Review

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Survivin as a Therapeutic Target for the Treatment of Human Cancer

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Simple Summary: Survivin is preferentially overexpressed in a variety of human cancers and is associated with increased, tumor recurrence, chemotherapy resistance, and shorter patient survival. Recent studies show that survivin plays a role in regulation of cell division and programmed cell death. Survivin has been proposed as a potential target for cancer therapy and various approaches have been investigated for survivin inhibition. Here we review our current understanding of the role of survivin in promoting malignancy and the strategies for development of survivin-targeted therapy for cancer.

Abstract: Survivin was initially identified as a member of the inhibitor apoptosis (IAP) protein family and has been shown to play a critical role in regulation of both apoptosis and mitosis. Survivin has emerged as an attractive target for cancer therapy because its overexpression has been found in most human cancers and is frequently associated with chemotherapy resistance, recurrence, and poor survival rate in cancer patients. In this review, we discuss our current understanding of how survivin mediates various aspects of malignant transformation and drug resistance, as well as efforts that have been made to develop therapeutics targeting survivin for the treatment of cancer.

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Survivin and Cancer

Survivin overexpression has been found in most human cancers and is associated with poor prognosis [1–8]. In particular, high levels of survivin expression are linked with metastasis of various forms of human cancers, including presence in circulating tumor cells [9–13]. Overexpression of survivin can facilitate bypassing of cell cycle checkpoints and promote survival of aneuploid cells [14,15]. Survivin renders cancer cells resistance to radiation [16,17].

While survivin plays an essential role in early embryogenesis [18,19], its expression levels are very low or undetectable in adult tissues, and usually restricted to stems cells and progenitor cells [15,20–23]. As shown in conditional knockout mice, survivin is required for T cell development and homeostasis, and triggers p53-dependent cell cycle arrest [24,25]. Similarly, suvivin also plays an essential role in B cell expansion [26]. Moreover, survivin is essential for pancreatic beta cell expansion [27–29], early brain development [30], and intestinal epithelial progenitor cells [31].

Survivin, encoded by the *BIRC5* gene, is a polypeptide of 142 amino acid residues. The transcription of the *BIRC5* gene is mediated through a TATA-less promoter that contains multiple Sp1 sites, a CpG island subjected to potential epigenetic modifications, and canonical CDE/CHR boxes that mediate cell cycle-dependent gene expression [32,33]. Survivin is up regulated by multiple pathways that are commonly activated in human cancers, such as EGFR, p185Her2/neu, PI-3 kinase, MAPK, NF-κB and mTOR [34–38]. The transcriptional events from the survivin promoter can also be modulated by Wnt/β-catenin [39], notch [40], YAP [41] and hedgehog signaling pathways [42,43]. In addition, survivin is regulated by Forkhead box m1 (Foxm1), a transcriptional factor critical for G1/S

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transition and mitotic progression [44]. Conversely, survivin expression can be downregulated by several tumor suppressors, such as TP53, PTEN, Rb, and BRCA1 [45–48], which are frequently silenced in human cancers.

At least five splicing variants of survivin have been described, which include survivin-ΔEx3 [49,50], survivin-2α [51], survivin-3α [52], survivin-2B [53], and survivin-3B [54]. The differential splicing events lead to generation of proteins with shortened BIR domain, or truncated polypeptides that do not have the intact NES or the coiled coil region in the c-terminus, which can exhibit distinct localization patterns. For example, survivin-Ex3 lacks the NES but contains a distinct bipartite nuclear localization signal (NLS) that mediates its localization to the nucleus [49]. In contrast, in survivin-2B, the BIR motif is interrupted by an in-frame insertion of a cryptic exon, generating a protein predominantly localized to the cytoplasm. Survivin-Ex3 and survivin-2B showed reduced affinity to CPC and cannot compensate for loss of survivin functions [54]. The survivin splicing variants have been reported to associate with certain transformed phenotypes and clinical outcome [55].

Role of Survivin in Cell Division

Survivin plays an essential in cell division, and loss of survivin leads to mitotic failure and cell death [32,56,57]. Survivin participates in mitotic checkpoint regulation, as a component of the chromosomal passenger protein complex that also includes Aurora kinase B, INCENP, TD-60, and Borealin [58]. The BIR domain of survivin can interact with a mitotically phosphorylated form of histone H3, which leads to recruitment of the other CPC proteins to the inner centromere [59–61]. Interference with the survivin-histone H3 interaction leads to mis localized aurora kinase B and mitotic defects [59–61]. Upon entry into mitosis, survivin is localized to the kinetochore in a manner that is dependent on inner centromere protein (INCENP) and cooperates with Aurora kinase B other CPC proteins to mediate spindle formation and proper chromosome alignment [62,63].

When chromosome segregation occurs at the initiation of anaphase, survivin is separated from the kinetochore but remains in the spindle midzone, subsequently becoming associated with the midbody. The molecular mechanism involved in the relocation of survivin to the midbody is not well understood. Nonetheless, survivin has been shown to interact with non-muscle myosin II and the midbody-localized survivin is implicated in playing a role in the formation of the contractile ring during cytokinesis [64]. Because of its essential role in mitotic checkpoint and cytokinesis, survivin abnormality is commonly accompanied with aneuploidy. Notably, loss of p53 function is required for re-entry to the cell cycle following depletion of survivin [65,66].

Role of Survivin in Apoptosis

Survivin was first identified as a member of the Inhibitor-of-Apoptosis (IAP) protein family, also known as the Baculoviral IAP repeat containing (BIRC) proteins, based on the presence of a Baculovirus IAP Repeat (BIR) in the N-terminus [32,56]. The IAP family proteins share the common feature of having at least one BIR domain, which consist of ~70 amino acid residues and are involved in mediating protein-protein interactions [67]. While ablation of survivin can lead to apoptosis, overexpression of survivin can protect cells from apoptosis under various experimental conditions [32,56,68,69].

Some IAP family proteins can inhibit apoptosis by directly bind to the activated form of caspase and abolish its activities [70,71]. For example, the second BIR domain and a linker region of XIAP can directly bind to caspase and block substrate access [72–75]. In addition, some IAPs also contain either a RING domain - which functions as an E3 ubiquitin ligase – or a ubiquitin-associated domain, which mediate ubiquitin-mediated proteolytic degradation of caspase [76]. In comparison, survivin contains only a BIR domain and, to date, no compelling evidence is available to show that survivin can directly bind and inhibit caspase activities.

Survivin has been reported to bind to DIABLO/SMAC [77,78], a mitochondrial protein that can potentiate certain forms of apoptosis, by blocking the action of IAPs and thereby activate caspases [79,80]. Thus, survivin may inhibit apoptosis by neutralizing an IAP antagonist, namely,

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DIABLO/SMAC. However, it remains to demonstrate the survivin-DIABLO interaction indeed participate in protection from apoptosis [81].

Role of Survivin in Mitochondrial Function and Autophagy

Survivin has been shown to inhibit mitochondrial-dependent apoptotic events [69]. It has been reported that the N-terminus of survivin contain a mitochondria-targeting sequence that can direct protein localization to the mitochondria when fused with a reporter protein [82]. Interestingly, survivin can be detected in the mitochondrial fraction in cancer cells but not in non-transformed cells [83,84]. Overexpression of mitochondria-targeted survivin can protect cells from apoptosis and enhance transformation, which may involve its binding to another IAP family member XIAP [83,85]. Localization of survivin to the mitochondria can also promote cancer cell invasion and metastasis [86]. Overexpression of survivin appears to alter the dynamic of mitochondrial fission and fusion [87], or inhibit mitophagy [84].

Paradoxically, it has been reported that both knockdown [86] and overexpression of survivin [84,87] can disable mitochondrial functions and reduce oxidative phosphorylation in cancer cells. It should be noted that the studies of the mitochondrial survivin were conducted using a fusion protein of survivin with the mitochondrial targeting sequence of cytochrome c and the knockdown approach used in the study does not specifically target the mitochondrial pool of the protein [83,84,86].

Survivin has been reported to physically interact with several proteins that are involved in autophagy. For example, beclin was found to bind to survivin, which may be involved in regulating survivin protein levels [88]. Intriguingly, ATG5 can form a complex with survivin in the nucleus upon exposure to DNA damage, leading to mitotic catastrophe in an autophagy-independent manner [89]. Conversely, the interaction between survivin and ATG5 may also impact on autophagy-mediated events responsive to DNA damage [90]. Ectopic expression of survivin enables autophagy, which renders the cells more sensitive to inhibition of glycolysis [91]. However, these observations were made only in cell lines with ectopic expression of survivin.

Survivin Localization

Survivin contains a nuclear export signal (NES) that binds to the nuclear export receptor Crm1, which is required for survivin cytoplasmic localization during the interphase [49,92–94]. Alteration of the NES, which is located between BIR and the c-terminal coiled coil structures, can disrupt survivin's nuclear export and localization to the kinetochore and midbody, but not homodimerization or binding to several CPC proteins [93–95]. The shift from a cytoplasmic localization pattern to a nuclear one caused by the NES mutations is associated with loss of survivin function to protect cells from apoptosis induced by genotoxic damage or external stimulus [92,94]. In addition, nucleus-directed survivin protein appears to enhance cancer cell sensitivity to apoptosis [96,97].

These observations led to the notion that cytoplasmic survivin is primarily involved in protection from apoptosis. However, it should be noted that the survivin localization patterns in the cytoplasm or nucleus may not a reliable biomarker for clinical outcomes, as it has been linked to both favorable [98–100], pancreatic cancer [8], and unfavorable prognosis of cancer patients [101–106].

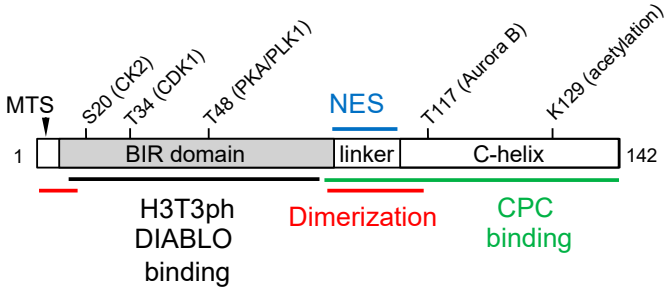

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Figure 1. Schematic representation of survivin structure features involved in dimerization (red), chromosome passenger complex (CPC) binding (green), histone H3 threonine 3 phosphorylated peptide (H3T3ph) and DIABLO binding (black), nuclear export (NES, blue), and mitochondria targeting (MTS, arrowhead). The amino acid residues that have been reported to be modified by acetylation or phosphorylation, as well as the kinases involved, are also indicated.

Survivin Protein Structure and Post-Translational Modification

The survivin protein structure in the form of a homodimer has been determined by both crystallography [107–109] and by nuclear magnetic resonance (NMR) [110]. The N-terminal BIR domain consists of a three-stranded β-sheet and four α-helices, with a zinc-binding fold, and the survivin protein forms a bow-tie shaped dimer via part of the N-terminal region and the linker region between the BIR domain and the C-terminal helix [107,108]. Notably, ubiquitination of survivin on several lysine residues within the BIR domain are implicated in playing a role in modulating localization to the centromere [111].

A second structure of survivin, which features heteromeric complex with borealin and INCENP has also been resolved [112]. In this structure, the C-terminus of survivin, which contains an extended α-helical coiled-coil domain, forms a three-helical bundle with elements of borealin and INCENP in 1:1:1 stoichiometry [112]. These interactions are essential for central spindle and midbody localization of the complex.

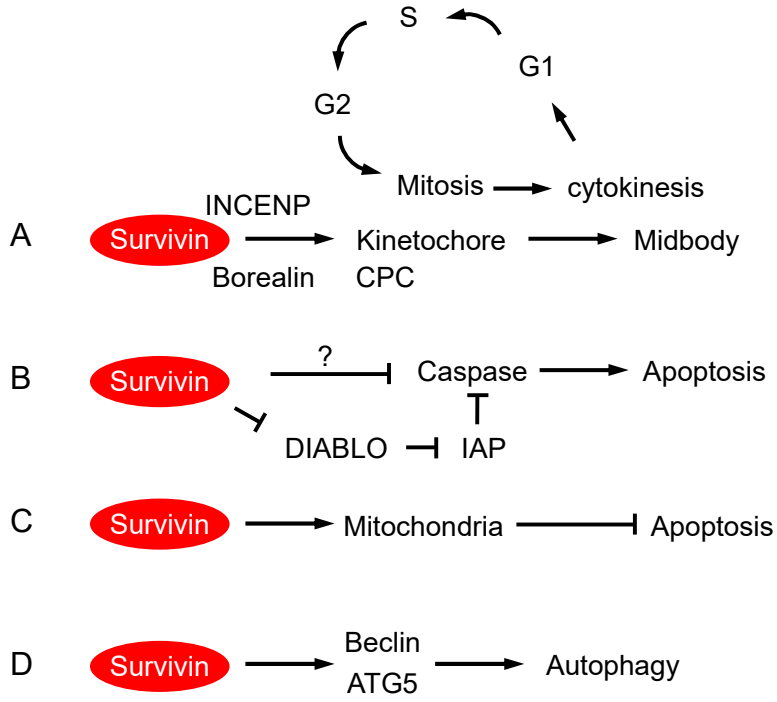

Figure 2. Functions of survivin. (A) Survivin is required for mitosis and cytokinesis. Survivin is associated with INCENP and borealin as components of the chromosome passenger complex (CPC) localized to the kinetochore during mitosis. Survivin remains associated with the spindle midbody from the anaphase of mitosis until the end of cytokinesis. (B) Survivin can protect cells from apoptosis. The binding of survivin to DIABLO may prevent the latter to inactivate other inhibitor of apoptosis (IAP) family proteins. Alternatively, survivin may directly inhibit caspase activity. (C) Survivin can be localized to the mitochondria and protect cells from mitochondria-mediated apoptosis (D) Survivin can associate with beclin or ATG5 and is postulated to be involved in aspects of autophagy.

An accumulating body of evidence show that survivin can be regulated by phosphorylation. Phosphorylation of survivin at T34 by CDK1 has been shown to be important for its anti-apoptotic role [113,114]. In addition, phosphorylation by PKA at Ser20 is also involved in protection against apoptosis by mediating the interaction with XIAP [85]. Moreover, survivin can be phosphorylated by

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aurora B at T117 and negatively regulates its localization to the kinetochore and function in mitosis [115]. CK2 can phosphorylate survivin at T48 in the BIR domain, which is critical for its mitotic and antiapoptotic functions [116]. Furthermore, PLK1 phosphorylates survivin at T20, which seems to be involved in chromosome orientation during mitosis [117].

Survivin is subject to other forms of post-translational modification. For example, survivin can be acetylated at K129, which affects its homodimerization, binding to Crm1 and nuclear export [118]. Survivin can also be modified via K48- and K63-linked ubiquitination during mitosis, which mediates survivin localization to the kinetochore and mitotic progression [111].

Therapeutic Strategies to Target Survivin

Efforts have been made in recent years to develop therapeutic strategies to disable survivin functionally. However, suvivin is an unconventional drug target, due to its unique structure and lack of enzymatic activity. Currently only a limited number of survivin inhibitors have been developed with success.

YM155, a small-molecule imidazolium-based compound identified by high-throughput screen, is one of the first selectively antagonists for inhibition of survivin expression. YM155 distinctively targets a 269-bp survivin promoter to inhibit gene transcription [119]. Preclinical research showed that YM155 can effectively decrease survivin expression in various cancer cell lines and xenografts mouse models, including prostate, non-Hodgkin lymphoma, and lung [119,120]. However, recent studies indicate that YM155 can elicit DNA damage in cell [121,122], which indicate that the compound may target other proteins and signaling events. Several phase I and phase II studies showed that YM155 generally show low toxicity but has limited antitumor efficacy when used as either a single agent or in combination with other therapeutic agents [123–128].

Several other molecules that suppress surivivn expression levels have been described. For example, FL-118 has been identified by HTS screen of a library of compound as a molecule that can reduce expression of survivin, as well as other IAP family members [129]. By using a similar approach to screen for drugs that can inhibit surviving promoter activities, a cytotoxic molecule, termed WM127, was also found to be capable of reducing survivin expression levels and causing cell cycle delay in G2/M the stage, which is accompanied with apoptosis [130]. In addition, EM-1421 (also known as terameprocol), a small-molecule that targets Sp1-dependent promoters, can reduce survivin expression levels and induce apoptosis [131]. Moreover, GDP366 is another a small molecule that can reduce survivin expression at both mRNA and protein levels [132], although the mechanism involved remains to be elucidated.

Strategies designed to reduce survivin protein stability have been reported. Based Heat shock protein 90 can bind to survivin and protect it from proteasomal degradation, and disruption of this interaction can lead to apoptosis [133]. Sheperdin, a peptidomimetic derived from the survivin region that is sufficient to bind to Hsp90, showed the ability to bind the ATP pocket of HSP90 and disrupt the interaction with several of its client proteins, including survivin [134]. This causes the degradation of survivin, among other proteins, leading to apoptosis in tumor cells [134].

In another example, by virtual screen of compounds that mimic the DIABLO/SMAC-IAP interaction, a series of small molecule IAP inhibitors have been developed [135,136]. These molecules can inhibit survivin and, to a lesser extent, XIAP, by downregulate their protein levels and showed efficacy to inhibit tumor growth [135,136]. Other small molecules that block the interaction between survivin and DIABLO/SMAC have been described and showed anti-cancer activities [137,138].

A high-throughput, affinity-based NMR screen has led to identification of several survivin-binding molecules that bind to the dimer interface [139–142]. Several of the compounds identified in the screen displayed activities to inhibit growth of tumor cells and appeared to cause cell cycle delay in the G0/G1 stage, rather in the mitotic stage [140]. One was of molecules was shown to sensitize colon cancer cells to topoisomerase inhibitor irinotecan [142].

We employed a unique structure-based approach to identify survivin inhibitors that bind directly to the protein and modulate its functions [143,144]. The method, termed as Cavity-Induced Allosteric Modulation (CIAM), was previously used successfully to develop inhibitors for other

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targets such as TNFR1[145]. With the CIAM method, we have identified a cavity close to the survivin dimeric interface. The compounds that fit into this cavity *in silico* were further tested for the ability to bind surviving protein and effect mitotic arrest, as one would expect from loss of survivn function. Several compounds identified by this approach, including S12, exhibits efficacy to inhibit growth of human cancer cell lines both *in vitro* and *in vivo* [26,43,143,144]. Notably, knockdown of YAP can increase sensitivity of cancer cell to S12 [144]. Finally, S12 can be modified and potentially used for imaging survivin in tumors by single-photon emission computerized tomography [146].

More recently, a separate group performed a virtual screen of molecules that target the survivin dimeric interface and identified a series of molecules (e.g. LQZ-7F and LQZ-7I) that can induce proteasomal degradation of survivin [147,148]. These molecules were also shown cause apoptosis and inhibit tumor growth in xenograft tumor models [147,148]. It is not clear how disruption of the survivin homodimer by these small molecule leads to reduction of protein stability.

Survivin based immunotherapy has been developed. Cytotoxic T lymphocyte (CTL) response to survivin can be detected in patients [149]. Survivin-derived, MHC-restricted T cell epitope has been identified and can be harnessed to trigger CTL response against survivin expressing cancer cells [150]. DNA vaccine encoding survivin and CCL12 can trigger strong immune response against lung cancer cells in an animal model [151]. Recent studies showed that long synthetic peptides derived from the survivin protein can generate both cytotoxic CD8+ and CD4+ T-cell responses, leading to tumor regression and prevention of relapse in animal models [152]. In particular, the survivin peptide mimic SurVaxM showed efficacy to stimulate anti-tumor immune responses against brain tumors in animal models and early promise in clinical trials [153–155]. A whole protein survivin dendritic cell vaccine has also been developed and tested for the treatment of myeloma patients [156,157].

Conclusions and Perspective

Because of its high expression levels in most tumors and absence in most normal tissues, survivin has been considered as a promising therapeutic target. Studies in the past 25 years showed that survivin plays a vital role in regulation of cell division as a component of the CPC on the mitotic apparatus. However, despite its structural similarities to the other IAP family proteins, how survivin acts as an inhibit of apoptosis remains elusive. Studies of the survivin protein ensembles in various subcellular pools, such as the mitochondria and the interphase or mitotic cytoplasm, may unravel a mechanism by which survivin links mitotic checkpoint regulation with apoptotic pathways. Progress has been made to develop survivin-targeted therapy, including small molecules that directly bind and disable survivin. Understand the signaling pathways that mediates cancer cell sensitivity to survivin targeted therapy may help to develop more effective therapeutic strategies. Conceivably, the combination of survivin inhibition with chemotherapy or other targeted therapeutics may achieve the maximal benefit clinically.

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