

# Survivin as a novel target protein for reducing the proliferation of cancer cells (Review)

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**Abstract.** Survivin, also known as baculoviral inhibitor of apoptosis repeat-containing 5, is a novel member of the inhibitor of apoptosis protein family. Survivin is highly expressed in tumors and embryonic tissues and is associated with tumor cell differentiation, proliferation, invasion and metastasis; however, survivin is expressed at low levels in normal terminally differentiated adult tissues. Meanwhile, the expression level of survivin is also a negative prognostic factor for patients with cancer. These unique characteristics of survivin make it an exciting potential therapeutic target for cancer treatment. This review will discuss the biological characteristics of survivin and its potential use as a treatment target to reduce cancer cell proliferation.

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## 1. Background

Cancer arises from when cell survival and proliferation are favored over cell death, resulting in a disequilibrium (1). Traditional cancer treatments include chemotherapy, radiation and surgery; however, these therapies have limitations and a

risk of cancer recurrence remains following the treatments (1). It has been reported that the recurrence rate of non-small cell lung cancer (NSCLC) is 30-50% (2). Furthermore, although chemotherapy and radiation are able to effectively control the mitosis of tumor cells, they also cause harm to normal tissues. In previous years, researchers have reported that cancer is associated with deficiencies of the immune system. In this regard, researchers have been prompted to consider immunotherapy as a potential approach for the treatment of cancer (3). To date, substantial research data have indicated the effectiveness of immunotherapy (2). Survivin is highly expressed in cancer cells (Table I), whereas it is expressed at a low level in normal adult tissues that have terminated proliferation (3). Survivin is considered as a breakthrough target in this approach and many therapeutic strategies, including small-molecule inhibitors and molecular antagonists, have been developed (3). Although low levels of survivin are expressed in terminally differentiated tissues, it is abundantly expressed in proliferating adult tissues; therefore, it is essential to investigate the potential for toxicity during therapy and to reduce the occurrence of adverse side effects (4,5). Unfortunately, survivin has no known catalytic activity, making it challenging to target (6).

## 2. Introduction

Survivin, also called baculoviral inhibitor of apoptosis repeat-containing 5, is a member of the inhibitor of apoptosis protein family (IAP), which also includes X-linked inhibitor of apoptosis (XIAP), cIAP1, cIAP2, NOD-like receptor family apoptosis inhibitory protein, livin, IAP-like protein 2 and baculovirus inhibitor of apoptosis protein repeat (BIR) containing ubiquitin-conjugating enzyme, isoform C (7,8). Survivin is a 142-amino acid, 16.5-kDa protein encoded by a single gene located on human chromosome 17q25, consisting of an N-terminal Zn<sup>2+</sup>-binding BIR domain linked to a 65Å° amphipathic C-terminal α-helix, as well as 3 introns and 4 exons (3,9-11). Heat shock protein 90 (HSP90) maintains the stability and folding of multiple bioenergetic effectors of survivin (12). Unlike other IAP members, survivin is highly expressed in the majority of neoplasms, whereas it is rarely expressed in normal adult tissues (13). Increased levels of survivin effectively inhibit apoptosis (14-17), and so survivin overexpression has an impact on the abnormal proliferation of

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various cancer cells. According to a previous study, survivin overexpression is associated with reduced expression of the cell adhesion molecules cluster of differentiation CD31 and CD44 in certain cells, which enable them to avoid contact inhibition and undergo abnormal proliferation (18). Furthermore, survivin has been reported to be overexpressed in gastric cancer cells during chemotherapy, suggesting that survivin may be responsible for chemoresistance in gastric cancer (19-21). In addition, a previous study demonstrated that survivin expression was enhanced in recurrent glioblastoma multiforme (GBM) tumors (22). Survivin may also be associated with cell-damaging processes, including transfection (22). Survivin expression has been demonstrated to be associated with p53 expression, which may be induced by cell damage (5). Together, the reported properties of survivin make it an effective prognostic index for postsurgical patients with GBM (22) and a notable tumor marker (23). Survivin overexpression affects cancer cell proliferation via a number of routes and researchers have developed corresponding survivin-targeted therapies, as discussed below.

### 3. Multiple roles of survivin

*Survivin as a regulator of cell division.* It has previously been reported that the major function of survivin is to cell division, rather than to act as a direct inhibitor of apoptosis (9). Survivin serves an essential role as a chromosomal passenger protein (CPP) and as a regulator of microtubule dynamics, ensuring that chromosomes occupy the correct positions during mitosis for accurate cell division (9). Survivin levels increase in G1 phase and reach a peak in G2M phase (9,24). Decreased transcription rates induce the upregulation of survivin in the G2/M phase (25). Survivin affects centrosomes and microtubules during metaphase and anaphase, stabilizing and ensuring the separation of sister chromatids (9). In addition, survivin is responsible for regulating chromosome congression and the progression of mitosis, along with microtubule dynamics and elevated microtubule stability (26). It has previously been reported that survivin interacts with both Aurora-B and inner centromere protein to form a CPP complex, which is vital to cytokinesis (27). Elimination of survivin results in deficient mitosis and the activation of spindle checkpoints regulated by the tumor suppressor protein p53, ultimately resulting in apoptosis of the dividing cells (28,29). Survivin silencing leads to DNA double-stranded breaks (DSBs) in cancer cells and functionally reduces homologous recombination (30). Even though it serves a critical role in regulating CPP targeting, survivin is not the only protein in the CPP family that contributes to the stability of the structure (23).

*Survivin as an inhibitor of apoptosis.* Survivin is a potent anti-apoptosis factor and is inversely mediated by p53 at the mRNA and protein levels (31,32). Survivin suppresses programmed cell death in two ways (Fig. 1); firstly, it directly suppresses the activities of terminal effector enzymes caspase-3 and caspase-7 to resist cell apoptosis induced by specific stimuli (33). Secondly, interactions between survivin and the cyclin-dependent kinase (CDK)-4 and CDK-2 suppress apoptotic signaling pathways (33). Survivin overexpression suppresses the extrinsic and intrinsic apoptosis pathways (23)

Table I. Ratio of survivin expression in various cancer cells.

Cancer	Expression (%)	Refs.
Hepatocellular	62	94
Prostate	71	95
Ovary	29-85	96
Lung	86	97
Breast	71-90	98
Gastric	35-68	99

and apoptosis is stimulated when survivin is depleted in human cells (34). During cell apoptosis, DNA damage activates p53, which stimulates the transcription of B-cell lymphoma 2-associated X protein Bax and p53 upregulated modulator of apoptosis (35). Subsequently, the gene products regulate the permeability of the mitochondrial membrane and cytochrome release. Cytochrome *c* binds with apoptotic protease activating factor-1, forming a complex with caspase-9; this complex activates caspase-3 and caspase-7 which in turn activate apoptosis (35). Through binding with the cofactor XIAP, survivin suppresses the activity of caspase-9, functioning as an anti-apoptosis factor (35). Functional inhibition of survivin using small interfering (si)RNA and ribozymes may therefore be used to enhance tumor cell sensitivity to existing pharmacological agents (35). Wheatley (36) confirmed that the C-terminus of survivin is essential for cell division, whereas the N-terminus of survivin serves a role in apoptosis. Although a dual role of survivin in apoptosis inhibition and spindle dynamics regulation has been reported (26), further studies are required to improve our understanding of the connection between the two roles of survivin.

*Survivin expression and cancer cells.* Survivin is undetectable in the majority of non-proliferating, fully differentiated cells, except for CD34<sup>+</sup> hematopoietic stem cells, placental cells and basal cells of the colonic epithelium and thymus (37). Survivin is highly expressed in a number of cancers, including lung, breast, colon, brain, gastric, esophageal, pancreatic, liver, uterine and ovarian cancer cells (37). The unique properties of survivin make it a useful molecule for studying the potential biology of tumorigenesis and provide a basis for modifying and constructing molecules that specifically target and suppress cancer cells (37). In tumor cells, survivin accumulates and localizes to the mitochondria (16), enhancing cell resistance to apoptosis (38) and impacting organelle bioenergy (39). In this way, survivin functions as a potential cancer driver. Survivin enhances the survival of cancer cells as part of several molecular networks associated with major apoptotic regulators, including caspases, XIAP and the endogenous survivin inhibitor second mitochondria-derived activator of caspases (38,40). DNA DSBs are a common challenge for cancer cells, the fate of which depend largely on their ability to perform DSB repair, which in turn depends on homologous recombination and non-homologous end joining (30). It has been reported that survivin elimination may impair DNA repair via homologous recombination (30). According to a previous study, survivin is vital for efficient DNA repair, as the

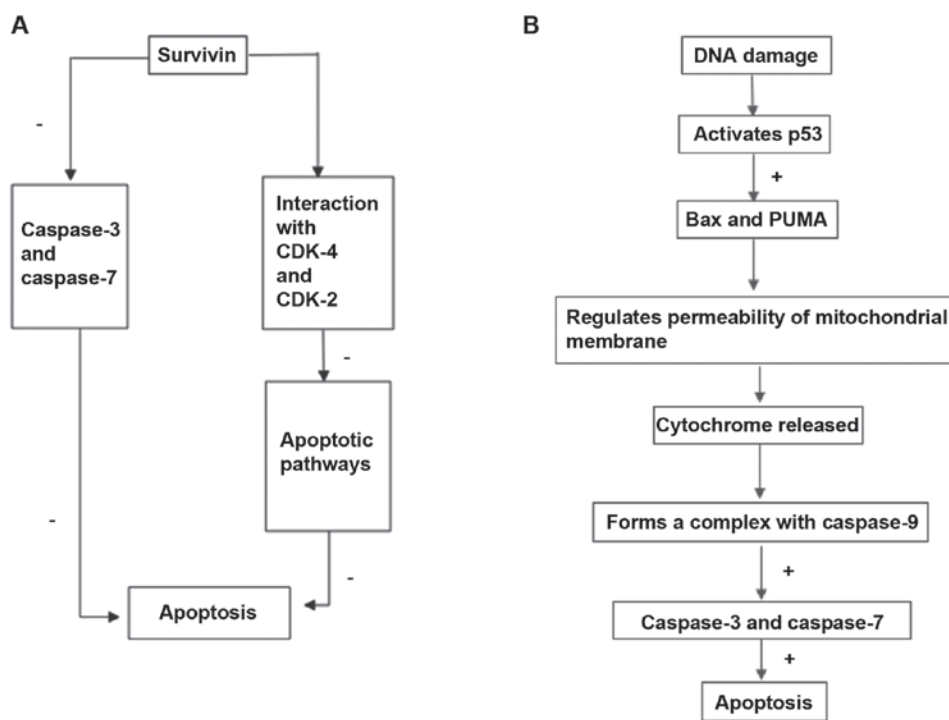


Figure 1. Mechanisms of survivin in apoptosis induction. (A) An illustration of the two ways in which survivin functions to inhibit apoptosis. (B) The mechanism of apoptosis induced by depletion of survivin. CDK, cyclin-dependent kinase.

elimination of survivin results in reduced expression of several major regulators of DNA repair and impairs gene expression essential to repair onset. Survivin silencing also resulted in DNA DSBs in breast cancer cells and a reduction in homologous recombination (30). Furthermore, survivin inhibition has been reported to initiate the p53 response and enhance the vulnerability of cells to poly ADP-ribose polymerase inhibition (30). According to other research, patients with higher survivin levels in tumor tissues are at increased risk of relapse and chemoresistance (37).

*Survivin and cancer stem cells (CSCs).* Scientific interest in CSCs has increased in recent years (41). CSCs, which are undifferentiated pluripotent cells with the ability to self-regulate, have been identified in acute myelogenous leukemia, breast cancer and a number of other tumors (42-44). Their existence is postulated to be a determining factor for cancer recurrence. CD133<sup>+</sup> CSCs are assumed to be correlated with tumor initiation, progression and chemoresistance (22). They are also able to activate transcription factor 3, the downstream target gene associated with survivin (45-47). Therefore, survivin expression in CSCs may also be associated with the regulation of CSC behavior (23). Survivin has been confirmed to be a downstream gene of the Wnt pathway, which has been demonstrated to be important in gastric CSCs (48-50). It has been reported that glioma stem cells (GSCs) induce therapy-resistance in tumor cells by upregulating DNA damage checkpoint proteins (51). CSCs and survivin are considered to be factors associated with tumor recurrence as well as the radiation- and drug-resistance of recurrent tumors (23). However, the exact role of CSCs in tumorigenesis is yet to be elucidated (52). Further studies are required to evaluate the interaction between CSCs and survivin during tumor cell proliferation and invasion.

#### 4. Recent therapeutic approaches

*Survivin inhibitor.* YM155 is a small-molecule survivin suppressor that distinctly interacts with the survivin core promoter region of 269 base pairs, specifically inhibiting the expression of survivin (4,53). YM155 has effects on gene expression and phosphorylation (54). A certain study demonstrated that YM155 effectively inhibited the expression of survivin mRNA in SGC-7901 and MKN-28 cells in a dose-dependent manner (55). YM155 inhibits survivin expression by interfering with the binding of Sp1 and survivin promoter (56). YM155 has been evaluated in phase II clinical trials for breast cancer (57), melanoma (58) and NSCLC (59). Furthermore, a number of studies have reported that YM155 is able to effectively inhibit survivin expression and induce the apoptosis of human cancer cells (60), as well as promoting the expansion of CD44<sup>+</sup> CSCs (55). It has been confirmed that YM155 is able to overcome drug resistance in tumors when used with other chemotherapeutical agents; for example, YM155 reversed rapamycin resistance in rapamycin-resistant renal cell carcinoma (61). It has also been reported that YM155 is able to inhibit the progression of gastric cancer cells. Notably, it was demonstrated that gastric cancer SGC-7901 cells treated with YM155 formed smaller and fewer colonies compared with a control group (55). These results indicate that YM155 suppresses anchorage-dependent and anchorage-independent proliferation in gastric cancer cells (55). It has been observed that YM155 exhibits potent antiproliferative effects against human leukemia cell lines in a dose-dependent manner (55). Furthermore, it has been demonstrated that activation of caspase-8, an important protein associated with the extrinsic apoptosis pathway, occurs in cell lines treated

Table II. Summary of treatments.

Name	Characteristics	Refs.
YM155	Inhibitor of Sp1; induces cancer cell apoptosis	(56,60)
LLP3	Inhibits the growth of glioma stem cells <i>in vitro</i> and <i>in vivo</i>	(22)
LY2181308	Second generation ASO; modest efficacy in phase I trial	(73,78)
Shepherdin	Survivin-HSP complex antagonist, HSP90 global inhibitor	(80)
siRNA	Induces gene silencing; needs sophisticated modification	(86,87,89)

Sp1, specificity protein 1; ASO, antisense oligonucleotide; HSP, heat shock protein; siRNA, small interfering RNA.

with YM155 (62). Rivadeneira *et al* (63) demonstrated that YM155 is able to disrupt mitochondrial bioenergetics and thus activate tumor suppressor mechanisms involving AMP-activated protein kinase activation or mammalian target of rapamycin inhibition. There may be other mechanisms by which YM155 inhibits cancer cell progression (54). According to Chang *et al* (54), YM155 activates the DNA damage pathway. Following 24-h treatment with 100 nM dasatinib DNA damage was significantly increased in the presence of YM155. This study confirmed that YM155 is able to activate the DNA damage response pathways via S phase arrest, which elevates p53, checkpoint kinase 2 and H2AX phosphorylation, eventually resulting in apoptosis (54). An increasing number of studies have suggested that YM155 may have more off-target effects that result in cell death, including inhibition of Mcl expression and direct DNA damage (62,64,65). It has also been reported that YM155 may induce autophagy-dependent DNA damage in breast carcinoma via a survivin-XIAP-dependent mechanism (66). YM155 inhibits survivin and also mediates the expression of major genes, including death receptor signaling and tumor necrosis factor receptor 1 signaling factors, that serve a role in apoptosis induction via the extrinsic apoptotic pathway (67). YM155 may have potential as an effective inhibitor of nuclear factor- $\kappa$ B and its downstream target gene matrix metalloproteinase-9, which in turn inhibits the growth, invasion and metastasis of survivin-enriched oral squamous cell carcinoma cells (68). Furthermore, YM155 does not affect normal tissues (55); in in phase I studies, YM155 was demonstrated to be tolerable in patients with advanced cancer, as well as exhibiting anti-tumor activity in patients with non-Hodgkin's lymphoma and hereditary papillary renal carcinoma (69,70). YM155 has been investigated as a single-agent first-line treatment in 34 patients with metastatic melanoma in a phase II study (71). Of these patients, one exhibited a complete response, one exhibited a partial response and 11 retained stable disease (71). A clinical trial, in which the efficacy of YM155 as a single agent or in combination with either immunotherapy or cytotoxic chemotherapy was investigated, confirmed that the drug is fairly tolerable under such conditions (72). However, the response has been minimal. Chang *et al* (54) suggested that patients need to be pre-selected for YM155 sensitivity to guarantee beneficial outcomes. Their findings confirmed that YM155 is an ideal candidate drug for therapeutic regimens when administered to a certain subgroup of patients (54). Further

study is required to identify the underlying mechanism of selective sensitivity to YM155 in cancer cells.

Guvenc *et al* (22) designed a small molecule inhibitor, LLP-3, using a structure-based computational drug design method. LLP-3 is able to inhibit the interactions between survivin and the small GTPase Ran, decreasing the proliferation of GSCs *in vitro* and *in vivo* (22). They also demonstrated that survivin and Ran are expressed in GSCs derived from patients with GBM (22). These results suggest that LLP-3-mediated inhibition of the survivin-Ran complex in GSCs results in diminished tumor growth *in vivo* and that the inhibitory effects of LLP-3 on the survivin-Ran complex are associated with p53 status in tumor cells (22).

*mRNA inhibitor.* LY2181308 is a novel second-generation 18-mer antisense oligonucleotide (ASO). LY2181308 is able to bind to human survivin mRNA and suppress translation, restoring the apoptotic pathway in cancer cells (73). In preclinical models, LY2181308 has exhibited antitumor activities when combined with docetaxel, which is one of several chemotherapeutic options for patients with advanced metastatic NSCLC who have not responded to first-line treatment (74,75). Compared with phosphorothioates, second-generation ASOs exhibit a higher level of stability, an improved pharmacokinetic profile, increased potency and reduced toxicity (76). However, many patients have exhibited flu-like symptoms in studies involving LY2181308 (77,78). In a phase I study involving 14 patients with malignant solid tumors, flu-like syndrome, prolonged prothrombin time-international normalized ratio, thrombocytopenia and fatigue were common reversible grade 1/2 toxicities (78). These results indicated that LY2181308 monotherapy is tolerable at doses up to 750 mg; however, the efficacy of LY2181308 in combination with other toxic therapeutic agents requires further study (78). A pharmacodynamics study was performed for 34 patients with advanced or metastatic malignancies, 22 of whom were available for pre- and post-treatment biopsies (79). Immunohistochemistry revealed a reduction in survivin levels in the nucleus and cytoplasm of 11/17 and 5/14 evaluable pairs, respectively. Gene expression analysis also indicated that there was a 20-50% reduction in survivin expression in 11/15 of the evaluable pairs. In addition, analysis of fresh tumor tissues revealed that 2/3 patients with NSCLC exhibited a near-complete elimination of survivin-positive cells along with an elevation in the fraction of cells with a sub-G1 DNA content, which is consistent with cell death (79).

**Small peptide survivin inhibitor.** Shepherdin is a small molecule peptidomimetic inhibitor of only 5 amino acids in length (80). It functions as an antagonist of the survivin-HSP complex and is now under early-stage clinical development (80). HSP90 binds to substrate proteins that are in a near-native state, contributing to the stability of survivin; it has been postulated that the ATP-bound state of HSP90 binds stably to substrate polypeptides, held by an internally dimerized clamp (80). ATP hydrolysis facilitates the release of the substrate, leading to conformational changes in HSP90 (81). Shepherdin is able to effectively counteract the binding of HSP90 with survivin (80). Therefore, it functions as an HSP90 global inhibitor via competition inhibition with ATP (80).

**siRNA.** RNA interference by siRNA may be used to reduce the expression of a target gene in a sequence-specific manner via degradation of the corresponding mRNA (82-85). siRNA molecules are 19-21 nt in length and have a molecular weight of 13-15 kDa with 38-46 negative charges (86). siRNA-induced gene silencing is highly efficient and specific to target genes, and so has applications in cancer treatment (87,88). Unmodified siRNA is problematic and modifying siRNAs may impair their activity, which makes the development of siRNA-based agents difficult (89,90). Furthermore, siRNAs are not taken up by the majority of mammalian cells in a way that maintains their activity (91). Recent progress in the structural modification of sticky siRNA includes hybridization reactions with sticky siRNA and chemical polymerization of sticky siRNA (89). However, building clinically successful siRNA-based structures remains challenging (89). A lack of effective siRNA delivery into target cells is the main issue preventing the clinical use of siRNA therapeutics. The cell trafficking pathways of siRNA are not well understood and so cannot inform pharmacological development (92,93). These factors suggest that siRNA should be studied further to elucidate its potential as a therapeutic agent.

A summary of the therapeutic approaches is provided in Table II.

## 5. Conclusion

The role of IAPs in cellular homeostasis has been widely investigated in the past decades. Of the IAP family, the survivin protein serves several roles in various processes related to the survival of cells. Survivin is highly expressed in a number of types of tumor and is associated with the proliferation and invasion of cancer cells, radiation and chemotherapy resistance and poor prognosis. Furthermore, survivin is highly expressed in tumor cells while it is expressed at low levels in normal, terminally differentiated cells. Survivin may serve roles in cell survival by affecting complex intracellular signaling, stabilizing mitosis and facilitating cellular adaptation. These properties make survivin a potential therapeutic target for the treatment of cancer. Further studies are required to identify other signaling pathways through which it functions, as its other effects in tumor cells. Elucidating the mechanisms by which survivin regulates cell growth may assist in the development of therapeutic approaches in pre-clinical settings. Recent progress in this field includes the discovery of transcriptional repressors, mRNA inhibitors, small molecule

survivin inhibitors and immunotherapy as potential treatments. However, these approaches are flawed and may not be suitable for use in clinical settings; as such, further investigation is required to better understand survivin.

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## Authors' contributions

HL designed the structure of the paper and advised DL and CH during writing. DL and CH wrote the majority of the contents in this manuscript. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

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## Consent for publication

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## Competing interests

The authors declare that they have no competing interests.

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