Trace of survivin in cancer

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Trace of survivin in cancer
Fereshteh Shojaei, Farshad Yazdani-Nafchi, Mehdi Banitalebi-Dehkordi, Mohammad Chehelgerdi and Milad Khorramian-Ghahfarokhi

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. European Journal of Cancer Prevention 00:000–000 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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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 XIAP, 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 (LaCasce 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.
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 (Aécian 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 G2/M phases of the cell-cycle, whereas a rapid decrease occurs in the G1 phase. Its expression level is controlled by two cell cycle-dependent
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 sensitize 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 ant apoptotic 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 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
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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; TRAIL, 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 chemo sensitization 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. Shepheardin 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). Tetraprocol [meso-tetra-O-methyl nor dihyroguaiaretic 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 trimane 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 polyplody, 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, researchers 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


