

Review Article

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Survivin: A molecular biomarker in cancer

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Survivin, a member of the inhibitor of apoptosis (IAP) protein family that inhibits caspases and blocks cell death, is highly expressed in most cancers and is associated with a poor clinical outcome. Survivin has consistently been identified by molecular profiling analysis to be associated with high tumour grade cancers, different disease survival and recurrence. Polymorphisms in the survivin gene are emerging as powerful tools to study the biology of the disease and have the potential to be used in disease prognosis and diagnosis. The survivin gene polymorphisms have also been reported to influence tumour aggressiveness as well as survival of cancer patients. The differential expression of survivin in cancer cells compared to normal tissues and its role as a nodal protein in a number of cellular pathways make it a high target for different therapeutics. This review discusses the complex circuitry of survivin in human cancers and gene variants of survivin, and highlights novel therapy that targets this important protein.

Key words Cancer - cancer therapy - gene polymorphism - survivin

Introduction

Cancer remains the second leading cause of death after cardiovascular diseases globally. Increasing evidence indicates that the unique member of the inhibitor of apoptosis (IAP) protein family, survivin, is not only an essential protein molecule for the regulation of mitosis and apoptotic inhibition but it also plays a role in certain physiological processes as well as in pathological conditions such as carcinogenesis in many human organs/cells. Eight members of the family of inhibitors of apoptosis proteins (IAPs) are reported, including X-linked inhibitor of apoptosis (XIAP), cIAP1, cIAP2, NAIP (NLR family, apoptosis inhibitory protein), livin, ILP2 (IAP-like protein 2), BRUCE and survivin¹⁻³.

Survivin is an inhibitor of apoptosis protein and is expressed in a large number of malignancies⁴. Its expression levels correlate with more aggressive disease and poor clinical outcome. Survivin expression is minimal in normal tissues, therefore, it has become a lead target for both as a tumour diagnostic, prognostic and as well as for anti-cancer therapies. Overexpression of survivin in cancer may overcome cell cycle checkpoints to facilitate aberrant progression of transformed cells through mitosis⁵.

Survivin is expressed highly at G2/M phase and declines rapidly in G1 phase of cell cycle. This is largely transcriptionally controlled and involves cell cycle-dependent elements (CDEs) and cell cycle homology regions (CHRs) located in survivin gene promoter⁶.

several single nucleotide polymorphisms (SNPs) have been identified in survivin gene, such as *-31G/C*, *-1547A/G*, *-625G/C* and *-644C/T*. Polymorphism at *-31G/C* in survivin is a common mutation in cancer cell lines leading to overexpression of survivin due to functional disruption of binding at the CDE/CHR repressor motifs⁷.

This review provides a brief description of the structure of survivin gene/protein, survivin expression and function in apoptosis, and gene variants of survivin.

Overview of survivin structure and functions

The gene encoding human survivin was cloned by Ambrosini *et al*⁸ in 1997. Survivin spans 14.7 kb at the telomeric end of chromosome 17 and encodes the 16.5 kD wild-type survivin protein of 142 amino acids in length⁹.

As the smallest member of the IAP family, all survivin isoforms characterized so far contain only one of the characteristic N-terminal BIR (Baculovirus IAP Repeats) domains; and an alpha-helix replaces the IAP characteristic RING finger domain involved in zinc ion-binding with the BIR domain (Fig. 1)⁸. The BIR domain is supposed to be important for anti-apoptotic function, whereas the coiled domain probably interacts with tubulin structures⁹. The survivin gene locus encodes multiple genetic splice variants with unique properties and functions. These isoforms include survivin, survivin-2B, survivin-ΔEx-3, survivin-3B, and survivin-2-alpha. Transcription and translation of these isoforms have been demonstrated by several groups of investigators¹⁰⁻¹². In malignant cells, all these isoforms are expressed at a very high rate as compared with normal tissues. Survivin has a dual function, playing both a role in cell death regulation and mitotic progression.

Survivin can be co-immunoprecipitated with caspases-3, -7, and -9 and it suppresses apoptosis induced by overexpression of these caspases, implying that survivin also is a caspase inhibitor¹³. It also inhibits cell death by interfering with caspase-9 processing, the main inhibitor in intrinsic pathway of apoptosis¹⁴. Activation of cell death pathways can be initiated through different mechanisms, including through ligand binding (FasL, TNF) to a death receptor on the cell surface (extrinsic pathway) or via direct mitochondrial signaling (intrinsic pathway). The mitochondrial pathway is initiated by activation of the Bax/Bcl-2 pathway leading to the release of apoptotic factors such as cytochrome c (cyt c) and apoptosis-inducing factor (AIF) from the mitochondrial intermembrane space into the cytoplasm. The release of cytochrome c from mitochondria results in caspase-3 activation through formation of the cytochrome c/Apaf-1/caspase-9 apoptosome complex. Caspase-3 cleaves a number of substrates including cytoskeletal proteins and DNA. Caspase-activated DNase (CAD) and inhibitor of CAD (ICAD) initiate cleavage and fragmentation of DNA. The IAPs inhibit cell death by physically interacting with caspases. Survivin has been shown to inhibit apoptosis through caspase-dependent and independent pathways (Fig. 2).

Consistent with the lack of a structural caspase activation and recruitment domain (CARD) motif, survivin does not directly bind to and inhibit caspases¹⁵. Instead, it interacts with several adaptor or cofactor molecules, one example being X-linked IAP (XIAP). By interacting with XIAP, survivin enhances XIAP stability. It can further act by sequestering SMAC/DIABLO (second mitochondria-derived activator of caspases/direct IAP binding protein with low pI), preventing XIAP's inhibition¹⁶. In each case, survivin enhances XIAP's inhibitor activity of caspase-9

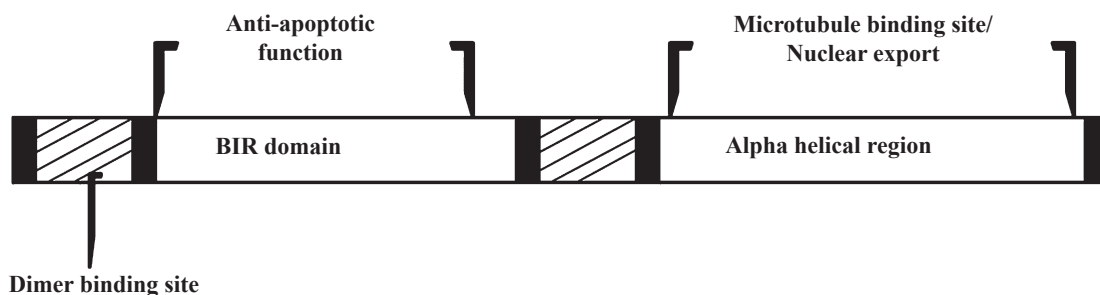


Fig. 1. Structure and function of survivin protein.

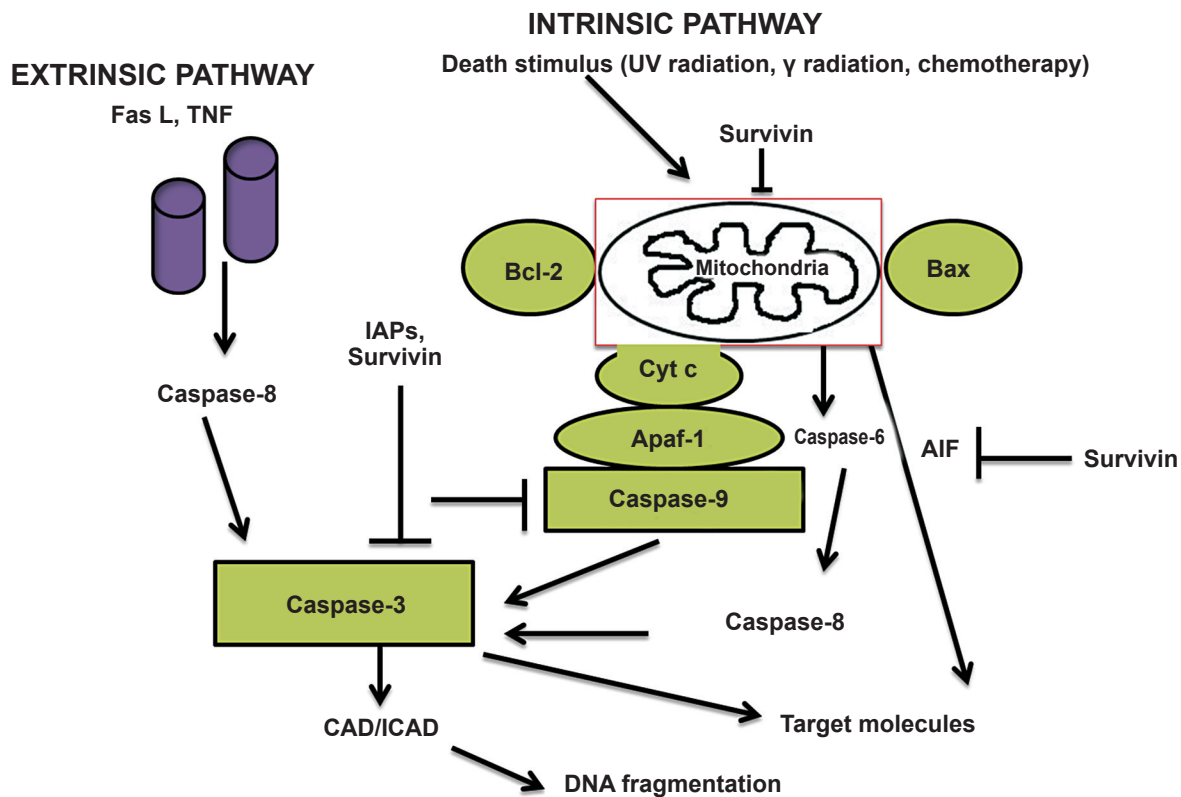


Fig. 2. Survivin (SVN) pathways to apoptosis. Activation of cell death pathways can be initiated through different mechanisms, including through ligand binding (FasL, TNF) to a death receptor on the cell surface (extrinsic pathway) or via direct mitochondrial signaling (intrinsic pathway). The mitochondrial pathway is initiated by activation of the Bax/Bcl-2 pathway leading to the release of apoptotic factors such as cytochrome c (cyt c) and apoptosis-inducing factor (AIF) from the mitochondrial intermembrane space into the cytoplasm. The release of cytochrome c from mitochondria results in caspase-3 activation through formation of the cytochrome c/Apaf-1 (apoptotic peptidase activating factor-1)/caspase-9 apoptosome complex. Caspase-3 cleaves a number of substrates including cytoskeletal proteins and DNA. Caspase-activated DNase (CAD) and inhibitor of CAD (ICAD) initiate cleavage and fragmentation of DNA. The inhibitors of apoptosis (IAPs) inhibit cell death by physically interacting with caspases. Survivin has been shown to inhibit apoptosis through caspase-dependent and independent pathways.

dependent cell death¹⁷ and of death receptor mediated apoptosis¹⁸.

Regulation of survivin and p⁵³

The p⁵³ protein is a transcription factor, which can induce apoptosis by regulating the apoptotic genes. Survivin is a target of p⁵³ for its action and downregulation, and p⁵³ may induce apoptosis by antagonizing the anti-apoptotic activity of survivin. Survivin may also influence p⁵³ activity through regulation of mouse double minute 2 homolog (mdm2) and proteasome¹⁹. However, the negative regulation of survivin by p⁵³ is poorly understood. Survivin promoter has a p⁵³ binding element. It may be possible that p⁵³ directly binds survivin promoter alone or in combination with other protein(s) to

repress survivin. E2F (a transcriptional activator) may also bind survivin promoter²⁰. Since p⁵³ has affinity with E2F, it is possible that both form a (p⁵³-E2F) complex that represses survivin gene expression²¹⁻²³. It also interacts with transcriptional repressor (sin3) and histone deacetylases (HDAC) that together can form a p53-sin3-HDAC complex and binds survivin promoter to repress it^{21,24}. p⁵³ represses survivin through a cascade, which involves Protein p²¹ complex p21/cip1, which is a p53-induced gene that inhibits cyclin-dependent kinase 2 (cdk2) to prevent phosphorylation of retinoblastoma (RB) proteins²⁵. This results in the accumulation of hypophosphorylated pRB. This protein binds E2F family transcription factor and forms a pRB-E2F complex, which may repress survivin gene expression^{20,21,26,27}.

Survivin expression and its role in different cancer

Regulatory mechanisms of survivin expression are yet not fully understood. At the transcriptional level, survivin expression has been demonstrated to involve cell-cycle-dependent element/cell cycle gene homology region (CDE/CHR) G1 repressor elements in the *BIRC5* (baculoviral IAP repeat containing 5) promoter⁴.

Survivin is expressed in embryonic and foetal tissues, but is undetectable in normal adult tissues⁸. However, overexpression of survivin has been reported in almost all human malignancies including bladder cancer, lung cancer, breast cancer, stomach, oesophagus, liver, ovarian cancers and haematological cancers^{8,28}. Based on detection of protein by immunohistochemistry and mRNA by polymerase chain reaction techniques, overexpression of survivin has been reported in various human malignancies (Table).

Almost all cancers have alternative survivin expression profile compared to normal tissues. Survivin is one of the important genes involved in tumour aggressiveness and therapy resistance. Salz *et al*⁴⁵ showed that survivin expression induced transcriptional changes in the tissue microenvironment further promoting tumourigenesis in the bladder tissue. Khan *et al*⁴⁶ reported higher expression of survivin as a critical factor for radioresistance in head and neck squamous cell carcinoma (HNSCC) cell lines. Dysregulation of oncoapoptotic genes, growth factors, receptors and their downstream signaling pathway

components represent a central driving force in tumour development in different cancer⁴⁷.

DNA polymorphisms with more than one variant (allele) having a frequency greater than 1 per cent in a human population have been estimated to occur on the average at one in every 1000 base pairs throughout the human genome⁴⁸. The incidences of polymorphism in genomic DNA, their susceptibility to genetic alterations, and the risk of tumour progression in patients with cancer can vary substantially between different racial groups⁴⁹⁻⁵¹. Although most polymorphisms are functionally neutral, some affect regulation of gene expression or the function of the coded protein⁵².

The survivin gene codifies a multifunctional protein involved in the regulation of the cell cycle and inhibition of the apoptotic pathway, and a polymorphism located in its promoter region is associated with gene regulation. Most of the polymorphic studies are confined in promoter region among which the single nucleotide polymorphism (SNP) at *-31G/C* is most studied in all cancers in comparison to other polymorphic sites⁵³⁻⁵⁶. The following are some examples of the survivin gene polymorphisms that were found to be associated with cancer:

Breast cancer

Breast cancer is the most common malignancy among women, accounting for nearly one in three cancers diagnosed among women in the United States, and it is the second leading cause of cancer death among women⁵⁷. A hospital-based case control study by Ulybina *et al*⁵⁸ showed no risk for breast cancer with survivin gene variants at +9194A/G. However, Boidot *et al*⁵⁹ showed that survivin expression might induce breast tumour proliferation by promoting genetic instability.

Bladder cancer

A case control study conducted in Japan showed two survivin polymorphisms associate with higher risk of bladder cancer⁶⁰. A hospital-based study from north India⁵³ showed that individuals with CC genotype of survivin *-31G/C* had 2.6 folds higher risk for bladder cancer. A study in Taiwanese population showed increased bladder cancer risk with *G/C* genotype⁶¹.

Colorectal cancer

Colorectal cancer is a major cause of morbidity and mortality worldwide. Alterations in pathways regulating important biological processes including cell survival, cell proliferation, epithelial to mesenchymal

Table. Expression of survivin protein in different cancer

Cancer	Expression (%)	References
Lung cancer	85.5	29
Oesophageal cancer	80.0	30
Breast cancer	70.70-90.2	31, 32
Pancreatic cancer	76.90-88.0	33, 34
Ovarian cancer	73.5	35
Malignant melanoma	67.0	36
Colorectal cancer	63.5	37
Hepatocellular cancer	41-87	38, 39
Gastric cancer	34.5-68	40
Bladder cancer	57.8	41
Acute myeloid leukaemia	54.8	42
Acute lymphocytic leukaemia	68.8	42
Oral cancer	72 - >75	43, 44

transition and stroma production have been shown to contribute to colorectal carcinogenesis and tumour progression. A real time PCR study showed association between survivin *31G/C* and development of colorectal cancer⁶². Another study showed that the frequencies of the survivin -31C allele and CC genotype were significantly higher in colorectal cancer patients than in healthy subjects⁶³. Variant CC genotype of -*31G/C* of survivin, expressed 1.6 fold higher mRNA levels compared to cases with the -*31G/G* and -*31G/C* genotypes⁶³.

Endometrial cancer

There is only one study on endometrial cancer and survivin gene polymorphism till date. Survivin is upregulated in endometrial cancer (EC). The presence of allele C of -*31G/C* was found to be significantly increased in EC tissues compared to the healthy tissues in case of Iranian population⁵⁴.

Oesophageal cancer

A case control study from north India showed that SNP -*31G/C* was found to be significantly associated with oesophageal cancer susceptibility at variant CC genotype⁶⁴. A study in Chinese population suggested that survivin promoter polymorphisms -*625G/C* might influence the susceptibility to oesophageal cancer by influencing survivin expression⁶⁵.

Gastric cancer

A study in Chinese population has demonstrated that survivin -*31G/C* polymorphism may be involved in distal gastric carcinogenesis and tumour differentiation⁶⁵. Another study on Brazilian population suggests that presence of C allele of -*31G/C* gene polymorphism may be a risk factor for gastric cancer⁶⁶.

Head and neck cancer

In a study conducted in Serbian population, -*31G/C* gene polymorphism in the promoter region of the survivin gene showed no association with risk for head and neck cancer⁶⁷. Radiotherapy is the main therapy for head and neck squamous cell carcinoma (HNSCC). Survivin showed the most promising biomarker of radioresponse in case of head and neck cancer cell lines⁶⁸.

Hepatocellular carcinoma

Early detection of hepatocellular carcinoma (HCC) is seldom available because of the lack of reliable markers. A study from Taiwanese population

suggested that survivin *T9809C* SNP might contribute to the prediction of susceptibility and pathological development to HCC while other polymorphisms of survivin at -*31G/C* and -*241C/T* did not show any association with HCC⁶⁹. Survivin -*31G/C* promoter polymorphism has not shown any major role in genetic susceptibility to hepatocellular carcinogenesis in Turkish population⁷⁰. SNPs of survivin at -*31G/C* and -*625G/C* did not show any significant association with HCC in Chinese Han population⁵⁵. Survivin +*9194A/G* polymorphism also did not show any significant association with hepatocellular carcinoma in Korean population⁷¹.

Lung cancer

A study conducted in Korean population showed that only the -*31G/C* genotype distribution was significantly different between the cases and controls. Individuals with at least one -*31G* allele were at a significantly decreased risk of lung cancer compared to those individuals with the -*31CC* genotype⁷². Polymorphism in survivin may be a genetic modifier for non-small cell lung cancer prognosis in Chinese population⁷³. The *BIRC5* promoter polymorphism at nucleotide -31 did not influence the expression of survivin mRNA and protein in non-small cell lung cancer cells and tumours in a study reported in Czech population⁷⁴.

Oral cancer

A study conducted in Taiwanese population reported significantly higher risk for oral cancer with -*31GG*, +*9194GG*, and +*9809 TT* homozygotes of survivin gene variants in comparison to wild type genotype⁷⁵. An expression study by Khan *et al*⁴⁶ showed 72 per cent of survivin expression in tissue samples of oral cancer. Lauxen *et al*⁴⁴ showed >75 per cent expression of survivin protein in oral squamous cell carcinoma (OSCC) tissue samples.

Pancreatic cancer

Only one study has been reported on pancreatic cancer and survivin gene polymorphism which showed significant association of survivin -*31G/C* with advanced tumour stage as well as the presence of lymph node metastasis⁵⁶.

Renal cell carcinoma

There is only one study reported in renal cell carcinoma (RCC) and survivin gene polymorphism showing a significantly increased occurrence of RCC associated with the CC genotype⁷⁶. The polymorphism

was associated with risk of developing advanced stage and moderately differentiated RCC. Patients carrying the CC genotype had a significantly greater prevalence of high clinical stage disease⁷⁶.

Role of survivin in cancer therapy

Evidences indicate that the expression of survivin is altered in cancer, and that certain changes may be directly implicated in the carcinogenic process. Due to its role as a cancer gene intersecting multiple cellular networks, survivin has been vigorously used as a cancer drug target. While comparing with other apoptosis-based cancer therapies⁷⁷, survivin provides several advantages. Firstly, the disabling survivin is expected to compromise multiple signaling networks required for tumorous maintenance⁷⁸. Second, survivin may be a unique target for molecular antagonists, cancer vaccine and gene therapy. Thirdly, expression of survivin is regulated by Wnt signaling pathway that has main role in stem cells and it is possible that survivin antagonists may affect cancer stem cells⁷⁹. Fourth, survivin is important in tumour formation/progression, especially angiogenesis⁸⁰, and survivin inhibitors have been shown to act on both the transformed population and endothelial cells in tumour. Fifth, although survivin expression has been shown in cytokine stimulated haematopoietic progenitors and in activated T cells, targeting this pathway does not affect the normal cells or tissues suggesting a favourable toxicity profile of survivin based therapeutics. Survivin-directed immunotherapy has been on the move and several phase I trials with administration of survivin peptides or survivin directed autologous cytotoxic T lymphocytes (CTL) generated *ex vivo* have been completed^{81,82}. Survivin-based vaccination was found to be safe, with no side effects and associated with antigen-specific immunologic responses^{81,83}. Different strategies have been targeted for inhibition of survivin *in vivo* such as identification of a specifically interacting peptide. This peptide can recognize survivin intracellularly and cause the degradation of the ligand survivin complex⁸⁴. Further, survivin inhibition can be achieved by targeting with nano-based drug delivery devices coupled with biocompatible natural product derived therapeutics⁸⁵. Other strategies under investigation to target survivin include antisense oligonucleotides, siRNA⁸⁶, ribozymes, immunotherapy and small molecular weight molecules. These include use of the antisense oligonucleotide LY2181308, the low molecular weight molecule inhibitor YM155 and survivin-directed autologous CTL. The optimum use of survivin in the treatment of cancer is likely to be

in combination with conventional cancer therapies for different cancer^{44,86,87,89,90}.

Conclusion

Since its discovery in 1997, survivin has provided unique opportunities for basic and translational studies. There are multiple strategies targeting the survivin network which have quickly passed proof of principle, and many have entered in the clinical trials in humans¹⁴. However, the results of these trials are still awaited. Further research in identifying the novel targets of survivin and understanding their biological functions will enhance our knowledge about the role of these novel regulators in tumour genesis and will facilitate the potential diagnosis and treatment of cancer.

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