

REVIEW

Survivin as a Potential Target for Cancer Therapy

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Abstract

In 1997 for the first time, survivin was described by Amborsini et al. as an anti-apoptotic protein. Subsequent studies revealed that survivin is a multifunctional protein that plays critical roles in several crucial cell processes such as apoptosis, cell cycle, chromosome movement, mitosis and cellular stress responses. Moreover, its over-expression in cancer cells versus normal cells is associated with chemotherapy resistance, increased tumor recurrence, and shorter patient survival. All of these features make survivin a promising target for cancer therapy. Here, we review the potential characteristics of survivin as a tumor marker.

Keywords: Survivin - cancer - antiapoptotic protein - apoptosis

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Introduction

Survivin, the protein that is also called baculoviral inhibitor of apoptosis repeat-containing 5 or BIRC5, is the smallest and last member of the Inhibitor of apoptosis (IAP) gene family (Altieri, 1994). Its function as an IAP has been conserved across evolution and its autologs have been found in other organisms such as yeast, worms and flies (Tamm et al., 1998). Alternative splicing of survivin gene results in different functional transcripts including survivin, survivin-2B, Survivin-delta-Ex-3, survivin-3B and survivin 2 α (Caldas et al., 2007). Vandghanooni et al (2011) analysed the expression level of survivin and its splice variant; survivin-deltaEx3 in tumoral and non-tumoral tissues of papillary thyroid carcinoma. They also introduced survivin and survivin-deltaEx3 as potential molecular marker in thyroid carcinomas. Interestingly, Functional assays have shown that survivin 2 α can attenuate the anti-apoptotic activity of survivin (Cheng et al., 2007). Based on this result, Kyani et al. (2014) reported that the expression of survivin 2 α is decreased in tumoral tissues.

It has been shown that survivin is a multifunctional protein that plays critical roles in several crucial cell processes such as apoptosis, cell proliferation, cell cycle, chromosome movement, mitosis and regulation of response to cellular stress (Altieri, 2013). Depending on the nature of function, survivin could be found in a monomer and/or dimer forms (Pavlyukov et al., 2011).

Cell cycle dependent expression of survivin is controlled by specific region in the promoter (Lens et al., 2006). Nevertheless, some reports showed that this gene could be ectopically expressed in response to growth factors and/or cytokines pretending its independent control of cell-cycle (Altieri et al., 2008). Several tumor suppressors like wild-type p53 (Mirza et al., 2002) and

retinoblastoma protein (Rb) (Jiang et al., 2004) repress expression of Survivin gene, while members of the Ras oncogene family, signal transducer and activator of transcription 3, and the antiapoptotic factor Wnt-2 up regulate its expression (Sommer et al., 2003; You et al., 2004).

For many years it was believed that despite during fetal development, expression of survivin in normal adult tissue is rare. But recent reports reveal survivin role in normal cell such as T-cells, hematopoietic progenitor cells, vascular endothelial cells, liver cells, gastrointestinal tract mucosa, erythroid cells, and polymorphonuclear cells (Mobahat et al., 2014). Significantly increased expression of survivin in transformed cells, suggesting a pathological role for the protein. For example, clinical study revealed that 66.6% of biopsy samples from osteosarcoma patients are survivin positive (Babaei et al., 2006).

Role of Survivin in Cancer

Survivin as a biomarker in cancer

Survivin is over-expressed in malignant tissues rather than benign and normal ones. Reports showed that different mechanisms including gene amplification, hypomethylation and upstream signalling factors influence the expression of survivin and its splice variants (Mita et al., 2008)

Over expression of survivin in various malignant tumors like oral squamous cell carcinoma (Poomsawat et al., 2014), breast cancer (Yong-Gang et al., 2010), osteosarcoma (Babaei et al., 2006), thyroid (Vandghanooni et al., 2011) and lung cancer (Mohamed et al., 2009) pretends a direct relationship between up-regulation of survivin, higher malignant grades and reduced survival rates. Based on this fact, survivin could be a suitable diagnostic and/or prognostic marker in cancer.

As an example, a study of the expression pattern of survivin and its 2 spliced variants, survivin- Δ Ex3 and survivin-2B in formalin-fixed paraffin-embedded samples of bladder tumors revealed that the expression of survivin, survivin- Δ Ex3, and survivin-2B were detected in 66.6%, 47.8%, and 54.7% of the specimens, respectively. The expression of survivin and survivin- Δ Ex3 were preferentially elevated in tumors with higher grades, while survivin-2B expression was lower in high grade tumors. Based on these findings they reported that overexpression of survivin and survivin- Δ Ex3 in bladder tumors correlates with poor prognosis of bladder cancer and suggested that survivin and its variants are suitable prognostic markers of bladder tumors (Nouraei et al., 2009).

On the other study, the expression of survivin was evaluated on osteosarcoma. Survivin gene expression was detected in 82.6% (19/23) of high-grade osteosarcomas whereas, there was no gene expression in non-tumoral bone samples as well as the normal tissues obtained from the margin of some osteosarcoma samples. These results revealed that the expression of survivin is limited to osteosarcoma cells and is associated with high-grade malignancies. Therefore, evaluating the survivin gene expression might have a potential usefulness in diagnosis and prognosis of bone tumors (Babaei et al., 2006).

Yamashit et al. (2007) also measured survivin mRNA expression in 48 early-stage breast cancer tissues and adjacent normal tissues. They reported that Survivin can be as an indicator of the recurrence of early-stage breast cancer. So, it might be used as a new marker to classify early stage breast cancer patients for more optimal treatment modalities, or it could be a promising target for therapy.

Moreover, Shariat et al. (2004) studied urine detection of survivin as a diagnostic marker of bladder cancer. They demonstrated that higher levels of urine survivin were associated with an increased risk of bladder cancer and tumors of higher grade. Survivin had the highest specificity and positive predictive value for the detection of bladder cancer across each tumor stage and grade. Urine detection of survivin is an accurate diagnostic test for bladder cancer that retains its efficiency regardless of cancer stage and grade. On the other investigation that carried out by Ziaee et al (2006) using urine survivin for diagnosing bladder cancer, they also reported that Urine survivin seems to have a higher sensitivity than urine cytology, especially in low-grade bladder cancer.

The role of survivin in apoptosis

Programmed cell death (PCD), referring to apoptosis, autophagy and programmed necrosis growth (Ouyang et al., 2012). Apoptosis not only is vital for proper development during embryonic and fetal but also is a natural defense mechanism to diminish damaged and/or unhealthy cells that arise in many ways (Mobahat et al., 2014). It strictly is regulated by the balance between pro-apoptotic and anti-apoptotic factors and on the other hand it makes the equivalence between proliferation and cell death, that is essential for maintenance of differentiated tissue (Mita et al., 2008).

Survivin also interferes with apoptosis both *in vitro* and *in vivo*, by inhibiting the activity of different caspases in cancer cell or via interaction with multiple regulators of both intrinsic and extrinsic pathways (Sung et al., 2001; Yamamoto et al., 2002). For example, it has been demonstrated that survivin binds to XIAP and after forming complex, protects XIAP against ubiquitination/ proteasomal destruction. The combination of survivin and XIAP inhibit the activation of caspase-9 while survivin alone does not show similar function (Coumar et al., 2013). This complex also activates multiple signalling pathways such as NF κ B and accelerates tumor progression *in vivo* (Altieri., 2013).

Whether survivin directly binds to caspases and consequently inhibits their function or indirectly suppresses caspases activity are not obvious yet (Coumar et al., 2013). Beside, some evidences suggest that interaction between survivin and caspases does not result caspase inactivation (Shin et al., 2001). There are two possibilities for these conflicting results, may be indicated that under certain conditions, survivin may inhibit apoptosis via caspase-independent mechanism (Mobahat et al., 2014) or may be caused by different forms of survivin being examined in different studies, as recent investigations reveal that phosphorylation of survivin at different sites (e.g. threonine 34, 48 and 117; serine 20) can drive survivin to exhibit different molecular functions (Coumar et al., 2013). For example, O'Connor et al. (2000) demonstrated that wild-type survivin binds to caspase-9 and inhibits apoptosis, moreover, they identify survivin as a substrate of p34 (cdc2) -cyclin B1 and suggested that phosphorylation of survivin on Thr(34) (T34A survivin mutant) made it unable to bind to caspase-9 in cancer cells. Another study showed that cdk1 can phosphorylate survivin at threonine 34 and this modification inhibited its mitotic function and enhanced its cytoprotective effect in cancer cells (Barrett et al., 2009). In contrast, Colnaghi et al (2010) showed that phosphorylation of survivin at Ser (20) by Plk1 kinase is essential for accurate chromosome alignment and cell proliferation.

As mentioned above, survivin is able to inhibit apoptosis by caspase-independent mechanism via AIF. AIF or apoptosis-inducing factor, translocate from the cytoplasm to nucleus and trigger caspase-independent apoptosis. Silencing survivin expression using siRNA strategies induced translocation of AIF from cytoplasm in nucleus in various cancer cells and increased cell apoptosis with no change in caspase-3 activation and Bid cleavage (Crocì et al., 2008).

Also, evidences indicate that survivin interferes with autophagy that its up-regulation inhibits autophagy, while down regulation of that promotes cell autophagy (Coumar et al., 2013)

Targeting Survivin in Cancer

Survivin, in addition of some roles that has been noted above, exhibits resistance to chemotherapeutic agents, including vincristine, cisplatin, bortezomib, tamoxifen, TNF- α and TRAIL in tumor cells (Zhang et al., 2006; Cheung et al., 2010; Ling et al., 2010; Liu et al., 2010).

Further investigation indicates that transient up-regulation of survivin by VEGF and bFGF in normal endothelial cells of blood vessels is rather responsible for tumor angiogenesis and tumor chemo-resistance (O'Connor et al., 2000; Tran et al., 2002).

There is also evidence that survivin suppresses radiation-induced apoptosis. In experiments using three colorectal cancer cell lines of different intrinsic radiosensitivity, survivin expression and radiation-induced apoptosis showed an inverse relation (Rodel et al., 2003). The same results have been reported in pancreatic, glioblastoma and melanoma cell line (Asanuma et al., 2000; Pennati et al., 2003). On the basis of these findings, through inhibition of survivin expression may be increased sensitivity to radiotherapy in cancer patients.

In the recent years, several research groups attempted to target survivin using different strategies include using small molecule inhibitors and peptidomimetic, transcriptional inhibitors such as survivin antisense oligonucleotides (ASO), gene therapy and immunotherapy (Coumar et al., 2013).

1-small molecules and peptidomimetic

YM155 (Cheng et al., 2012; Na et al., 2012; Nakahara et al., 2012), FL118 (Li, 2014), shepherdin, M4N (Castro-Gamero et al., 2013) and 5-Deazaflavin analog are some small molecules and peptidomimetics that suppress survivin by targeting it in various ways. For example YM155 and FL118 suppress survivin promoter activity (Ling et al., 2012; Coumar et al., 2013).

Shepherdin, a cell-permeable peptidomimetic, destabilizing many Hsp90 client protein such as Akt, telomerase, CDK6 and survivin through interaction with the ATP pocket of Hsp90, and subsequently induces death of tumor cells by apoptotic and non-apoptotic mechanism. (Plescia et al., 2005). M4N, as a global transcriptional repressor, by selectively targeting Sp1-regulated proteins, including survivin and cdc2, controls cell cycle, tumor progression and apoptosis (Castro-Gamero et al., 2013). Some of them are currently in the pre-clinical phase.

2- Transcriptional inhibitors (Survivin antisense oligonucleotides)

Antisense oligonucleotides (ASO) are defined single stranded RNA or DNA sequences that are 8-50 nucleotides in length, complementary to a specific RNA strand and by hybridization through Watson-Crick base pairing to the target mRNA strand, suppress the expression of the particular gene. Oligonucleotide 4003, LY2181308, SPC3042 are three generations of survivin specific ASOs that target different regions of survivin mRNA, down-regulate survivin mRNA and induce apoptosis (Olie et al., 2000; Hansen et al., 2008; Carrasco et al., 2011).

SPC3042's potency for nuclease stability and survivin inhibition is higher in comparison with earlier generations. It is shown that the down-regulation of survivin with SPC3042 induced cell cycle arrest at the G2/M phase, pronounced cellular apoptosis, down-regulation of Bcl-2 and the activation of caspase-3/-7 in prostatic cancer cells (Hansen et al., 2008).

Furthermore, down-regulation of survivin via ASO

was shown to enhance sensitivity to cytotoxic agents such as TRAIL (Azuhata et al., 2006), cisplatin (Sharma et al., 2005), taxol (Fisker et al., 2007), imatinib (Carter et al., 2006), etoposide (Sharma et al., 2005), as well as to cytotoxicity induced by radiation therapy (Sah et al., 2006).

3- Gene therapy

Cell-permeable dominant-negative survivin protein

Using dominant-negative survivin, as a mutant form, for targeting and inhibiting survivin, is one of the earliest and most successful approaches. A substitution mutation in a specific site of survivin can make a mutant form that behaves as a competitive antagonist of wild-survivin (Coumar et al., 2013). For example, substitution of Cys84 to Ala in BIR domain of survivin can disrupt its ability to inhibit apoptosis (Li et al., 1998). Further studies reported that transfection with dominant-negative mutants of survivin led to suppression of growth and increased apoptosis in gastric cancer cell lines (Tu et al., 2003), breast cancer (Mesri et al., 2001) and thymic lymphoma (Kanwar et al., 2001) animal models.

As mentioned above, Thr 34 phosphorylation of survivin, stabilizes survivin and subsequently promoting caspase inhibition (O'Connor et al., 2000). Mutation of Thr34 to Ala disable cyclin-dependent kinase, p34cdc2-cyclinB1, to phosphorylate survivin, resulting dissociation of the survivin-caspase-9 complex (Coumar et al., 2013). The use of cell permeable dominant-negative survivin in treating cancers is still clinically impractical.

Conclusions

The differential expression of survivin in malignant versus normal cells, its role in inhibiting apoptosis and its association with various cell-signalling cascades including PI3K/AKT, mTOR, ERK, MAPK, STAT, HIF-1 α , HSP90, p53, Bcl2, EGFR, VEGF (Kanwar et al., 2013) are strong reasons for development of survivin-based cancer therapeutics. A variety of methods to alter survivin or targeting it in cancer cells have emerged, although some limitation such as tumor specificity, sustainability and toxicity of treatments and durability of patient response still has remained. Based on recent advances in nanotechnology, using variable biodegradable delivery platforms like liposomes, dendrimers and polymeric nanocarriers may have overcome these limitations. However, the existing survivin targeting methods that noted in this review have only yielded partial positive response in pre-clinical and clinical trials. Survivin-targeting with chemotherapeutic drugs in combination with anti-cancer drug may be promising for cancer treatment.

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