *Toxicol Pathol* **35**:495–516.

Erba HP, Sayar H, Juckett M, Lahn M, Andre V, Callies S, *et al.* (2013). Safety and pharmacokinetics of the antisense oligonucleotide (ASO) LY2181308 as a single-agent or in combination with idarubicin and cytarabine in patients with refractory or relapsed acute myeloid leukemia (AML). *Invest New Drugs* **31**:1023–1034.

Felix S, Sandjo LP, Opatz T, Erkel G (2013). SF002-96-1, a new drimane sesquiterpene lactone from an Aspergillus species, inhibits survivin expression. *Beilstein J Org Chem* **9**:2866–2876.

Fisker N, Westergaard M, Hansen HF, Hansen JB (2007). Survivin mRNA antagonists using locked nucleic acid, potential for molecular cancer therapy. *Nucleosides Nucleotides Nucleic Acids* **26**:1427–1430.

Fuessel S, Kueppers B, Ning S, Kotzsch M, Kraemer K, Schmidt U, *et al.* (2004). Systematic in vitro evaluation of survivin directed antisense oligodeoxynucleotides in bladder cancer cells. *J Urol* **171**:2471–2476.

Giodini A, Kallio MJ, Wall NR, Gorbsky GJ, Tognin S, Marchisio PC, *et al.* (2002). Regulation of microtubule stability and mitotic progression by survivin. *Cancer Res* **62**:2462–2467.

Gu F, Li L, Yuan QF, Li C, Li ZH (2017). Down-regulation of survivin enhances paclitaxel-induced Hela cell apoptosis. *Eur Rev Med Pharmacol Sci* **21**:3504–3509.

Guo R, Huang Z, Shu Y, Jin S, Ge H (2009). Tamoxifen inhibits proliferation and induces apoptosis in human hepatocellular carcinoma cell line HepG2 via down-regulation of survivin expression. *Biomed Pharmacother* **63**:375–379.

Huang Q, Zeng Y, Lin H, Zhang H, Yang D (2017). Transfection with Livin and Survivin shRNA inhibits the growth and proliferation of nonsmall cell lung cancer cells. *Mol Med Rep* **16**:7086–7091.

Ito S, Oyake T, Murai K, Ishida Y (2010). Deguelin suppresses cell proliferation via the inhibition of survivin expression and STAT3 phosphorylation in HTLV-1-transformed T cells. *Leuk Res* **34**:352–357.

Iwasa T, Okamoto I, Takezawa K, Yamanaka K, Nakahara T, Kita A, *et al.* (2010). Marked anti-tumour activity of the combination of YM155, a novel survivin suppressant, and platinum-based drugs. *Br J Cancer* **103**:36–42.

Jaiswal PK, Goel A, Mittal RD (2015). Survivin: a molecular biomarker in cancer. *Indian J Med Res* **141**:389–397.

Jeyaprakash AA, Klein UR, Lindner D, Ebert J, Nigg EA, Conti E (2007). Structure of a survivin-borealin-INCENP core complex reveals how chromosomal passengers travel together. *Cell* **131**:271–285.

Jiang G, Li J, Zeng Z, Xian L (2006). Lentivirus-mediated gene therapy by suppressing survivin in BALB/c nude mice bearing oral squamous cell carcinoma. *Cancer Biol Ther* **5**:435–440.

Kang S, Kim EO, Kim SH, Lee JH, Ahn KS, Yun M, *et al.* (2017). Morusin induces apoptosis by regulating expression of Bax and survivin in human breast cancer cells. *Oncol Lett* **13**:4558–4562.

Kar R, Palanichamy JK, Banerjee A, Chattopadhyay P, Jain SK, Singh N (2015). Survivin siRNA increases sensitivity of primary cultures of ovarian cancer cells to paclitaxel. *Clin Transl Oncol* **17**:737–742.

Khan Z, Khan AA, Yadav H, Prasad G, Bisen PS (2017). Survivin, a molecular target for therapeutic interventions in squamous cell carcinoma. *Cell Mol Biol Lett* **22**:8.

Kim YS, Jin HO, Seo SK, Woo SH, Choe TB, An S, *et al.* (2011). Sorafenib induces apoptotic cell death in human non-small cell lung cancer cells by down-regulating mammalian target of rapamycin (mTOR)-dependent survivin expression. *Biochem Pharmacol* **82**:216–226.

Kita A, Nakahara T, Yamanaka K, Nakano K, Nakata M, Mori M, *et al.* (2011). Antitumor effects of YM155, a novel survivin suppressant, against human aggressive non-Hodgkin lymphoma. *Leuk Res* **35**:787–792.

Kusner LL, Ciesielski MJ, Marx A, Kaminski HJ, Fenstermaker RA (2014). Survivin as a potential mediator to support autoreactive cell survival in myasthenia gravis: a human and animal model study. *PLoS One* **9**:e102231.

LaCasse EC, Baird S, Korneluk RG, MacKenzie AE (1998). The inhibitors of apoptosis (IAPs) and their emerging role in cancer. *Oncogene* **17**:3247–3259.

Li F (2005). Role of survivin and its splice variants in tumorigenesis. *Br J Cancer* **92**:212–216.

Li F, Altieri DC (1999). Transcriptional analysis of human survivin gene expression. *Biochem J* **344** (**Pt 2**):305–311.

Li F, Ambrosini G, Chu EY, Plescia J, Tognin S, Marchisio PC, *et al.* (1998). Control of apoptosis and mitotic spindle checkpoint by survivin. *Nature* **396**:580–584.

Li F, Ackermann EJ, Bennett CF, Rothermel AL, Plescia J, Tognin S, *et al.* (1999). Pleiotropic cell-division defects and apoptosis induced by interference with survivin function. *Nat Cell Biol* **1**:461–466.

Li Z, Zhang L, Tang C, Yin C (2017). Co-delivery of doxorubicin and survivin shRNA-expressing plasmid via microenvironment-responsive dendritic mesoporous silica nanoparticles for synergistic cancer therapy. *Pharm Res* **34**:2829–2841.

Liu H, Guo S, Roll R, Li J, Diao Z, Shao N, *et al.* (2007). Phi29 pRNA vector for efficient escort of hammerhead ribozyme targeting survivin in multiple cancer cells. *Cancer Biol Ther* **6**:697–704.

Liu Z, Wang T, Zhang Z, Tang S, Feng S, Yue M, *et al.* (2017). Survivin down-regulation using siRNA nanoliposomes inhibits cell proliferation and promotes

the apoptosis of MHCC-97H hepatic cancer cells: an in vitro and in vivo study. *Oncol Lett* **13**:2723–2730.

Lu M, Strohecker A, Chen F, Kwan T, Bosman J, Jordan VC, *et al.* (2008). Aspirin sensitizes cancer cells to TRAIL-induced apoptosis by reducing survivin levels. *Clin Cancer Res* **14**:3168–3176.

Marusawa H, Matsuzawa S, Welsh K, Zou H, Armstrong R, Tamm I, *et al.* (2003). HBXIP functions as a cofactor of survivin in apoptosis suppression. *EMBO J* **22**:2729–2740.

McKenzie JA, Grossman D (2012). Role of the apoptotic and mitotic regulator survivin in melanoma. *Anticancer Res* **32**:397–404.

Mita AC, Mita MM, Nawrocki ST, Giles FJ (2008). Survivin: key regulator of mitosis and apoptosis and novel target for cancer therapeutics. *Clin Cancer Res* **14**:5000–5005.

Mobahat M, Narendran A, Riabowol K (2014). Survivin as a preferential target for cancer therapy. *Int J Mol Sci* **15**:2494–2516.

Nakahara T, Takeuchi M, Kinoyama I, Minematsu T, Shirasuna K, Matsuhisa A, *et al.* (2007). YM155, a novel small-molecule survivin suppressant, induces regression of established human hormone-refractory prostate tumor xenografts. *Cancer Res* **67**:8014–8021.

Nakahara T, Yamanaka K, Hatakeyama S, Kita A, Takeuchi M, Kinoyama I, *et al.* (2011). YM155, a novel survivin suppressant, enhances taxane-induced apoptosis and tumor regression in a human Calu 6 lung cancer xenograft model. *Anticancer Drugs* **22**:454–462.

Nakao K, Hamasaki K, Ichikawa T, Arima K, Eguchi K, Ishii N (2006). Survivin downregulation by siRNA sensitizes human hepatoma cells to TRAIL-induced apoptosis. *Oncol Rep* **16**:389–392.

Nitta T, Koike H, Miyao T, Miyazawa Y, Kato H, Furuya Y, *et al.* (2017). YM155 reverses statin resistance in renal cancer by reducing expression of survivin. *Anticancer Res* **37**:75–80.

Oh TI, Lee YM, Nam TJ, Ko YS, Mah S, Kim J, *et al.* (2017). Fascaplysin exerts anticancer effects through the downregulation of survivin and HIF-1α and inhibition of VEGFR2 and TRKA. *Int J Mol Sci* **18**:E2074.

Onoda C, Kuribayashi K, Nirasawa S, Tsuji N, Tanaka M, Kobayashi D, *et al.* (2011). (−)-Epigallocatechin-3-gallate induces apoptosis in gastric cancer cell lines by down-regulating survivin expression. *Int J Oncol* **38**:1403–1408.

Pazhang Y, Ahmadian S, Mahmoudian M, Shafiezadeh M (2011). Berberine-induced apoptosis via decreasing the survivin protein in K562 cell line. *Med Oncol* **28**:1577–1583.

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

Pennati M, Binda M, Colella G, Folini M, Citti L, Villa R, *et al.* (2003). Radiosensitization of human melanoma cells by ribozyme-mediated inhibition of survivin expression. *J Invest Dermatol* **120**:648–654.

Pennati M, Binda M, Colella G, Zoppe M, Folini M, Vignati S, *et al.* (2004a). Ribozyme-mediated inhibition of survivin expression increases spontaneous and drug-induced apoptosis and decreases the tumorigenic potential of human prostate cancer cells. *Oncogene* **23**:386–394.

Pennati M, Binda M, De Cesare M, Pratesi G, Folini M, Citti L, *et al.* (2004b). Ribozyme-mediated down-regulation of survivin expression sensitizes human melanoma cells to topotecan in vitro and in vivo. *Carcinogenesis* **25**:1129–1136.

Pennati M, Folini M, Zaffaroni N (2007). Targeting survivin in cancer therapy: fulfilled promises and open questions. *Carcinogenesis* **28**:1133–1139.

Plescia J, Salz W, Xia F, Pennati M, Zaffaroni N, Daidone MG, *et al.* (2005). Rational design of shepherdin, a novel anticancer agent. *Cancer Cell* **7**:457–468.

Pyrko P, Soriano N, Kardosh A, Liu YT, Uddin J, Petasis NA, *et al.* (2006). Downregulation of survivin expression and concomitant induction of apoptosis by celecoxib and its non-cyclooxygenase-2-inhibitory analog, dimethyl-celecoxib (DMC), in tumor cells in vitro and in vivo. *Mol Cancer* **5**:19.

Rodel F, Frey B, Leitmann W, Capalbo G, Weiss C, Rodel C (2008). Survivin antisense oligonucleotides effectively radiosensitize colorectal cancer cells in both tissue culture and murine xenograft models. *Int J Radiat Oncol Biol Phys* **71**:247–255.

Ryan BM, O'Donovan N, Duffy MJ (2009). Survivin: a new target for anti-cancer therapy. *Cancer Treat Rev* **35**:553–562.

Salzano G, Navarro G, Trivedi MS, De Rosa G, Torchilin VP (2015). Multifunctional polymeric micelles co-loaded with anti-survivin siRNA and paclitaxel overcome drug resistance in an animal model of ovarian cancer. *Mol Cancer Ther* **14**:1075–1084.

Sanomachi T, Suzuki S, Kuramoto K, Takeda H, Sakaki H, Togashi K, *et al.* (2017). Olanzapine, an atypical antipsychotic, inhibits survivin expression and sensitizes cancer cells to chemotherapeutic agents. *Anticancer Res* **37**:6177–6188.

Sato A, Oya M, Ito K, Mizuno R, Horiguchi Y, Umezawa K, *et al.* (2006). Survivin associates with cell proliferation in renal cancer cells: regulation of survivin expression by insulin-like growth factor-1, interferon-gamma and a novel NF-kappaB inhibitor. *Int J Oncol* **28**:841–846.

Shan BE, Wang MX, Li RQ (2009). Quercetin inhibit human SW480 colon cancer growth in association with inhibition of cyclin D1 and survivin expression through Wnt/beta-catenin signaling pathway. *Cancer Invest* **27**:604–612.

Sharma H, Sen S, Lo Muzio L, Mariggio A, Singh N (2005). Antisense-mediated downregulation of anti-apoptotic proteins induces apoptosis and sensitizes head and neck squamous cell carcinoma cells to chemotherapy. *Cancer Biol Ther* **4**:720–727.

Shi X, Wang D, Ding K, Lu Z, Jin Y, Zhang J, *et al.* (2010). GDP366, a novel small molecule dual inhibitor of survivin and Op18, induces cell growth inhibition, cellular senescence and mitotic catastrophe in human cancer cells. *Cancer Biol Ther* **9**:640–650.

Song H, Xin XY, Xiao F, Wang DT, Yue QH, Han X (2008). Survivin gene RNA interference inhibits proliferation, induces apoptosis, and enhances radiosensitivity in HeLa cells. *Eur J Obstet Gynecol Reprod Biol* **136**:83–89.

Sun C, Nettesheim D, Liu Z, Olejniczak ET (2005). Solution structure of human survivin and its binding interface with Smac/DIABLO. *Biochemistry* **44**:11–17.

Suzuki S, Okada M, Kuramoto K, Takeda H, Sakaki H, Watarai H, *et al.* (2016). Aripiprazole, an antipsychotic and partial dopamine agonist, inhibits cancer stem cells and reverses chemoresistance. *Anticancer Res* **36**:5153–5161.

Tanioka M, Nokihara H, Yamamoto N, Yamada Y, Yamada K, Goto Y, *et al.* (2011). Phase I study of LY2181308, an antisense oligonucleotide against survivin, in patients with advanced solid tumors. *Cancer Chemother Pharmacol* **68**:505–511.

Terzis AJ, Thorsen F, Heese O, Visted T, Bjerkvig R, Dahl O, *et al.* (1997). Proliferation, migration and invasion of human glioma cells exposed to paclitaxel (Taxol) in vitro. *Br J Cancer* **75**:1744–1752.

Trabulo S, Cardoso AM, Santos-Ferreira T, Cardoso AL, Simoes S, Pedroso de Lima MC (2011). Survivin silencing as a promising strategy to enhance the sensitivity of cancer cells to chemotherapeutic agents. *Mol Pharm* **8**:1120–1131.

Turk B, Turk D, Turk V (2000). Lysosomal cysteine proteases: more than scavengers. *Biochim Biophys Acta* **1477**:98–111.

Ue S, Luk I, Xue H, Cheng H, Lin D, Gout PW, *et al.* (2014). The BIRC6 gene as a novel target for therapy of prostate cancer : dual targeting of inhibitors of apoptosis. *Oncotarget* **5**:6896–6908.

Van der Waal MS, Hengeveld RC, van der Horst A, Lens SM (2012). Cell division control by the chromosomal passenger complex. *Exp Cell Res* **318**:1407–1420.

Wang TT, Qian XP, Liu BR (2007). Survivin: potential role in diagnosis, prognosis and targeted therapy of gastric cancer. *World J Gastroenterol* **13**: 2784–2790.

Wang T, Liu Z, Zhang Z, Tang S, Yue M, Feng S, *et al.* (2017a). Evaluation of antitumor activity of survivin short interfering RNA delivered by lipid nanoparticles in colon cancer in vitro and in vivo. *Oncol Lett* **14**:2001–2008.

Wang J, Liu Z, Zhang D, Liu R, Lin Q, Liu J, *et al.* (2017b). 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* **9**:3676–3686.

Wheatley SP, McNeish IA (2005). Survivin: a protein with dual roles in mitosis and apoptosis. *Int Rev Cytol* **247**:35–88.

Wiechno P, Somer BG, Mellado B, Chlosta PL, Cervera Grau JM, Castellano D, *et al.* (2014). A randomised phase 2 study combining LY2181308 sodium (survivin antisense oligonucleotide) with first-line docetaxel/prednisone in patients with castration-resistant prostate cancer. *Eur Urol* **65**:516–520.

Xu Y, Wang S, Chan HF, Lu H, Lin Z, He C, *et al.* (2017). Dihydromyricetin induces apoptosis and reverses drug resistance in ovarian cancer cells by p53-mediated downregulation of survivin. *Sci Rep* **7**:46060.

Yamanaka K, Nakahara T, Yamauchi T, Kita A, Takeuchi M, Kiyonaga F, *et al.* (2011). Antitumor activity of YM155, a selective small-molecule survivin suppressant, alone and in combination with docetaxel in human malignant melanoma models. *Clin Cancer Res* **17**:5423–5431.

Yang L, Zhu H, Liu D, Liang S, Xu H, Chen J, *et al.* (2011). Aspirin suppresses growth of human gastric carcinoma cell by inhibiting survivin expression. *J Biomed Res* **25**:246–253.

Ye L, Yang Y, Ma XY, Li D, Xu ML, Tan P, *et al.* (2017). 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* **14**:4721–4728.

Yoo J, Lee YJ (2007). Aspirin enhances tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis in hormone-refractory prostate cancer cells through survivin down-regulation. *Mol Pharmacol* **72**:1586–1592.