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Review Article

Survivin: Transcriptional Regulation and Protein Function in Cancer

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Abstract

Survivin, the smallest Inhibitors of Apoptosis Protein (IAP) family member has essential roles in mitosis, inhibition of programmed cell death and the cellular stress response. Survivin is physiologically expressed during embryonic development where it acts by antagonizing apoptosis and promoting proliferation in the developing tissues. In terminally differentiated normal human tissues, Survivin is either undetectable or expressed at very low levels; it is however, highly expressed in all primary tumor types and is considered a predictor of tumor aggressiveness and a biomarker of poor prognosis and bad clinical outcomes. Moreover, Survivin expression is correlated with resistance to chemotherapy and radiotherapy-induced apoptosis. In this short communication we review the most important information regarding the transcriptional regulation of the survivin gene. Furthermore, we examine how the Survivin protein is implicated in cell cycle transition and how it is inhibiting apoptosis in cancer. Finally, we discuss selective therapeutic approaches targeting this small but very important gene and its protein.

ABBREVIATIONS

BIR: Baculovirus Inhibitor Repeat; BRUCE/Apollon: BIR-repeat-containing Ubiquitin-Conjugating Enzyme; CARD: Caspase Recruitment Domain; CPC: Chromosomal Passenger Complex; HBXIP: Hepatitis B X-interaction Protein; IAPs: Inhibitors of Apoptosis Proteins; ILP-2: IAP-like protein 2; INCENP: Inner Centromere Protein; MHC: Major Histocompatibility Complex; ML-IAP: Melanoma IAP; mTOR: Mammalian Target of Rapamycin; NAIP: Neuronal Apoptosis Inhibitor Protein; NF-kB: Nuclear Factor Kappa-light-chain-enhancer of Activated B cells; PTX: Paclitaxel; SMAC/DIABLO: Second Mitochondria-Derived Activator of Caspase/Direct Inhibitor of Apoptosis Protein Binding Protein with a Low Pi; TPGS: d-α-Tocopheryl Polyethylene Glycol 1000 Succinate; UBCs: Ubiquitin-conjugating Enzymes; VEGF: Vascular Endothelial Growth Factor; WT: Wild Type; XIAP: X-linked Inhibitor of Apoptosis.

INTRODUCTION

Tumor cells can become resistant to apoptosis by overexpressing certain anti-apoptotic proteins called Inhibitors of Apoptosis Proteins (IAPs). IAPs compose a class of regulatory proteins with eight family members, X-linked inhibitor of apoptosis (XIAP), BIR-repeat-containing ubiquitin-conjugating enzyme (BRUCE/Apollon), inhibitors of apoptosis1 and 2 (c-IAP1 and c-IAP2), neuronal apoptosis inhibitor protein (NAIP), melanoma IAP (ML-IAP/Livin), IAP-like protein 2 (ILP-2) and Survivin [1].

IAP family members contain one or more amino-terminal, 70-amino acid zing-finger domains, called the baculovirus inhibitor repeat (BIR) domain. XIAP, NAIP, c-IAP1 and c-IAP2 each containthree BIR domains that have different functions; in XIAP, the third BIR domain (BIR3) inhibits the activity of caspase 9, while the region between BIR1 and BIR2 specifically targets caspases -3 and -7 [2]. The RING domain contained in ILP2, Livin, c-IAP-1, c-IAP-2 and XIAP can catalyze the transfer of ubiquitin onto target proteins by recruiting E2 ubiquitin-conjugating enzymes (UBCs), leading to proteasomal degradation. c-IAP and c-IAP-2 have been associated with malignancy by promoting the degradation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) family transcriptional activators [3]. c-IAP1 and c-IAP2 also contain a caspase recruitment domain (CARD); regardless, these proteins have not been found to directly bind caspases.

IAPs are implicated in the regulation of apoptosis in cancer cells by inhibiting the activation of caspases [4]. The activity of IAP family members can be modulated by pro-apoptotic factors released by mitochondria. Smac/DIABLO and Omi/HtrA2, for example, inhibit the caspase-inhibitory effects of XIAP during the progression of apoptosis. Aberrant IAP levels are commonly observed in many human cancer types and are associated with

chemoresistance, disease progression and poor prognosis [4,5]. For example, c-IAP1, c-IAP2, NAIP, XIAP and Survivin have been found to be overexpressed in breast cancer cells [6]. In addition, in low and high grade pancreatic intraepithelial neoplastic lesions and pancreatic ductal adenocarcinomas, c-IAP2 is overexpressed and is considered an early event in the progression of pancreatic cancer [7]. XIAP is overexpressed in esophageal cancer tissues; this may lead to resistance to apoptosis by inhibiting the activation of caspase-3 [8].

Survivin, comprised of just 142 amino acids, is the smallest IAP family member, containing a single BIR domain [9]. Survivin is encoded by the BIRC5 gene located on chromosome 17q25. It consists of 14,796 nucleotides including 4 exons and 3 introns. In addition to the wild type Survivin, there are six known slice variants, Survivin-ΔEx3 (removal of exon 3), survivin-2b (inclusion of part of intron 2), survivin-3b (inclusion of part of intron 3), survivin-2a (insertions of exon 1 and 2 at the 5' end of intron 2), survivin-2b +32 (intronic sequence of 2b plus 32 additional nucleotides from intron 2) and Survivin-image (part of the *survivin* gene, part of the image gene of eye cancer plus 7 bp). Survivin isoforms have different expression patterns and cellular localization and can heterodimerize with WT Survivin [10]. The expression of Survivin-2b and Survivin-ΔEx3 variants is correlated with tumor grade [11].

TRANSCRIPTIONAL REGULATION AND LOCALIZATION OF SURVIVIN IN CANCER CELLS

The regulation of the transcription of the *survivin* gene is a highly complex process that involves numerous players implicated in developmental, cell proliferation, or cell survival pathways. At the transcriptional level Survivin is repressed by established tumor suppressor genes such as p53 [12], PTEN [13] and BRCA1-SIRT1 [14]. In normal cells, WT p53 directly or indirectly represses Survivin transcription and p53 is considered a regulator for Survivin [12,15]. In cancer cells, often these tumor suppressor genes are non-functional, leading to Survivin overexpression. For example mutations in the *p53 gene* and its functional losses has been positively correlated with the up-regulation of Survivin [16].

The upregulation of Survivin in cancer cells is partly attributed to the aberrant activation of upstream signaling pathways. Most notably, Survivin expression is up-regulated at the transcriptional level by NF-kB [17]; NF-kB activation can be achieved indirectly by growth factors via the PI3K/AKT pathway [18-21]. Activated p-AKT can phosphorylate both IKK and p65 (RELA). The activation of IKK leads to enhanced phosphorylation of IκB, followed by its ubiquitylation and degradation by the 26S proteasome. This frees the NF-κB p50 and p65 subunits to be transported to the nucleus, bind to the Survivin promoter region, and activate transcription [22]. In addition, other survival pathways including MEK/MAPK and mTOR have been found to induce Survivin expression in Chronic myeloid leukemiaand glioblastoma respectively [23,24]. Hypermethylation of the Survivin promoter inhibits the binding of p53 and leads to overexpression of the Survivin protein in endometrial tumors [25]. Gene amplification of the *surviving* locus on chromosome 17q25 has been reported to promote cell survival in human neuroblastoma. [26] Increased promoter activity has been shown to induce Survivin overexpression in cancer cells. Thus, a 269-bp *surviving* core promoter was highly active and specific for driving target gene expression in cancer but not normal cells [27].

The Survivin protein, depending on its localization, may exert different functions. Thus, cytosolic Survivin acts as an anti-apoptotic protein, while nuclear Survivin is responsible for regulating cell cycle division as described below. Although high Survivin levels have been correlated with worse disease outcome, the importance of nuclear Survivin in the progression of cancer is still unclear [28]. In addition, Survivin is located in the mitochondria and is released into the cytosol following cellular stress to suppress caspase-3 and caspase-9 activation and to inhibit apoptosis [29]. Tumor cells may also secrete Survivin, which localizes extracellularly in exosomes [30]. Survivin-containing exosomes can be taken up by other cells and increase invasiveness, proliferation and chemoresistance [31]. In fact, in the plasma of prostate cancer patients, high levels of exosomal Survivin have been associated with disease severity [32].

SURVIVIN'S ROLE IN REGULATING THE CELL CYCLE

The role of Survivin in the regulation of the G2/M phase of the cell cycle is well established. Survivin functions as a subunit of the chromosomal passenger complex (CPC) during cell division; it localizes on the kinetochores of metaphase chromosomes and associates with regulators of cytokinesis, such as Inner Centromere Protein (INCENP), Aurora B kinase and Borealin/Dasra [33-36]. Consequently, Survivinis essential for proper chromosome segregation and cytokinesis. The CPC regulates the attachment of chromosomes to microtubules and ensures fidelity in microtubule-kinetochore attachment; this is achieved via phosphorylation of target substrates by Aurora B. Survivin is responsible for the localization of Aurora B to the inner centromere, and is therefore essential for the proper CPC checkpoint function [37].

Furthermore, growing evidence suggests a role for Survivin in promoting cancer cell transition at the G1/S phase and proliferation. Survivin down regulation and knockdown led to G1 arrest in breast cancer cells [38]. Survivin translocates to the nucleus and initiates the cell cycle entry by direct interaction with p21/CDK4, leading to release of p21 and activation of Cdk2/Cyclin E [39,40]. It has also been reported that Survivin inhibits the expression of p21 by physically interacting with p53 on the two p53-binding sites in the p21 promoter, thereby neutralizing p53-mediated transcriptional activation of the p21 gene in cancer cells, suggesting that it may act as a transcriptional repressor [41]. The role of Survivin in regulating the transition of the G1 to the S phase remains unclear.

SURVIVIN'S ROLE IN REGULATING APOPTOSIS

IAPs were originally characterized as physical inhibitors of caspases, providing a cytoprotective step downstream of the exogenous or endogenous pathway of apoptosis [42]. Further studies revealed, however, that only XIAP can directly bind and inhibit caspases [43]. The anti-apoptotic mechanism of Survivin has not been thoroughly characterized. Even though

Survivin does not contain a Caspase Recruitment Domain, it has been suggested that itcan bind directly tocaspase-9in HeLa cells [44]. In addition, immunoprecipitation experiments using 293T human kidney cells showed that Survivin may inhibit the activation of caspase-9 by forming a complex with hepatitis B X-interaction protein (HBXIP). This was demonstrated by a yeast two-hybrid cDNA library screening assay using Survivin as bait. The BIR domain was indispensable for binding of Survivin fragments to HBXIP *in vitro*. Survivin-HBXIP complexes bind the inactive pro-caspase-9, preventing its recruitment to Apaf1 and consequently the formation of the apoptosome [45]. Survivin was immunoprecipitated with active caspases -3 and -7 but not with their inactive form; this interaction disrupts caspase-mediated substrate cleavage (and also blocks active caspases from cleaving their own pro-forms), and thereforeit inhibits apoptosis [46]. In experiments with *in vitro* lysates, Survivin was able to inhibit cytochrome-c and caspase 8 activation, and prevent the cleavage of substrates containing the DEVD sequence [46].

Survivin may also inhibit apoptosis by facilitating the stabilization of other IAP family members. In MCF-7 cells, Survivin creates an IAP-IAP complex with XIAP in order to enhance XIAP stability against ubiquitin-dependent degradation, and increase the activity of XIAP for caspase inhibition [47]. Furthermore, using HeLa cells, it has been shown that Survivin acts cytoprotectively by sequestering pro-apoptotic Smac/DIABLO away from XIAP [48], or by preventing its release from mitochondria [49]. Some reports also implicate Survivin in CI-PCD. Survivin targeting precedes translocation of AIF from the mitochondria to the nucleus and mediates caspase-independent DNA fragmentation in melanoma cells [50]. The major findings concerning Survivin are summarized in Figure 1.

THERAPEUTIC STRATEGIES TARGETING SURVIVIN: CURRENT AND FUTURE PERSPECTIVES

Since overexpression of Survivin in cancer cells conveys a proliferative and survival advantage, and leads to chemoresistance, it has become an attractive target for re-sensitizingcells to chemotherapy or targeted therapeutics. For example, the therapeutic potential of Survivin with special reference to squamous cell carcinoma (SCC) has been nicely presented in a recent review article [51]. Several therapeutic strategies have been developed over the years for targeting Survivin in cancer cells, including vaccines, small-molecule inhibitors, small interfering RNAs, antisense oligonucleotides, ribozymes and dominant negative mutants of Survivin [52].

Because Survivin is immunogenic, it is an ideal candidate for cancer immunotherapy. Following degradation of the protein from the proteasome, Survivin epitopes are presented by major histocompatibility complex (MHC) molecules on the surface of tumor cells to T cells for activation [53]. Antibodies against Survivin have also been detected in the serum of lung and colorectal cancer patients and may be used as marker for the diagnosis of the disease [54]. Importantly, T-cell reactivity against Survivin epitopes was detected in tumor-infiltrated lymph nodes from melanoma patients and in the peripheral blood from chronic lymphatic leukemia patients, while no response was detected in

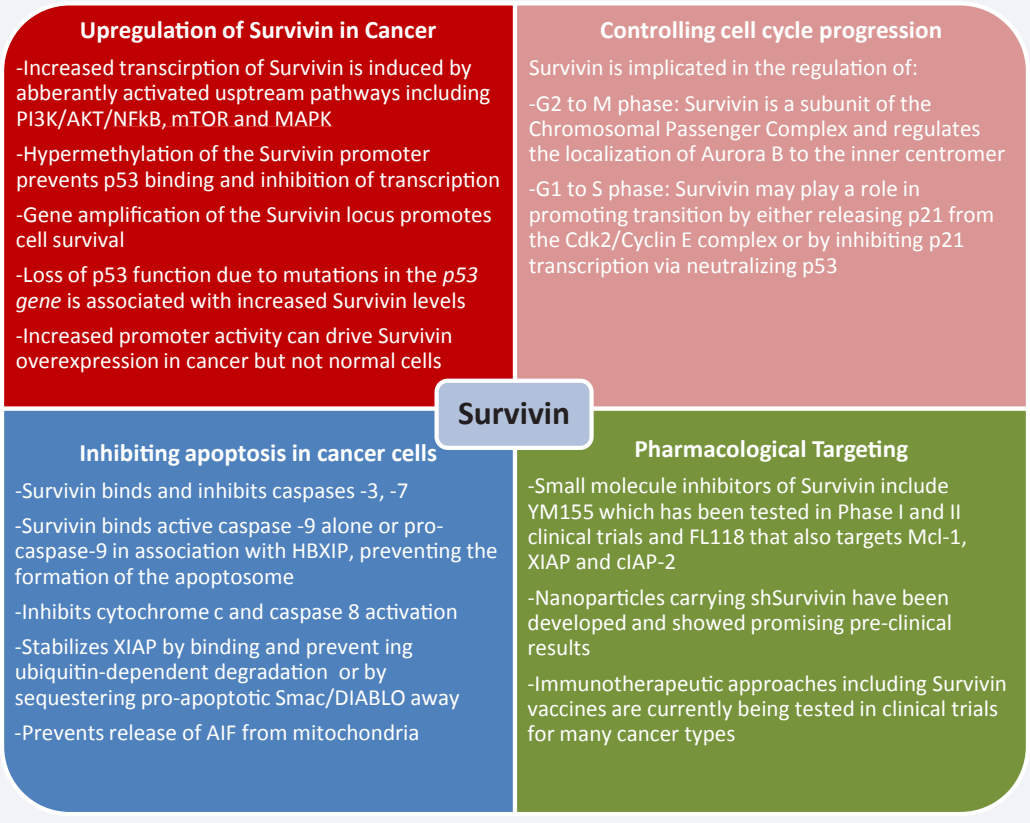

Figure 1 Transcriptional regulation of Survivin, its major roles in cancer and recent advances in its pharmacological targeting.

peripheral blood lymphocytes from healthy donors [55]. This suggests that the immune response against Survivin is tumor specific. Vaccine approaches to target Survivin are currently in clinical trials. A conjugated Survivin peptide-mimic containing amino acids 53-67 of the Survivin protein, SurVaxM, induced both cellular and humoral immune responses in patients with recurrent malignant glioma [56]. Survivin vaccines are being tested in multiple myeloma, glioblastoma, renal cell carcinoma, prostate, non-small cell lung and breast cancer patients. Even though preclinical studies of vaccines against Survivin have shown effective anti-tumor responses *in vivo*, the immunogenicity may not be high enough to eliminate tumor cells. Future approaches should therefore focus on effective antigen delivery to enhance the immunogenicity of Survivin.

Small molecule approaches to target Survivin have been developed and are being tested in pre-clinical and clinical studies [57]. One disadvantage in the use of small molecule inhibitors is the fact that they need to disrupt protein-protein interactions (PPIs) between Survivin and other proteins which is challenging because most interphases between proteins are not suitable for small molecule binding. In addition, most Survivin small molecule inhibitors do not directly target Survivin but other biomolecules to reduce Survivin levels. A successful small molecule inhibitor of Survivin, YM155 binds to the *surviving* promoter and inhibits transcription [58]. YM155 induces apoptosis in various human cancer models [58] and has entered phase I and phase II clinical trials. Rapamycin, a mammalian target of rapamycin (mTOR) inhibitor, and YM155 exerted a synergistic effect in oral squamous cell carcinoma *in vitro* and *in vivo*. Rapamycin and YM155 inhibited Survivin and vascular endothelial growth factor (VEGF) through the mTOR pathway [59]. Another promising small molecule inhibitor of Survivin that also targets Mcl-1, XIAP and cIAP-2 is FL188. This molecule is currently being developed for clinical testing with reduced toxicity and increased bioavailability [60].

Although Survivin is highly expressed in cancer tissue, it is also present at low levels in normal cells and this may cause a complication in targeting Survivin. Thus, a functional role of Survivin has been demonstrated in T cells, vascular endothelial cells, hematopoietic progenitor cells, polymorphonuclear cells, erythroid cells, and liver cells [61]. Hence therapeutic approaches aimed at targeting Survivin could have adverse consequences and must be carefully considered. Regulating the transcription of Survivin specifically in cancer cells may also prove challenging, as similar structural elements that promote Survivin expression have been detected in both normal and cancer tissue. An enhancer-like 3'-fragment of the CpG is land found in the transcribed region of the BIRC5 gene, stimulates the gene promoter activity both in normal and lung cancer cells [62]; regulating transcription through this sequence would therefore not affect solemnly cancer cells.

Novel approaches to overcome the non-specific effects of Survivin targeting include the development of nanoparticles for the delivery of Survivin small molecule inhibitors or shRNA for the downregulation and knockdown of Survivin specifically in cancer cells. To counter Survivin-mediated apoptosis-resistance, a liposome carrying dominant negative mutant of Survivin along with DOX was conjugated with truncated basic fibroblast growth factor (tbFGF) peptides that are overexpressed in lung cancer cells [63]. Survivin and DOX were effectively delivered, and displayed an enhanced effect, compared to the agents alone. d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)-based nanoparticles carrying Paclitaxel (PTX) as well as shSurvivin were effective in overcoming resistance to PTX in lung cancer cells [64]. Co-delivery of PTX and siSurvivin via liposomes had a synergistic effect on suppressing tumor growth and pulmonary metastasis *in vivo* [65].

CONCLUSION

The discovery of genes such as Survivin, that are selectively overexpressed in cancer cells, provide opportunities for the development of targeted cancer therapies that could eliminate tumor cells without harming normal cells, diminishing adverse effects in patients. There is great potential in the development of nanoparticles that will not only effectively deliver Survivin inhibitors to cancer cells, but will also enhance the uptake of established chemotherapeutic drugs and promote synergistic effects between them and the Survivin-targeting anticancer drugs.

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