



# Survivin in lung cancer: a potential target for therapy and prevention – a narrative review

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**Background and Objective:** A versatile biomarker, survivin, is highly expressed in proliferating cells of multiple cancers in humans and animals. It is an apoptosis-regulating protein, engaging in a cascade of reactions that involve several other genes and protein interactions. Currently, researchers are investigating its therapeutic potential due to the evidence linking its overexpression to advanced-stage lung cancer. This review is centered around examining survivin-related molecular mechanisms and its therapeutic role specifically in lung cancer. Our objective is to discuss the role of survivin in prognosis and treatment response, shedding light on immune-targeted therapies, as well as outlining future directions for survivin-based vaccines in lung cancer.

**Methods:** The PubMed database and the United States National Library of Medicine search engine at the National Institutes of Health were searched on 24 August 2023 to identify published research studies. Searching “((((((airway [Title/Abstract]) OR (lung [Title/Abstract])) OR (pulm[Title/Abstract])) OR (bronch[Title/Abstract])) OR (nslc[Title/Abstract])) AND (((cancer[Title/Abstract]) OR (carcino[Title/Abstract])) OR (oncol[Title/Abstract])) AND (survivin[Title/Abstract])” gave 728 results. After screening the title and abstracts and excluding the review articles 168 titles were shortlisted and full text studied. The discussions are added to relevant sections.

**Key Content and Findings:** Survivin is a cell cycle-dependent, inhibitor of apoptosis protein that contributes to carcinogenesis, tumor vascularization, metastasis, and treatment resistance. Several treatments that impact survivin either directly or indirectly have been reported as effective in treating lung cancer. Immunity-based therapy, a novel approach known for its targeted nature and minimal side effects, is currently under investigation for lung cancer treatment. Emerging survivin-centered vaccines exhibit promising attributes in terms of safety, effectiveness, and ability to stimulate an immune response. These factors point towards a significant potential for advancing the future of lung cancer prevention and enhancing overall survival rates.

**Conclusions:** Nuclear survivin is a potential biomarker for advanced non-small cell lung cancer. It plays a role in determining drug responsiveness and is found to be significantly elevated in cases of resistance to chemotherapy. Multiple compounds and immunization strategies have been identified to impact lung cancer cells; however, they are currently in the early stages of phase I or phase II clinical trials. The substantial promise of survivin-based immunogenicity-focused treatments warrants in-depth investigation and exploration.

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## Introduction

Dysregulated apoptosis results in prolonged cell survival in various cancers, autoimmune disorders, and certain viral illnesses (1). Inhibitors of apoptosis proteins (IAPs) are a family of molecules that play a role in cell death, prolong cell viability, and may contribute to cancer cell viability (2). Evidence suggests that identifying and targeting genes encoding such proteins could open a new avenue for cancer treatment. A recently identified gene of interest is *survivin*, which is generally absent in normal mature adult cells but expressed in transformed cell lines. This makes it a potential target for cancer therapy (3). IAPs are a group of heterogeneous proteins expressed in various human malignancies including lung, colon, brain, pancreas, prostate, breast, and lymphatic cancers. Of the various IAPs, survivin is the most extensively studied in lung cancer. Increased expression of survivin in lung cancer tissue samples is reported to be associated with poor prognosis and resistance to chemotherapy (4).

Lung cancer is the most common cause of cancer mortality worldwide and is responsible for one-quarter of all cancer-related deaths (5). Non-small cell lung cancer (NSCLC), including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounts for over 85% of lung cancers. Although surgical resection is the curative treatment for lung cancers, 70% of patients present at an advanced stage (stages III and IV) when inoperable (6). Identification of novel molecular markers which characterize lung cancer biology can help find new directions for early diagnosis and treatment at a molecular level. Since the early 2000s, researchers have focused on the diagnostic and prognostic significance of several molecular markers, which lead to the development of targeted therapies centered on endothelial-derived growth factor (EGFR) and BRAF mutations, ALK, ROS1 and RET rearrangements, NTRK and anti-PD-L1 fusions (7). Survivin is one such potential biomarker. It is essential for mitosis, can inhibit apoptosis, is differentially expressed in tumor and normal adult cells, and acts both by intrinsic and extrinsic apoptosis pathways (8). Here, we review the role of survivin in lung cancer, starting from the structure and expression of survivin,

polymorphisms, and its role in therapy. We present this article in accordance with the Narrative Review reporting checklist (available at <https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-621/rc>).

## Methods

The PubMed medical literature database and the United States National Library of Medicine search engine at the National Institutes of Health were used on 24 August 2023 to identify published research studies. Literature published in English till 2023 that included all study designs that were possibly relevant to this review were included. Only full manuscripts were considered. Reviews of existing literature, abstracts, preprints, and letters to editors were excluded. The search string, designed to cover the primary themes of the review and optimized for high sensitivity, was: “((((airway [Title/Abstract]) OR (lung [Title/Abstract]) OR (pulm[Title/Abstract]) OR (bronch[Title/Abstract]) OR (nslc[Title/Abstract]) AND (((cancer[Title/Abstract]) OR (carcino[Title/Abstract]) OR (oncol[Title/Abstract])) AND (survivin[Title/Abstract]))”). This yielded 728 results. After screening the title and abstracts, 168 titles were shortlisted, and full text studied. The discussions are added to relevant sections. The strategy is summarized in *Table 1*.

## Survivin-structure and function

All the proteins in the IAP family are characterized by a domain of 70 amino acids known as baculoviral IAP repeat (BIR). Survivin is the best studied and the smallest member of the IAP family, with a weight of 16.5kda. It contains a single BIR and lacks a carboxy-terminal RING finger unlike other proteins of the family (*Figure 1A*) (9). It is encoded by the *BIRC5* gene on chromosome chr17q25 (3). It undergoes multiple constitutional changes, which influence its various functions such as its stability, role in mitosis, role in apoptosis, intracellular localization, and proliferation signaling. Survivin is expressed maximally in the G2/M phase and rapidly declines thereafter (10). This implies the important role of survivin in cell-cycle regulation, affecting

**Table 1** The search strategy summary

Items	Specification
Date of search	8/24/2023
Databases and other sources searched	PubMed; United States National Library of Medicine search engine at the National Institutes of Health
Search terms used	"((((airway [Title/Abstract]) OR (lung [Title/Abstract])) OR (pulm[Title/Abstract])) OR (bronch[Title/Abstract]) OR (nslc[Title/Abstract])) AND (((cancer[Title/Abstract]) OR (carcino[Title/Abstract])) OR (oncol[Title/Abstract])) AND (survivin[Title/Abstract])"
Timeframe	1997–2023
Exclusion criteria	Excluded: narrative reviews, non-English articles, full article unavailable online
Selection process	Primary author went through the articles and decided the relevance

cell proliferation and cell stability (*Figure 1B*). Survivin plays a major role in cell division at multiple steps as a part of a complex called the chromosomal passenger complex (11). In proliferating cells, after phosphorylation by aurora B, survivin binds to the centromeres in the G2 phase. It communicates with the spindle checkpoint tension sensor BubR1 (BUB1B) to ensure that chromosomes are properly aligned (12). This association lasts until the metaphase-anaphase transition. Thereafter, survivin plays a role in cytokinesis by delineating the cleavage planes (13). It also influences events like mitotic spindle assembly, control of the mitotic checkpoint, and chromosomal condensation (14). By promoting microtubule stability, survivin plays a role in acquiring resistance to anti-cancer agents.

In a non-dividing cell, survivin is localized to the nucleus and/or cytoplasm and rarely in the mitochondria. Although no correlation has been established regarding the significance of the nuclear-to-cytoplasmic ratio of survivin (15), it is observed that there is a progressive increase in the cytoplasmic proportion over time in cancer cells (16). Mitochondrial survivin is specifically seen in cancer cells and is thought to play an active role. This pool increases during stress, is released into the cytosol in response to apoptotic stimuli, and has enhanced anti-apoptotic activity (17).

Survivin is expressed in cells during fetal development (18), in proliferating cells (19) and is thought to be largely undetectable in mature adult cells. Recent evidence suggests that it is expressed in activated T lymphocytes, erythroblasts, and self-renewing stem cells (20–22). Expression in these cell types is regulated by multiple factors including miRNAs and various downstream signaling pathways, during transcription and via post-translational modifications. The promoter region of the *survivin* gene contains a cell cycle-dependent element (CDE)/cell cycle

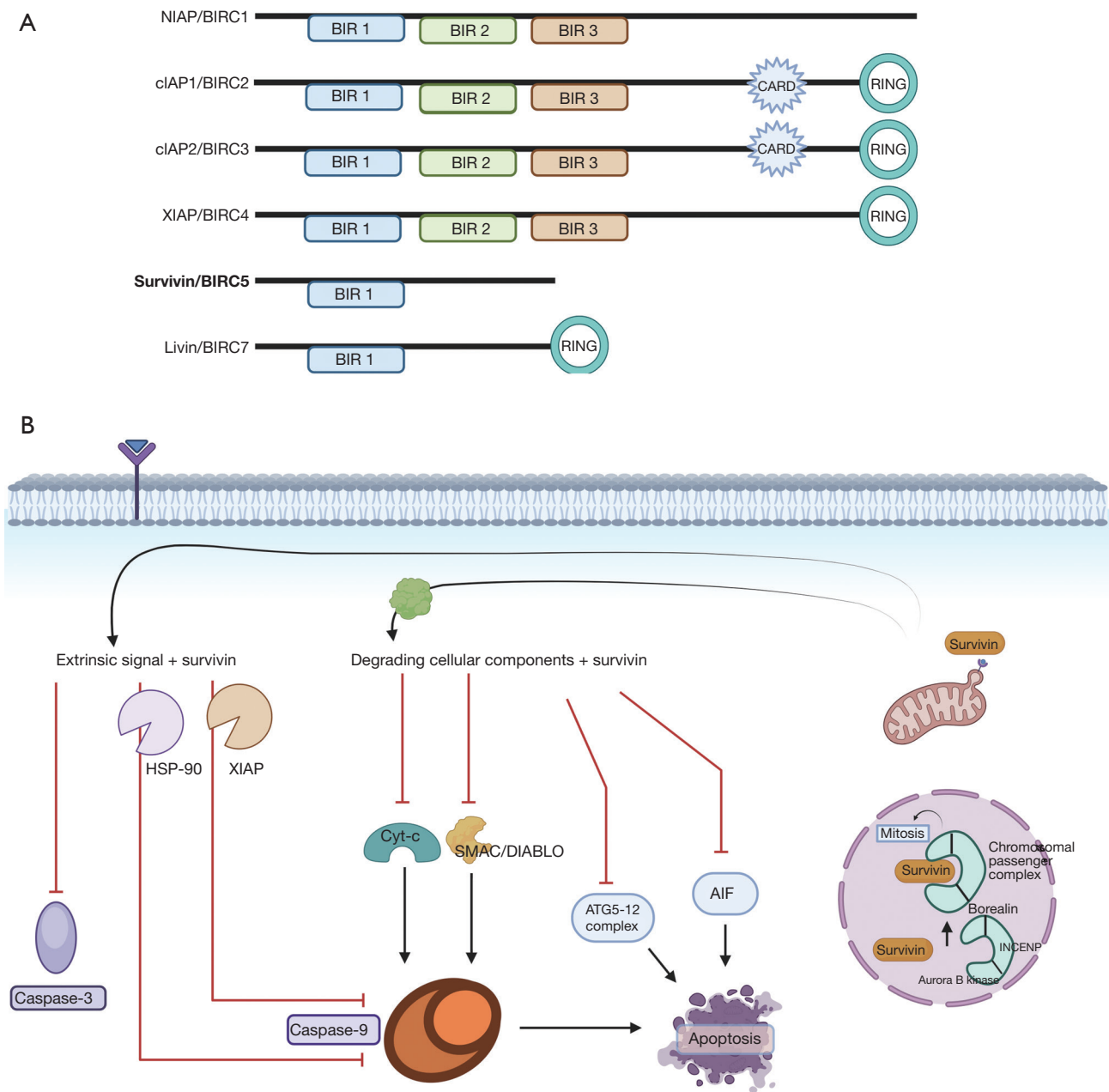
genes homology region element, indicating that *survivin* may be a gene regulated by the cell cycle. Thus, *survivin* expression is influenced by the various phases of the cell cycle (23).

A variety of miRNAs have also been identified to regulate survivin expression via binding to the survivin mRNA, thereby resulting in the alteration of survivin protein translation or leading to its degradation. Out of the multiple miRNAs, molecular mechanisms of miR-34a and miR-203 have been extensively studied. While miRNA-203 directly interacts with the *survivin* gene and contributes to cancer progression and metastasis, miRNA-34 was shown to reduce survivin via both direct and indirect regulation (24). *Table 2* presents multiple other miRNAs which regulate survivin in other malignancies (*Figure 2*).

Post-translational regulation occurs through protein modifications like phosphorylation and polyubiquitination, affecting survivin levels (23). Activation of EGFR can increase survivin protein levels in a phosphatidylinositol 3-kinase (PI3K)-dependent pathway (27). On stimulation by insulin-like growth factor 1 (IGF-1), survivin expression is enhanced through a mechanism mediated by the mammalian target of rapamycin (mTOR) pathway (28). The PI3K/Akt (protein kinase B) signaling-dependent transcription has a role in the expression of genes such as *survivin* and vascular endothelial growth factor (*VEGF*), a critical regulator of tumor angiogenesis (29). Signal transducer and activator of transcription 3 (*STAT3*), a proto-oncogene, on activation, mediates cancer progression through a pathway involving survivin, and *STAT3* inhibition leads to apoptosis due to reduced survivin (30).

### Survivin and carcinogenesis

As discussed previously, survivin, unlike other IAPs, is



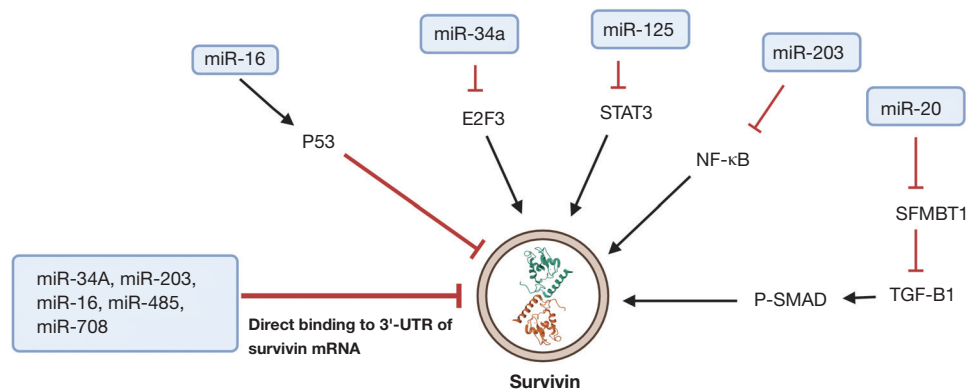
**Figure 1** Structure and functional pathways of survivin. (A) Structure of survivin in relation to other IAPs, single BIR domain with no RING or CARD moiety for ubiquitination. (B) Role of survivin in apoptosis; nuclear survivin forms CPC and controls cytokinesis and chromosomal segregation; mitochondrial survivin released in response to apoptotic stimulus inhibits caspase-3,8,9 (created with Biorender.com). AIF, apoptosis inducing factor; IAPs, inhibitors of apoptosis proteins; BIR, baculoviral IAP repeat; HSP, heat shock protein; SMAC, second mitochondrial-derived activator of caspases; CPC, chromosomal passenger complex.

exclusively expressed in proliferating cells, making it a key biomarker of cancer proliferation and tumor cell death. As noted above, it is upregulated in many mammalian cancers. More recently, survivin expression has been observed in

several preneoplastic lesions, including Bowen’s disease, hypertrophic actinic keratosis (31), polyps of the colon (32), cervical squamous intraepithelial lesions (33), and precancerous oral lesions (34). Kawasaki *et al.* showed

**Table 2** MicroRNAs affecting survivin expression

MicroRNA	Type of cancer	Mode of action	Reference
miR-34a	Multiple cancers	Direct and via E2F3	(23)
miR-542-3p	Non-small cell lung cancer	Direct	(23)
miR-708	Human renal cell carcinomas	Direct	(23)
miRNA125a, miR-125b and miR-205	Breast cancer	Via STAT3 pathway	(25)
miR-203	Laryngeal cancer, hepatocellular carcinoma, lung cancer, and pancreatic cancer	Direct and via NF- $\kappa$ B	(23)
miRNA-218	Nasopharyngeal cancer, osteosarcoma	Affects multiple oncogenes	(23)
miRNA-150	Burkitt's	Via p53	(23)
miRNA-16	Colorectal cancer	Via p53	(26)

**Figure 2** MicroRNA regulating survivin expression and respective pathways. UTR, untranslated region.

increased survivin immunoreactivity along the adenoma-carcinoma sequence providing evidence for the role of survivin in tumorigenesis (32). Puccio *et al.* studied the expression of survivin in non-dysplastic Barrett's esophagus, concluding that survivin levels progressively increase in the transition from metaplasia to dysplasia to adenocarcinoma (35). Similarly, Nakanishi *et al.* studied levels of survivin in various premalignant lesions of lung cancer low-grade atypical adenomatous hyperplasia (AAH), high-grade AAH, and adenocarcinoma (36). It was found that an increasing proportion of patients expressed survivin as the grade of the lesions increased. These observations underscore survivin's significance as an early-stage biomarker in multiple human cancers, contributing to carcinogenesis.

Mechanistically, survivin plays a major role in tumorigenesis by regulating programmed cell death at the molecular level. The mechanism of apoptosis can be an intrinsic pathway for intra-cellular stress stimuli or an extrinsic

pathway for tumor necrosis factor-mediated cell lysis, both of which are mediated by caspases (37,38). After initiation by cytochrome C and initiator caspases, through a cascade of reactions, caspase 3 and caspase 7 (executioner caspases) bring about cell death (38). The current consensus is that survivin binds to complexes such as XIAP and hepatitis B virus X-interacting protein (HBXIP, also known as LAMTOR5) to interact with caspases or to enhance the effect of other IAPs (39). Other actions include the prevention of the release of apoptotic protease activating factor-1 (APAF-1) from mitochondria and the sequestration of IAP inhibitor—the second mitochondrial-derived activator of caspases (SMAC) (40,41). Survivin may also act independently of caspases by interfering with mitochondrial apoptosis-inducing factor, which acts through DNA fragmentation (41). Furthermore, the survivin-XIAP complex enhances NF- $\kappa$ B and upregulates the genes responsible for cell invasion and metastasis (42). Apart

from these mechanisms, results from two of the early studies testing survivin-based vaccines showed significantly reduced tumor volumes, number of blood vessels, and delay in metastases in *in vivo* studies showing that survivin participates in tumor angiogenesis and helps in tumor growth and metastasis (10,43).

Survivin knockdown studies undertaken to prove the biological causation also consolidate the hypothesis about its effect on cancer cell growth. Combined knockdown of anti-apoptotic proteins Livin, XIAP, and survivin reduced human bladder cancer cell proliferation, due to disinhibition of caspases (44). Another study where survivin was knocked down by vector-based shRNA showed suppressed tumor growth *in vitro* and reduced tumorigenesis in mice (45). A549/DDP lung cancer cells with survivin knockdown showed reduced proliferation and increased sensitivity to cisplatin (46).

### Survivin in lung cancer

Consistent with the role of survivin in other cancers, the expression of survivin is higher in lung cancer compared to normal lung (47). Compared to normal lung epithelium, the promoter region of survivin in lung cancer cells is activated (48). This is true in almost all types of lung cancer. However, survivin expression depends on multiple factors like pathological type, metastasis, smoking, and others. Hirano *et al.* studied the association between smoking, ki67, and nuclear survivin levels revealing that smokers with lung cancer have elevated levels compared to non-smokers (49). Mohamed *et al.* showed that nuclear survivin can be an independent prognostic marker by comparing the overall survival in lung cancer patients. Such a correlation between survival and nuclear survivin is not found in patients of small cell lung cancer (50). However, the nearly ubiquitous expression of survivin in lung cancer makes it an attractive target for various diagnostic purposes and novel therapies. A retrospective study of 102 patients with NSCLC showed elevated survivin in 53% of patients and there was a correlation with the size of the tumor, stage of tumor, and a negative correlation with survival. This clinical study showed that survivin is a good biomarker for malignancy and suggested that it can potentially be a therapeutic target due to its selective expression (51). In contrast, no correlation was found between survival and survivin expression in several other studies that looked at survivin protein and mRNA overexpression (52). In a study of circulating cancer cells, 63 of 143 patients expressed survivin

positivity and correlated with cancer stage, poorer survival, and nodal status (53). In another study, where 210 NSCLC tissues were examined, survivin expression was detected in 53.3%. Out of these, 67% of patients had VEGF-positivity. This study not only established the reduced survival in patients with increased survivin expression but confirmed its correlation with tumor vascularity and a higher chance of early metastasis (54). Apart from being correlated with prognosis, survivin expression has been associated with response to chemotherapy. A prospective study with 47 patients undergoing chemotherapy showed a significantly increased expression of survivin in patients with cisplatin resistance (55). Similarly, survivin is noted to have increased expression in patients with a diminished response to tyrosine kinase inhibitors and vincristine (56). YM155, a small molecule survivin suppressor, is shown to sensitize NSCLC cells to tyrosine kinase inhibitors when given in combination (57). Transfection of carboplatin-resistant lung cancer cell lines with microRNA, miR-205, and miR-218 induced survivin knockdown and resulted in the downstream cascade leading to apoptosis (58). YM155 also has an interesting role in enhancing the effect in response to radiation, through dedifferentiation of non-stem cancer cells to cancer stem cells (59).

### Survivin as a therapeutic target

Presented below is a comprehensive list of therapeutic agents investigated in lung cancer treatment, focusing on their impact on survivin regulation and survivin-associated downstream pathways. These agents are classified into two groups: one that directly influences survivin expression (*Table 3*), while the other group affects downstream complexes in survivin immune pathways, thereby influencing chemotherapy resistance (*Table 4*). It's important to note that while this list is exhaustive, most of these agents are currently in either preclinical or phase I/II of clinical trials. Ongoing clinical trials currently underway are tabulated in *Table 5*.

### Direct survivin inhibitors

A multicenter phase II trial with YM155, a small molecule survivin suppressor was tried as a single agent, in lung cancer patients after treatment failure. Their results showed slightly improved efficacy with respect to objective tumor response rate and overall survival, with a good safety profile (60). A camptothecin-derived product, FL118 (such as

**Table 3** Direct survivin inhibitors

Class of drugs	Therapeutic agent	Action	Reference
Transcription inhibitors	YM155	Single-agent activity in refractory, advanced NSCLC without significant toxicity profile	Giaccone <i>et al.</i> , 2009, (60)
	FL118	Activity against cancer stem cells, option in resistant and metastatic cancer	Wang <i>et al.</i> , 2017, (61)
Protein-protein interaction blockers			
SMAC mimetics	UC-112 analogs	Potential in multi-drug resistant tumors	Wang <i>et al.</i> , 2018, (62)
Heat shock protein 90-survivin inhibitors	Shepherdin	Extensive suppression of survivin and Akt <i>in vivo</i> experiments	Plescia <i>et al.</i> , 2005, (63)
Survivin homodimerization inhibitors	Abbott 8, LQZ-7, LQZ-7F	Showed small molecular binding sites which can be targeted to inhibit dimerization and promote degradation	Wendt <i>et al.</i> , 2007; Qi <i>et al.</i> , 2016, (64,65)
Mitosis-related protein inhibitors	Indinavir	Interacts with aurora-b and affects the survivin-XIAP complex	Martínez-García <i>et al.</i> , 2019, (66)

NSCLC, non-small cell lung cancer; SMAC, second mitochondrial-derived activator of caspases.

irinotecan), showed a decrease in downstream markers of the survivin signaling pathway when studied *in vitro* in human lung cancer cell lines. This resulted in the inhibition of cell growth, reduced invasion capacity, and resistance-associated proteins (61). SMAC is an apoptosis mediator released from mitochondria that releases caspase-9 after binding to IAPs. Overexpression of survivin can sequester SMAC, leading to the inhibition of its pro-apoptotic function. SMAC mimetics such as UC-112 and its analogs act as competitive binders to survivin, thereby facilitating the liberation of caspases to execute apoptosis (62). Shepherdin, a protein that disrupts the guarding chaperone protein heat shock protein-90 (HSP-90) from survivin, affects the stability and function. Administration of Shepherdin induced tumor cell death in both *in vitro* and *in vivo* experiments with human cell lines in mice (63). An *in vitro* study identified a compound, LQZ-7F, which targets survivin dimerization cores resulting in survivin degradation and reduced tumor growth, as noted in human cancer cell lines and xenograft mouse models (64).

### Indirect survivin inhibitors

A novel tyrosine kinase inhibiting compound, named SP101, reduced survivin expression and tumor growth in gefitinib-resistant human lung cancer cells xenografted into mice (69). An experiment conducted on human lung cancer cell lines (A549 cells) showed survivin downregulation and apoptosis prevention in the presence of sulindac and simvastatin, mediated by the Akt signaling pathway. This

study also showed suppression of Akt or PI3K inhibitor, LY294002 acts synergistically with sulindac and simvastatin resulting in enhanced apoptosis (70). Src homology phosphotyrosyl phosphatase 2 (SHP-2) is an important domain in cytokine growth and migration, with a role in lung cancer cell resistance to cisplatin. Tang *et al.* studied the protective effect of it in H446 cell lines and noted that, the cells that overexpressed SHP-2 also led to significant survivin upregulation along with Akt and pAkt (71).

Jin and colleagues postulated that deguelin, a natural plant-derived compound, has the potential to suppress survivin expression and trigger apoptosis in both premalignant and malignant cells. This effect is primarily achieved through modulation of the mTOR pathway, with Akt and adenosine monophosphate-activated protein kinase (AMPK) regulation serving as key mediators (72). Amid recent reports of anti-cancer activity, the antidiabetic drug metformin also showed a decrease in survivin expression in A549 & H460 cell lines *in vitro*. This is attributed to AMPK activation along with suppression of protein kinase A (PKA) and glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ) activation (73). Using the same pathway is an 8-subunit chaperonin, Chaperonin-containing TCP-1 (CCT) promoted chemoresistance and enhanced metastasis, as seen in the *in vitro* study conducted on human lung cancer cell line CL1-5 (74).

Therapeutic agents with the potential to disrupt survivin-mediated apoptotic processes may be strategically integrated into chemotherapy protocols, thereby augmenting the sensitivity of these treatment regimens. Arctigenin, a dibenzyl butyrolactone lignan, enhanced

**Table 4** Indirect survivin inhibitors

Pathway	Therapeutic agent	Action	Reference
PI3K/Akt	LY294002	Both anti-apoptotic and cell survival inhibiting, p53 independent heat sensitizer	Peng <i>et al.</i> , 2006, (67)
	Dihydromyricetin	A compound from <i>Ampelopsis grossedentata</i> with EGFR-related anti-tumor activity	Yu <i>et al.</i> , 2021, (68)
	SP101	Survivin suppression in tumor cells and xenograft along with efficacy against gefitinib-resistant cell lines	Kim <i>et al.</i> , 2015, (69)
	Simvastatin	Synergistic effect with LY294002 and sulindac	Hwang <i>et al.</i> , 2011, (70)
	Src homology phosphotyrosyl phosphatase 2 (SHP2)	Response in cisplatin-resistant cell lines mediated by survivin	Tang <i>et al.</i> , 2018, (71)
	Deguelin	In vitro experiments show downregulation of survivin mediated by Akt	Jin <i>et al.</i> , 2007, (72)
	Metformin	Downregulates survivin in in vitro lung cancer cells	Luo <i>et al.</i> , 2019, (73)
	Chaperonin-containing TCP-1 (CCT)	Increases chemoresistance and metastasis by regulating survivin	Chang <i>et al.</i> , 2020, (74)
JAK/STAT	Arctigenin	Enhances chemosensitivity to cisplatin through this pathway	Wang <i>et al.</i> , 2014, (75)
	Ritonavir	Causes G0/G1 arrest and apoptosis by regulating survivin. It has synergistic actions with several chemotherapy agents	Srirangam <i>et al.</i> , 2011, (76)
	T21	Natural-based compound regulating survivin, tested on human cell lines from resected tumor tissue	Martínez-García <i>et al.</i> , 2019, (77)
mTOR	Docetaxel	Docetaxel increases cytotoxicity and has synergistic activity with mTOR inhibitors	Niu <i>et al.</i> , 2011, (78)
CDK2/4	Fascaplysin	Downregulates survivin and HIF-1 $\alpha$ , resulting in suppression of tumor growth in xenograft tumor tissues	Oh <i>et al.</i> , 2017, (79)
P38 MAPK	COX 2 inhibitors	Induces IL-6 which regulates survivin expression via cascade	Dalwadi <i>et al.</i> , 2005, (80)
P53 signaling	Matrine	Causes mitochondrial apoptosis in cisplatin-resistant tumors	Liao <i>et al.</i> , 2017, (81)
	Phoyunnanin E	Plant-based protein induces apoptosis in H460 lung cancer cells by downregulating survivin	Phiboonchaiyanan <i>et al.</i> , 2018, (82)

PI3K, phosphatidylinositol 3-kinase; JAK-STAT, Janus kinase-signal transducer and activator of transcription; mTOR, mammalian target of rapamycin; CDK2/4, cyclin dependent kinase 2/4; MAPK, mitogen-activated protein kinases; EGFR, endothelial-derived growth factor; HIF-1 $\alpha$ , hypoxia-inducible factor 1-alpha.

cisplatin-mediated apoptosis in NSCLC H460 cells., by significantly downregulating survivin and inducing G1/G0 cell cycle arrest (75). Anti-retroviral agent Ritonavir, with some evidence of anti-cancer activity, is noted to be active across a wide range of lung adenocarcinoma cell lines, by STAT3-mediated survivin suppression. It is also shown to have a synergistic effect with standard lung cancer regimen gemcitabine + cisplatin (76). Likewise, mTOR inhibitors enhance the effectiveness of docetaxel, by synergistically reducing survivin levels and increasing apoptosis in human lung cancer cell lines A549 and SPC-A-1 (78). Fascaplysin,

which is thought to be a CDK4 inhibitor, reduced survivin protein expression but not mRNA, in a time and dose-dependent manner, thereby increasing the cell viability and inhibiting angiogenesis (79).

Not all the agents identified above could progress to clinical trials because these therapeutic agents and the trials had their limitations. The phase II trial looking at the effect of YM155, although proved the safety profile, showed only a marginally improved disease control rate compared to the standard chemotherapy (60). The sample was too small to examine the correlation between survivin downregulation



**Table 5** Ongoing phase I and phase II clinical trials

Study title	ID	Investigator/sponsor	Website address
Study of an Immunotherapeutic, DPX-Survivac, in Combination With Low Dose Cyclophosphamide & Pembrolizumab, in Subjects With Selected Advanced & Recurrent Solid Tumors	NCT03836352 active, ongoing	ImmunoVaccine Technologies, Inc. (IMV Inc.)	<a href="https://clinicaltrials.gov/study/NCT03836352">https://clinicaltrials.gov/study/NCT03836352</a>
Survivin Long Peptide Vaccine in Treating Patients with Metastatic Neuroendocrine Tumors	NCT03879694 active, ongoing	Roswell Park Cancer Institute-Renuka V. Iyer	<a href="https://clinicaltrials.gov/study/NCT03879694">https://clinicaltrials.gov/study/NCT03879694</a>
A Phase I/II Study of Paclitaxel, Carboplatin and YM155 (Survivin Suppressor) in Subjects with Solid Tumors (Phase I) and Advanced Non-Small Cell Lung Carcinoma (Phase II)	NCT01100931 completed	National Institutes of Health Clinical Center	<a href="https://clinicaltrials.gov/study/NCT01100931">https://clinicaltrials.gov/study/NCT01100931</a>
Survivin and Fibulin-3 in Benign and Malignant Respiratory Diseases	NCT04413292 completed	Mohammed H. Hassan, South Valley University	<a href="https://clinicaltrials.gov/study/NCT04413292">https://clinicaltrials.gov/study/NCT04413292</a>

and clinical response. Most of the indirect survivin inhibitors act by affecting one of the many survivin signaling pathways, due to which the pre-clinical observations are not translated into effective clinical responses. This occurs when the targeted pathway is bypassed by another compensatory mechanism (83). This validates the idea of using combination agents with synergistic effects, which could also help in reducing dose, reducing systemic toxicity, and enhancing patient benefit.

### Survivin as an immunotherapy target

Studies were undertaken to investigate whether the survivin protein expressed by tumor cells exhibits immunogenicity comparable to the products of proto-oncogenes and tumor suppressor genes. A high prevalence of anti-survivin antibodies was noted in sera from the patients of lung cancer (84). Schmitz *et al.* showed that dendritic cells loaded with survivin-specific peptides *in vitro* generated widespread cytotoxic T-cell responses against multiple tumor cell lines (85). Therefore, survivin's potential immunogenicity to provoke both T-cell mediated, and humoral immunity could serve as a foundation for eliciting therapeutic anti-tumor immunity for cancer patients. In such an attempt, a DNA-based vaccine was developed by fusion of soluble PD-1, tumor antigens, survivin, and MUC1 which produced anti-tumor immune CD8<sup>+</sup> T cell responses (86). This marked the beginning of the exploration for clinical trials aimed at inducing anti-tumor immune responses as a potential therapy for lung cancer. Later, Xiang *et al.* developed a DNA vaccine with chemokine CCL21 co-expression and proved that this vaccine could suppress angiogenesis and result in the eradication of lung tumors (43). Similar

vaccines were tried on several tumors and promising results were seen in oral, colorectal, breast, and melanoma. A survivin long peptide vaccine, SurVaxM was studied in patients with malignant glioma, and immunogenicity, safety, and tolerability were demonstrated (87).

The current survivin-based therapies are primarily directed towards mitigating multi-drug resistance and advanced metastatic cancers, with reasonable success in *in vitro* and *in vivo* studies. An avenue that is still open to investigate would be mediators of survivin regulatory pathways useful for chemo-immunoprevention. Given its dual role in regulating tumor growth and modulating immune responses, survivin stands out as a highly promising target for investigation. Exploring this avenue will require high-standard clinical studies that show efficacy in not merely decelerating the cancer progression but also laying the path for cancer prevention.

### Future directions

Further exploration and advancement of survivin-targeted therapies through rigorous clinical trials are essential. Simultaneous studies on combinational therapies and newer drug delivery systems need to be planned for enhanced therapeutic efficacy.

Continuation of research into survivin-based immunotherapies, including vaccines and immune checkpoint inhibitors, can harness the body's immune response to effectively target lung cancer cells with limited systemic toxicity.

Further understanding of the molecular and cellular mechanisms of survivin regulation could uncover new therapeutic avenues and potential drug regimens for

immuno-prevention before the onset of carcinogenesis or slow progression for premalignant lesions of lung cancer.

## Conclusions

Survivin plays a distinct role in cell division and programmed cell death. The transcription, interactions, and signaling have been extensively studied to be used in the management of multiple cancers. Survivin is selectively upregulated in malignant cells, making it a potential target for therapy and a molecular marker for early diagnosis. Several tumor-specific transcriptional and post-translational therapeutic modalities with good safety profiles have been described. This knowledge of survivin-regulated pathways can be harnessed to revolutionize the fields of lung cancer prevention and treatment of advanced-stage cancers. Further phase II and III trials need to be planned with the objective of targeted therapy based on individual tumor histological findings, laying special emphasis on vaccines, immunotherapy, and gene targeting, for highly selective tumor-specific action, and limited systemic side effects, to increase survival in patients of lung cancer.

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