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REVIEW

Survivin: Potential role in diagnosis, prognosis and targeted therapy of gastric cancer

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Abstract

Survivin is a protein that is highly expressed in a vast number of malignancies, but is minimally expressed in normal tissues. It plays a role as an inhibitor of cell death in cancer cells, thus facilitating the growth of these cells. In the case of gastric cancer, survivin is over-expressed in tumor cells and plays a role in the carcinogenesis process. Several studies on gastric cancer have indicated that there is a relationship between survivin expression and the ultimate behavior of the carcinoma. Since the expression pattern of survivin is selective to cancer cells, it has been described as an "ideal target" for cancer therapy. Currently, several pre-clinical and clinical trials are on-going to investigate the effects of interfering with survivin function in cancer cells as a biologic therapy. Survivin is a potentially significant protein in the diagnosis, prognosis and treatment of gastric tumors.

Key words: Survivin; Gastric neoplasm; Diagnosis; Prognosis; Targeted therapy

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INTRODUCTION

Carcinomas in the upper gastrointestinal (GI) tract constitute a major health problem world wide. It is estimated that approximately 36 830 new cases of upper GI carcinomas and 25 200 deaths due to upper GI carcinomas occurred in the United States in 2006[1]. This fact emphasizes the importance of identifying useful diagnostic and prognostic markers in the earliest stage of the disease. As to the treatment of gastric cancer, surgical therapy is the primary treatment, with combination of adjuvant chemotherapy. Most anticancer drugs in use today were discovered based on the ability to kill rapidly dividing cancer cells *in vitro*. Predictably, when administered to patients, many of these drugs also injure rapidly dividing normal cells, such as bone-marrow haematopoietic precursors and gastrointestinal mucosal epithelial cells. In addition, many of these drugs are toxic to normal cells that are not rapidly dividing[2]. The need for effective targeted treatment strategies is evident.

Survivin is an inhibitor of apoptosis protein (IAP) and is expressed in a large number of malignancies[3]. Its expression levels correlate with more aggressive disease and poor clinical outcome. Since its expression is restricted in normal differentiated tissues, it has become of great interest as both a tumor diagnostic, prognostic marker and as a potential biologic target for future anticancer therapies. Recently the use of survivin has been described in bladder cancer[4] and other cancers, but not in gastric cancer. For example, urine testing for survivin has been used as a diagnostic tool for an early detection of bladder cancer[5].

This review will provide a brief introduction about the structure of the survivin gene and protein and survivin expression and function in apoptosis will be discussed. The significance of survivin in gastric cancer will be discussed in two sections: the possible diagnostic and prognostic importance of its expression, and the possibility of modulating survivin function for therapeutic gain. Survivin can be considered as a potentially significant protein in the diagnosis, prognosis and treatment of gastric tumor.

BIOLOGY OF SURVIVIN

Structure and function

Survivin belongs to the apoptosis inhibitor gene family[6], in which the proteins are characterized by a domain of about 70 amino acids, termed baculovirus IAP repeat (BIP), which is evolutionarily conserved. The human survivin gene, spanning 14.7 kb on the telomeric position of chromosome 17, contains 4 exons and 3 introns and produces a 16.5-kDa protein (Figure 1). Unlike other IAPs, survivin is small and has only a single N-terminal BIR domain, a long C-terminal alpha-helix coiled region, and forms a stable dimmer in solution. The BIR domain is thought to be critical for anti-apoptotic function, whereas the coiled domain probably interacts with tubulin structures[7]. The survivin gene locus encodes multiple genetic splice variants with unique properties and functions. These isoforms include survivin,

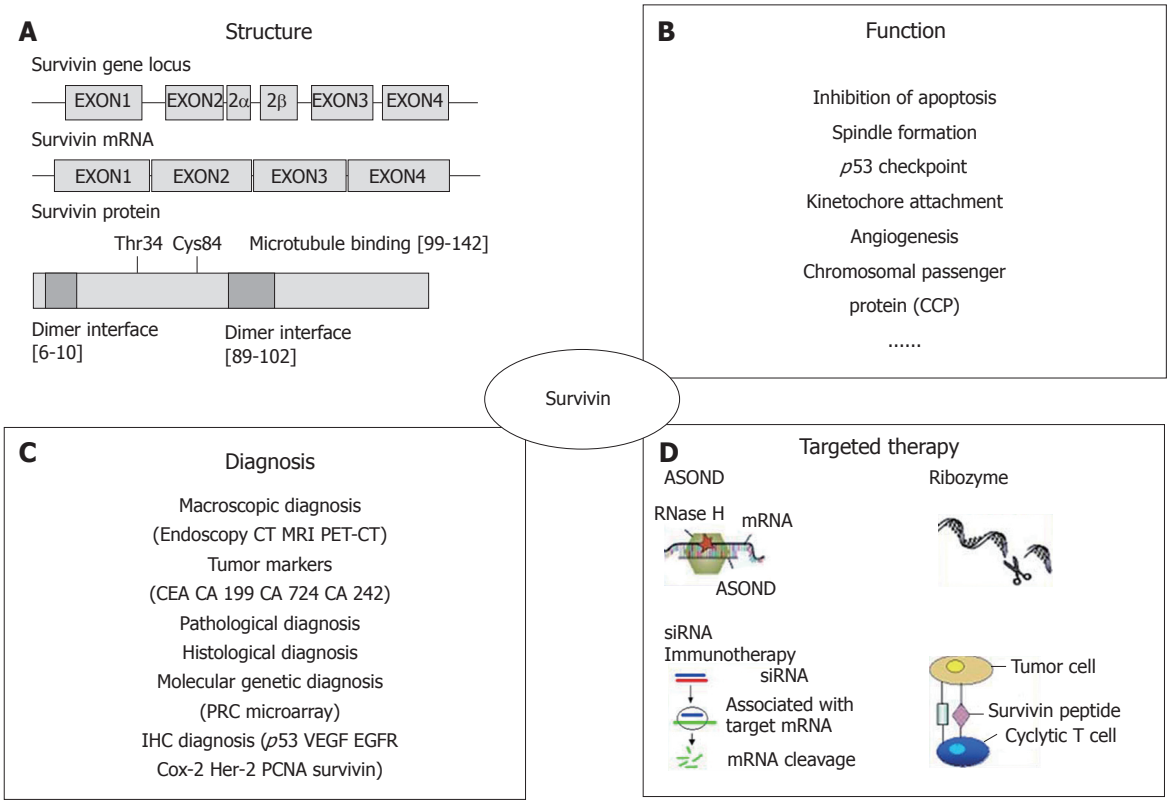

Figure 1 Survivin: from basic knowledge to clinicl application. **A**: the structure of surviving gene, mRNA and protein. The survivin gene is composed of exons 1-4, and produces a 16.5 kDa protein. **B**; Survivin has a dual function in apoptosis and mitotic progression; **C**: the proposal of modern gastric cancer diagnostic methodology and marker panel, with combination of the conventional diagnostic procedure and the new diagnostic methods. The latter was based on the examination of further molecular markers in less advanced stages of tumor and can be used for super-early diagnosis; **D**: the targeted therapy based on survivin nowadays.

survivin-2B, survivin-ΔEx-3, survivin-3B, and survivin-2alpha. Transcription and translation of these isoforms have been demonstrated by several groups of investigators[8-10]. In malignant cells, all of these isoforms are expressed at very high levels, when compared with normal tissues. Survivin has a dual function, playing a roll in cell death regulation and mitotic progression.

Survivin inhibits apoptosis, *via* its BIR domain, by either directly or indirectly interfering with the function of caspase-3 and caspase-7. It also counteracts cell death by interfering with caspase-9 processing, the upstream inhibitor in the intrinsic pathway of apoptosis[11]. Preferentially expressed at mitosis in a cell cycle-dependent manner and physically associated with the mitotic apparatus, survivin is essential for proper completion of various stages of cell division, from centrosomal functions to proper kinetochore attachment to spindle formation, potentially via regulation of microtubule dynamics (Figure 1).

Expression characteristics

The expression of survivin is tissue specific and cell cycle specific. During human development, survivin is expressed in fetal lung, heart, liver, kidney, gastrointestinal tract and in other fetal tissues where apoptosis occurs, such as the stem cell layer of stratified epithelia, endocrine pancreas and thymic medulla. Survivin was strongly expressed in the most common solid tumors of adults, including those of the lung, breast, colon, brain, stomach, esophagus, pancreas, liver, prostate, uterus, and ovaries, but it was not found in normal, adult tissues[12]. These findings suggest that the cell division and anti-apoptosis functions of survivin could be important not only during early development but also during cancer progression. In actively proliferating cells, survivin expression is cell cycle regulated, being virtually undetectable in G1 and S phases, with a peak level in G2/M[13].

SURVIVIN EXPRESSION AND DIAGNOSIS IN GASTRIC CANCER

Approximately 50% of patients have gastric carcinoma that extends beyond the locoregional confines at diagnosis. In addition, approximately 50% of patients with locoregional gastric carcinoma cannot undergo a curative resection (R0). About 70% to 80% of resected gastric carcinoma specimens have metastases in the regional lymph nodes[1]. Based on these facts, gastric carcinoma is often diagnosed at an advanced stage, and continues to pose a major challenge for healthcare professionals. Now, with the development of expression microarray technology, a large number of genes and molecules have been studied regarding the relationship between the development, progression, and metastasis of gastric cancer[14]. These genes include oncogenes, tumor suppressor genes, genes controlling apoptosis (e.g., survivin), cell cycle control genes, DNA synthesis genes, cell division genes, and genes for transcription and translation factors. They offer opportunities not only for early cancer diagnosis but for molecular-based, histological, exact diagnosis of tumors.

Figure 1 shows a proposal for modern gastric cancer.

Development of gastric cancer, like many other malignancies, is a multi-step process involving the accumulation of mutations and changes in cell cycle regulatory mechanisms. The detection of these alterations in the early stage of cancer development may shed new light on the gastric carcinogenesis process. In the gastrointestinal tract, there are indications that activation of survivin may be required for carcinogenesis. Yu *et al*[15] showed that survivin expression is frequently (68%) present in gastric cancer tissues and is also present, albeit at lower frequency (27%), in gastric mucosa of first-degree relatives. Survivin expression was also found in 22% of the non-cancerous tissues adjacent to gastric cancer tissues, but was not detectable in all of the normal, non-adjacent gastric mucosal tissues. Survivin expression is found in cancerous tissue, as well as in normal adult tissues that are predisposed to malignancy, indicating that survivin function may be required for carcinogenesis itself.

As we have already mentioned, survivin shows significant differential expression between malignant and normal adult cells, with very low to absent levels in normal adult tissue but increased levels in a wide variety of tumors. Therefore, the detection of survivin in body fluids could serve as a diagnostic marker that allows the early detection of malignancy. Such a study was firstly performed by Smith *et al*[5]. They measured survivin protein in urine samples from patients with bladder cancer and controls. Using a novel detection method for survivin, urine samples were filtered onto nitrocellulose membranes and probed with an anti-survivin antibody. Its presence in urine has been used to diagnose bladder cancer and to differentiate neoplastic lesions from inflammatory conditions with a sensitivity of 100% and specificity of 95%. This result suggests that survivin can be measured in samples easily obtained from patients and can be used to screen for the presence of malignancy. Furthermore, the result suggests that survivin expression can identify the lesions at highest risk for malignant transformation and invasion. As to gastric cancer, Wang *et al*[16] studied the expression of survivin in the peritoneal lavage fluid from 48 patients with gastric carcinoma using RT-PCR. They found survivin expression in the peritoneal cavity significantly correlated with depth of cancer invasion, lymph node metastasis, and TNM stage. Ninety two percent of clinically evident peritoneal metastasis cases showed detectable survivin expression. This result suggests that survivin can serve as a molecular marker for detecting peritoneal micrometastasis. Its ubiquitous expression in peritoneal cancer cells and metastatic nodules also suggests a promising future therapeutic strategy based on survivin inhibition for cases of gastric cancer involving peritoneal metastasis. This application, however, has not been tested in clinical trial.

SURVIVIN EXPRESSION AND PROGNOSIS IN GASTRIC CANCER

The outcome of gastric cancer depends on the initial stage of the cancer at diagnosis. Surgical therapy is the standard treatment for gastric carcinoma, and patients who can undergo a curative resection of the tumor may have a better outcome. However, even with surgery, recurrence rates range from 30%-60% depending on the pathologic stage, and five-year survival rate is only 20%. With the emergence of partially effective but potentially toxic (neo-) adjuvant chemotherapy, it has become increasingly important to discover biomarkers that will identify those patients who have the highest likelihood of recurrence and who might benefit most from adjuvant chemotherapy.

Numerous papers have appeared over the past several decades proposing a variety of molecular markers or proteins that may have prognostic significance in gastric cancer. Although no single marker has yet been shown to be perfect in predicting patient outcome, a profile based on survivin may be helpful in directing patient therapy[17-19]. The prognostic importance of survivin expression at both the level of the message and protein has been demonstrated in multiple studies (Table 1). Clinical studies correlating survivin expression with disease aggression in adult cancer have shown that survivin is a reliable marker of unfavorable disease and decreased survival. High survivin expression by neoplasms correlates with more aggressive behavior and invasive clinical phenotype, decreased response to chemotherapeutic agents, increased rates of relapse and shortened survival times. For example, in a study of 106 patients with gastric tumors, survivin mRNA expression in the tumor was associated with tumor size, depth of invasion, lymph node metastasis, tumor stage and decreased overall survival[30]. In addition to its level of expression, the localization of survivin may also be prognostically important. In a study of 84 patients with esophageal carcinoma, increased nuclear survivin expression correlated with reduced overall survival (estimated mean survival of 28 mo for patients with nuclear survivin versus 108 mo for patients with no nuclear survivin), but cytoplasmic levels of survivin were not predictive of outcome[31]. This discrepancy between nuclear and cytoplasmic survivin highlights the different anti-apoptotic functions of survivin and suggests that the role of survivin as a cell cycle regulator may be a more important determinant of patient outcome than its role as a caspase inhibitor. This phenomenon has not been detected in gastric cancer, and needs further investigation. High expression of survivin also revealed a decreased responsiveness to chemotherapeutic agents. Gastric carcinoma is one of the most intractable cancers and is known for resistance to various chemotherapeutic agents. Although cisplatin demonstrated better clinical efficacy against gastric cancer than other anti-neoplastic drugs, the overall response rate to CDDP-based treatment was only 33%. The mechanism of CDDP includes inducing apoptosis via caspase-3 activation, and therefore, survivin may mediate the drug resistance. Nakamura *et al*[32] transfected wild-type and dominant-negative mutants of the survivin gene into gastric cancer cells using a lipofection method. Overexpression of survivin protected MKN45 cells from CDDP-induced apoptosis. Expression of the dominant-negative mutant of the survivin gene sensitized NUGC-3 cells to drug-induced apoptosis. These results indicate that survivin may be central for exhibition of not only intrinsic resistance, but also acquired resistance to CDDP, and could be a predictive marker for response

Table 1 Expression of survivin in gastric cancer in association with cancer progression and malignancy

Author /Year	Number of patients	Diagnostic technique	Survivin expression	Correlation with (*P* value)	References
LUCD /1998	174	IHC	60 (34.5%)	Apoptotic index (< 0.001)	20
Okada E /2001	133	IHC	60 (82.0%)	–	21
Krieg A /2002	30	RT-PCR	30 (100.0%)	Tumor stage (0.033)	22
Yu J /2002	50	RT-PCR/IHC	34 (68.0%)	Apoptotic index (0.02), Cox-2 overexpression (0.001)	15
Tsuburaya A /2002	25	RT-PCR	16 (64.0%)	Depth of tumor (< 0.05) peritoneal metastasis (< 0.05)	23
Wakana Y /2002	42	RT-PCR/IHC	–	Apoptotic index (< 0.05), histological type (< 0.001)	24
Miyachi /2003	107	RT-PCR	105 (98.1%)	Lymph node metastasis (< 0.01)	25
Yao XQ /2004	120	IHC	59 (49.2%)	Histological subtypes, lymph node metastasis apoptotic index (< 0.05)	26
Wang ZN /2004	48	RT-PCR	32 (66.7%)	Depth of cancer invasion, peritoneal lavage fluid, lymph node metastasis, TNM stage (< 0.05)	16
Meng H /2005	77	RT-PCR	77 (100.0%)	Survival rate (< 0.01)	27
				Docetaxel-resistance (< 0.05)	28
Sun YS /2006	96	IHC	55 (57.2%)	Serosal infiltration, lymphatic invasion, regional lymph node metastasis, TNM stage, distant metastasis, survival rate (< 0.05), VEGF-C (< 0.001)	29
Lee GH /2006	106	IHC	53 (50.0%)	Tumor size (0.011), tumor stage (0.002), depth of invasion (0.004), poor survival (0.046), lymph node metastasis (0.020)	30

IHC: Immunohistochemistry; RT-PCR: Reverse transcriptase PCR.

to CDDP-based treatment. Given these compelling data, survivin should be considered as a potentially key biological marker in gastric cancer. In addition, with the emergence of survivin-targeted therapies that are known to be effective in pre-clinical trials, survivin could be used as a marker to identify patients that might be good candidates for therapies. The prognostic importance of survivin in gastric tumor has been demonstrated repeatedly, but the challenge remains how to incorporate these molecular markers into clinical algorithms. Perhaps patients with elevated survivin could be offered more intensive or novel therapies at diagnosis. However, such investigational approaches need to be done in a properly controlled trial.

TARGETED THERAPY

Because survivin is preferentially expressed in malignant cells and is prognostically important, it acts as an attractive therapeutic target. Efforts are under way to develop surviving inhibitors for clinical use with the dual aim to inhibit tumor growth through an increase in spontaneous apoptosis and to enhance tumor cell response to apoptosis-inducing agents[12]. Different kinds of survivin molecular antagonists, including antisense oligonucleotides, ribozymes, small interfering RNAs (siRNAs), as well as cancer vaccines, have been used (Figure 1).

Antisense Oligonucleotides

One therapeutic strategy to inhibit survivin uses antisense oligonucleotides (ASONDs) to decrease the target survivin mRNA and subsequently decrease the protein. ASONDs inhibit survivin by forming duplexes with intracellular native mRNA. The duplexes disrupt ribosome assembly and inhibit protein translation. More importantly, the mRNA-ASONDs complex recruits RNase H enzymes that cleave the native mRNA strand while leaving the ASOND intact. The ASOND is then released back into the cytosol, where it is capable of inhibiting additional native mRNA. ASONDs have been actively developed against survivin in gastric cancer. The efficacy of survivin ASONDs has been demonstrated both *in vitro* and *in vivo*. *In vitro*, several ASONDs that target different regions of survivin were designed[33], and one of them (ASOND3) caused a statistically significant loss of survivin mRNA, reduction of cell viability to 60.6% and inhibition of cell growth. The protein level was significantly decreased 48 h after survivin ASODN transfection compared with untreated controls. This result shows survivin antisense molecules directly induce apoptosis in gastric cancer cell lines overexpressing survivin. *In vivo*, antisense survivin oligonucleotides, administered by transfecting tumor cells with plasmids encoding survivin antisense before tumor implantation, reduced tumor growth in xenograft models of gastric carcinoma[34]. Clinical grade antisense surviving oligonucleotides (LY2181308) are currently under development by Isis Pharmaceuticals and Lily Pharmaceuticals in the United Kingdom as a single agent in patients with refractory malignancies. In preclinical studies, LY2181308 demonstrated activity in multiple *in vivo* models of cancer. In November 2004[35], Lilly initiated phase 1 clinical trials in cancer patients. Given the current developmental status of survivin, antisense oligonucleotides against survivin will likely be used in clinical practice before chemical inhibitors. Furthermore, a synergistic effect was noted when tumor cells were treated with ASOND and the chemotherapeutic agent. Targeting of the survivin pathway in cancer, alone or in conjunction with chemo-therapeutic agents, has potential as a novel therapeutic regimen.

Survivin ribozyme approach

As an alternative strategy for survivin inhibition, ribozymes directed against different portions of survivin mRNA were developed. Ribozymes are small RNA molecules that possess specific endonucleolytic activity and catalyse the

hydrolysis of specific phosphodiester bonds[36], resulting in the cleavage of the RNA target sequences. In particular, the hammerhead ribozyme consists of a highly conserved catalytic core, which cleaves substrate RNA at NHH triplets 3' to the second H, where N is any nucleotide and H is any nucleotide but guanidine. Pennati *et al*[37] have done several studies in this area. They found ribozyme-mediated inhibition of survivin expression increases spontaneous and drug-induced apoptosis and decreases the tumorigenic potential of human prostate cancer cells, and it also causes chemosensitization and radiosensitization of human melanoma cells[38,39]. This may be an effective alternative tool for research purposes but appears to be unsuitable for clinical treatment of cancer.

Survivin RNA interference approach

Recently, studies suggest that RNA interference (RNAi) technology is a powerful approach to silence mammalian gene expression for gene function studies[40]. Two approaches can effectively inhibit expression of the targeted genes in mammalian cells without activation of the nonspecific interferon response. These approaches are the *in vitro* synthesized 21-25 nucleotide (nt) double-stranded RNAs (small inhibitory RNA, siRNA) or the 21-29 nt short hairpin double-stranded RNAs (shRNA). Several studies on experimental human tumor models have demonstrated the feasibility of this technology for the inhibition of cancer-related genes including survivin[41-43]. Carvalho *et al*[44] first used RNA interference to specifically repress survivin in HeLa cells. These authors showed that survivin was no longer detectable in cultures 60 h after transfection with specific siRNA and that survivin-depleted cells were delayed in mitosis and accumulated in prometaphase with misaligned chromosomes. Moreover, siRNA-mediated survivin knock down caused radio-sensitization, which was paralleled by an increased activity of caspase-3 and caspase-7, in wt-*p*53 but not in mutant-*p*53 sarcoma cells[45]. It is widely accepted that RNAi provides a powerful tool for targeted inhibition of gene expression, with respect to conventional antisense strategies presumably, because it relies on a natural process. Ribozymes as well as siRNAs can lead to nonsequence specific effects (off-target effects) that are strongly dependent on the concentration of oligomers. Until recently, there were no studies focused on gastric tumor cells and further research is needed in this field.

Survivin-derived cancer immunotherapy

Immunotherapy also appears to be a plausible approach for treating survivin-positive tumors. Current research suggests that tumors of different origin appear to be able to present the same set of survivin-derived peptide epitopes. CD8+ T cells and monocyte-derived DCs can home to the primary solid tumor site, which provides the feasibility for cancer cells to act as survivin-antigen presenting cells to prime CD8+ T cells. Metastatic tumor cells can act as survivin antigen presenting cells to mature CD8+ T cells in the immune system (lymph node) into CTL, and these can be released into the circulation system and home to the primary tumor site[46,47].Spontaneous cytotoxic T lymphocyte response to survivin, in a major histocompatibility complex class I restricted manner, has been detected in patients with chronic lymphocytic leukemia, melanoma, and breast cancer. In addition, *in vitro* cytolytic T-cell induction against a survivin epitope results in cytolytic activity against a wide variety of human tumors, including gastric cancer[48]. Hence, survivin appears to be a universal tumor antigen and immunotherapy is a conceivable approach to treating survivin-positive tumors. Survivin-directed immunotherapy has been quickly moved to the clinic, and several phase I trials with administration of survivin peptides or survivin-directed autologous CTL generated *ex vivo* have been recently completed. In a phase study[49], an HLA-A24-restricted antigenic peptide, Survivin-2B80-88, which is recognized by CD8+ cytotoxic T-lymphocytes, was used to vaccinate patients with recurrent colorectal cancer. Results showed a decrease in expression of tumor markers in 40% of patients and a reduction in tumor size in one of fifteen patients. An open phase I / II cancer vaccine study is evaluating the toxicity and efficacy of HLA-A1, -A2, and -B35 restricted survivin epitopes in patients with tumors other than gastric cancer[50]. When used as an oral DNA vaccine, the survivin-directed immune response affected both tumor cells and tumor-associated angiogenesis, eradicating pulmonary metastases without toxicity in preclinical studies[51]. Survivin-based vaccination was found to be safe, devoid of significant side effects, and frequently associated with antigen-specific immunologic responses.

Others therapies

There are many other anti-survivin therapies, for example, the dominant negative (DN) mutant approach and approaches using small organic compounds or other small antagonists such as small peptides. As to dominant negative mutant, plasmid constructs expressing survivin antisense and DN mutant replacing the cysteine residue at amino acid 84 with alanine (Cys84Ala) were prepared and introduced into BCG-823 and MKN-45 gastric cancer cells[34], with a result of decreased cell growth and increased rate of apoptosis and mitotic catastrophe. This result was found also in nude mice xenografts. This approach is a good tool for research on demonstrating the principles of the survivin pathway, but it is not suitable for direct cancer therapy. While use of small antagonists will be a very exciting area of research in the coming years, it also appears to be the most practical way towards suitable approaches for clinical application. The potential small chemical molecules include those that either transcriptionally or post-transcriptionally inhibit survivin expression or abrogate survivin function, such as disruption of survivin-caspase interactions. For example, tetra-O-methyl nordihydroguaiaretic acid was shown to function by directly suppressing Sp1-dependent surviving gene expression, resulting in activation of mitochondrial apoptosis in tumor cells[52]. These phase I trials with small-molecule inhibitors that directly target survivin are approaching completion. Several small-molecule antagonists indirectly affect survivin levels include cyclin-dependent kinase inhibitors[53], antagonists of STAT3[54], T-cell factor[55], Hsp90[56], and ErbB2[57]. These compounds

reduce survivin levels by different mechanisms. Molecules that target survivin will initially be used as single agents or in combination with low-dose chemotherapy in patients with relapsed or refractory disease. As more experience is gained, these targeted therapies will be used upfront in the treatment of disease in combination with standard chemotherapy. In the future, when more small molecules that modulate the apoptosis cascade are developed, they will be used together to simultaneously target different molecular defects.

In summary, survivin is a potent caspase inhibitor, but it also inhibits cell death by modulating cell cycle progression, cell division, and signal transduction pathways. The vast difference in expression patterns of survivin between normal tissues and cancer cells has identified survivin as an exciting molecule to consider in the study of the underlying biology of tumorigenesis and to provide a platform to design molecules that can specifically target and eliminate cancer cells[11]. Despite its relatively recent discovery in 1997, survivin has attracted considerable interest from several viewpoints in the biochemical sciences. Our basic understanding of the structure and function of survivin is now being translated into clinical practice. Survivin-positive neoplasms are often more aggressive and less responsive to chemotherapeutic agents making survivin an independent negative prognostic parameter in gastric tumors. Survivin is also a potential therapeutic target for development of new anti-cancer therapies. However, mechanisms by which survivin suppresses apoptosis are still under considerable debate, and it is not yet known how survivin is upregulated in neoplastic cells. The challenge in all of these studies will be to prove that survivin based therapies are both efficacious and are, indeed, less toxic for normal human proliferating cells than standard therapies.

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