Review Article

Survivin for chemotherapy efficacy in gastric cancer

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Abstract: Survivin belongs to the inhibitor of apoptosis protein family. Its bi-functional role in apoptosis and in cell division makes it an important molecule for the progress of cancer. Survivin is over-expressed in most malignancies but not in normal differentiated tissues. As far as gastric cancer is concerned, survivin is highly expressed in tumor cells and plays a role in the development of carcinogenesis. High rate of survivin influences overall survival of patients and is correlated with poor prognosis in gastric cancer. Moreover, survivin seems to provide gastric cancer cells with chemo and radio-resistance, similar with other type of cancers. The association between over-expression of survivin and resistance to various chemo-drugs and radiation renders this molecule as a significant biomarker. Survivin is considered as an ideal therapeutic target of cancer due to its capacity to inhibit apoptosis and to promote tumor growth and its selective expression in cancer cells. Since survivin expression might be a useful diagnostic, prognostic, and predictive marker in certain malignancies, many studies aim to counteract survivin in order to inhibit tumor growth and to enhance tumor cell response to apoptosis-inducing anticancer agents. Different approaches are used including antisense oligonucleotides (AO), ribozymes and siRNA, gene therapy through dominant negative mutants, synthetic small molecules and immunotherapy.

Keywords: Survivin; cancer; gastric cancer; single nucleotide polymorphisms; pharmacogenomics

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Introduction

Survivin is the smallest member of the inhibitor of apoptosis protein family (IAPs). In contrast to the other IAPs, it contains only a single copy of the 70 amino-domain called baculoviral IAP repeat (BIR) (1,2). Human survivin consists of 142 aminoacids, has a molecular weight of 16.5 kDa and is localized in nucleus, cytoplasm, mitochondria and in extracellular space. Recently, it was found that the multiple function of the protein depends on its subcellular localization (3). The subcellular distribution of survivin seems to be changing through the cell cycle progression and the different pools are modulated independently (4). The gene encoding survivin is 14.5 kb, located at the telomeric region of chromosome 17. Unlike other member of IAPs, it does not contain really interesting new gene (RING) finger motifs or other common structural elements (5,6). Instead of this, it contains an extended carboxyl-terminal alpha-helical coiled-coil. The human *survivin* gene can give five different transcripts due to alternative splicing (survivin, *survivin 2B*, survivin-3B, survivin-2a and survivin-ΔEx-3) (7).

This protein has a bi-functional role in apoptosis and in cell division. Its anti-apoptotic function occurs via two main apoptosis pathways, the mitochondrial-intrinsic pathway and the death receptor pathway. Survivin blocks the apoptosis pathway either by its binding directly on initiator caspase 9 or indirect by the inhibition of effector caspases 3, 7. Survivin can efficiently protect cells from caspase-dependent apoptosis interacting with other molecules as SMAC/DIABLO and XIAP (8). There is also a caspase-independent inhibition of apoptosis (9). As far as the cellular division is concerned, survivin acts as a mitotic regulator through its association with kinetochores, centrosomes (microtubule-organizing centers), spindle microtubules, central spindle midzone and midbodies. There is a >40

fold up-regulation of the protein during G2/M phase (10,11). Survivin is normally expressed during embryonic development but not in most normal differentiated adult tissues, suggesting its role in pathogenesis when it is expressed in differentiated tissues (12). Survivin's up-regulated expression lies on a variety of molecular mechanisms and epigenetic modifications, including gene amplification, promoter and exon demethylation, and enhanced promoter activity by various transcriptional factors (7,13). However, some studies have revealed the expression of survivin in fast dividing normal cells, such as CD34+ bone marrow derived stem cells, basal epithelial cells, thymocytes and basal epithelial cells of normal uterine cervix, is playing an important role in maturation, survival and proliferation (14-16). Furthermore, survivin has also been detected in the nuclei of mucosal surface epithelial cells and in both nuclei and cytoplasm of chief and parietal cells in human gastric mucosa (17).

Survivin and cancer

Survivin is highly expressed in the majority of cancers and malignancies suggesting its role in tumorigenesis (12). Survivin, as an antiapoptotic protein, reduces the cell loss rate and promotes both cell proliferation and angiogenesis providing advantage to a rapidly growing tumor and consequently to a neoplastic transformation (4). In addition to its direct role in carcinogenesis, survivin may also play a key role in progression of cancer and tumor angiogenesis because of its high expression in endothelial cells during the remodeling and proliferative phase of angiogenesis (18,19). Both gene and protein expression are evaluated in human malignancies usually by molecular and immunological assays such as semi-quantitative real time PCR and immunohistochemistry, respectively. Up-regulation of survivin has been reported in almost all human cancers including gastric cancer, lung, colon, breast, stomach, esophagus, liver, pancreatic, prostate, ovary cancer, gliomas and in hematopoietic malignancies (20-23). More aggressive behavior of some types of cancer, such as colorectal and gastric carcinomas, can be correlated with overexpression of survivin (24,25). Similar to its expression, survivin promoter activity is largely silent in normal cell types, but is increased in tumor cell lines. A research by Dohi *et al.* showed that mitochondrial survivin promotes tumor growth and inhibits tumor cell apoptosis contrary to cytoplasmic surviving (26). Survivin splice variants expression in tumor samples is related with various clinicopathologic characteristics in different cancers (27). Kim *et al.* revealed the relationship of survivin and TCF/catenin signaling axis and the increased cell proliferation and survival in colorectal cancer (28). Nuclear localization of survivin has been reported as a favourable prognostic marker for gastric, bladder and breast in contrast to esophageal, hepatocellular, lung and ovarian cancers (29). Many single nucleotide polymorphisms (SNPs) have been identified in survivin gene but mainly –31G/C is thought to participate in carcinogenesis. Two studies have found an association between –31G/C and gastric cancer (30,31). Recently, two different meta-analysis by Srivastava *et al.* and Wang *et al.* have shown that the survivin –31G/C polymorphism is overall correlated with cancer susceptibility especially in Asian population but there is no significant correlation with esophageal or gastric cancer (32,33).

Survivin and gastric cancer

Gastric cancer is one of the most common malignancies and is probably the second leading cause of cancer death (34). Highly expressed survivin is correlated with poor prognosis (19). Lee *et al.* suggested that survivin triggers tumor angiogenesis in gastric cancer (18). Nuclear localization of survivin does not have a significant impact on overall patients' survival in contrast to its cytoplasmic localization (35). Yu *et al.* supported that survivin might play an important role in the early stage of development of gastric cancer within the members of a family due to the increased survivin expression both in patients with gastric cancers and their first degree relatives (36). At the later-stage of gastric cancer, *survivin* 2B is under-expressed, suggesting its association with tumor progression (37,38). Contrary, survivin-ΔEX3 was increased in cancer tissues in comparison with para-cancerous tissues (30). A recent study indicates a relationship between PI3K/Akt and survivin in the gastric cancer. In normal gastric mucosa, survivin protein was undetectable and its mRNA was low. In contrast, elevated survivin mRNA and protein levels in biopsy specimens of gastric cancer indicated that alterations in survivin expression are involved in the development of gastric cancer (39). PI3K/Akt pathway regulates survivin and these proteins could possibly be used as markers for the prognosis and the treatment of gastric cancer as they participate in cell proliferation (40). Survivin's interaction with other proteins such as RUNX3 regulates its promoter activity and promotes gastric cancer cells apoptosis (41). Moreover, survivin has a multifunctional role including the

association with STAT3, activated phosphorylated form of signal transducer and activator of transcription 3 (pSTAT3), suppressor of cytokine signaling-1 (SOCS-1) and Bcl2 in gastric cancer. The expression of these molecules and cytoplasmic survivin is associated with poor prognosis and more aggressive cancer. Furthermore, surveys in gastric cancer have shown that as survivin signaling seems to have a major impact on STAT3 downstream targets—MMP-9, MMP-10, cyclin D1, VEGF-C, and VEGFR-3, this molecule may be used for diagnostic and therapeutic purposes in the future (42). A recent meta-analysis study in gastric cancer highlights an association between survivin expression levels and metastatic lymph nodes and overall survival in patients (43). Tu *et al*. confirmed the relationship between survivin and gastric cancer as their experiments resulted that suppression of *survivin* also inhibits *de novo* gastric cancer formation and angiogenesis *in vivo* (44).

Chemo-resistance

It is widely known that cancer cells develop multiple mechanisms of resistance to therapy. The resistance to conventional cytotoxic drugs and molecular targeted agents share similar mechanisms, including genetic/epigenetic alterations induced and/or constitutive activation of pro-survival pathways to avoid cell death, and increased drug efflux via ATP-binding cassette (ABC) transporters (45). It is clear that resistance to chemotherapy is associated with reduced susceptibility to apoptosis. Evidence shows a relationship between chemo-drugs and expression of survivin in most malignancies. Apart from tumorigenesis, tumor progression and poor prognosis, survivin also seems to increase tumor resistance to various apoptotic stimuli (9). Survivin acts as a strong inhibitor of cell death and protects cells against unfavourable environments antagonizing drug and radiation induced apoptosis (46). Survivin seems to contribute to chemo-resistance by protecting cell survival through two main mechanisms: (I) the inhibition of apoptosis by blocking activated caspases; (II) by stabilizing the microtubule cell network to prevent cell catastrophe. Depending on the cancer type, these two mechanisms contribute in different rate to cancer cell survival (47). Growth factors as VEGF induce the expression of *survivin* through PI3K/PKB pathway and render chemo-protection (48). Chemo-resistance related to survivin has been referred to gastric cancer (49), glioblastoma (50), neuroblastoma (51), chondrosarcoma (46), lung (52), breast (53), pancreatic cancer (54) and thyroid carcinoma (5).

It has been 15 years since Ikeguchi *et al*. noted a connection between survivin expression in gastric cancer cells (cell line MKN-45) and chemotherapy treatment. Their findings showed that both survivin mRNA and protein expression levels at the cells treated with cisplatin were 2 to 6 fold higher than the expression levels of the untreated cells. These results suggested that survivin expression may correlate with the chemo-resistance of malignant gastric cells (55,56). Survivin's splice variants also seem to play a role in chemo-protection of cancer cells and their targeting could result in sensitization to chemotherapy. Survivin 3B is referred as an interesting therapeutic target since it is only present in tumors (57). However, wild-type survivin is mentioned that promote doxetaxel-resistance in gastric cancer (58) and its mRNA level is suggested as a useful tool for evaluating the docetaxel-response in patients with gastric cancer (59). Nevertheless, high expression of nuclear survivin seems to evoke better response to platinum/taxane chemotherapy, so nuclear survivin becomes an independent prognostic factor (52). A recent study demonstrated that lower expression of survivin was associated with better response to paclitaxel in gastric cancer, validating the role of survivin as a biomarker for chemo-sensitivity in this malignancy (49). Moreover, Zheng *et al*. confirmed the association between survivin overexpression and resistance to docetaxel chemotherapy in advanced gastric cancer (60).

Knock down of survivin expression clearly sensitizes gastric cancer cells to chemotherapy both *in vitro* and in nude mice (61). Additionally, Wang *et al*. indicated the synergistic effect of gambogic acid and docetaxel in gastric cancer cell lines via inhibition of survivin (62). Their results are in consintence with previous studies that showed the cytotoxic effect of gambogic acid in human gastric carcinoma MGC-803 cells and BGC-823 inducing apoptosis (63,64).

Survivin appears to be a useful biomarker of resistance to chemotherapeutic drugs or a therapeutic tool through its targeted inhibition in gastric cancer. However, there are only few studies about this cancer type for making safe conclusions. The relationship between chemo-resistance and survivin is confirmed by reports about other type of cancers. An extended study of tumor-associated brain endothelial cells has indicated resistance to multiple classes of drugs as VP-16, paclitaxel, thapsigargin and temozolomide (65). Many studies in breast cancer have been accomplished about the effectiveness of various apoptotic stimuli. Tamoxifen, paclitaxel and transtuzumab seem to be suspended by survivin through caspase inhibitor mechanism

in breast cancer cells (62,66). However, Nestal de Moraes *et al*. have claimed that survivin does not influence the response to doxorubicin and other dox-based drugs (67) and moreover, high levels of cytosolic survivin have been related to advanced chemotherapeutic efficacy by Span *et al.* in breast cancer (53).

Targeted agents, that can silence the *survivin* gene and inhibit DNA repair, increase sensitivity to chemotherapy. These agents, like YM155 and FL118, are used in combination with cytotoxic chemo drugs such as various platinum based drugs in order to increase efficacy and reduce toxicity after their synergistic action (51,68,69). Faversani *et al*. transcriptionally suppressed survivin through YM155 and this enhanced doxorubicin treatment in breast cancer cells (70). Bortezomib downregulates survivin in many solid and hematological malignancies but, according to a recent study, bortezomib manage therapeutic response to multiple myeloma irrespective the expression of survivin (71).

Radio-resistance

Radiation, similar to chemotherapy, provokes death of tumor cells by causing irreparable cellular damage and triggering apoptosis. Therefore, inhibitor of apoptosis protein family affects tumor cells inversely and promotes radio-resistance. The relationship between survivin expression and the ability of cancer cells to undergo apoptosis can influence negatively their sensitivity to radiotherapy. It is not clear enough how survivin decreases radio-sensitivity since it is a multifaceted issue. Many mechanisms seem to be involved concluding either caspase-dependent or caspase-independent mechanisms, like impaired DNA repair, altered cell-cycle distribution, mitotic arrest and subsequent cell death (72,73). Studies on colorectal and pancreatic cancer cells have demonstrated that highest level of survivin protein and mRNA are associated with low rate of apoptosis and resistance to radiation. Insensitivity in these cancer cells may rely on the inductive expression of survivin after radiation (54,74). Likewise, a study in glioblastoma have indicated higher survivin expression in radio-resistant cell lines compared with radiosensitive cell lines (75). Overexpression of survivin has been correlated to radio-resistance in breast (76), esophagus (77) and renal cancer cells, as well (78). Different isoforms of survivin have various effects on radio-resistance, wild type and 3b-survivin protects cancer cells against radiation, while the other splice variants seem to have no impact (73). Farnebo *et al*. have claimed that survivin has a converse effect on head and squamous cancer cells. Highly expressed survivin resulted in better response to radiotherapy and its downregulation leads to increased radio-resistance in this type of carcinoma (79). Recent studies have concentrated in counteracting survivin's expression in order to induce radio-sensitivity in cancer cells. Inhibition of survivin results in radiation-induced apoptosis and enhances radio-treatment. Two researching teams have asserted that targeting survivin leads to inefficient DNA repair exposure in radiation exposed human glioblastoma and colorectal tumor cells (72,75). Correspondingly, Reichert *et al*. have confirmed the protective role of survivin in radio-induced cell death by stimulating DNA double-strand break repair in glioblastoma and suggest targeting survivin as a strategy to increase therapeutic efficacy of radiation (80). Song *et al*. have revealed that targeting *survivin* gene by RNA interference induces apoptosis and promotes radio-sensitization in human cervical carcinoma cells Hela (81). Likewise, silencing of *survivin* gene in gastric cancer cells improves their radio-sensitivity. Gastric cancer colony formation and viability were highly reduced, while apoptosis rate was up-regulated in *survivin*-silenced tumor cells after radiation (61).

Therapeutic applications

As it is already mentioned above, survivin expression may be a useful diagnostic, prognostic, and predictive marker in certain malignancies. The overexpression of survivin in human cancers and its dual role in malignancy has led to an intense interest in it as a target of therapeutic applications (82). Survivin's unique nodal properties have made its antagonists an attractive potential therapeutic solution to the heterogenous human cancers (83). Inhibition of survivin with molecular genetic approaches additionally to the use of chemotherapeutic drugs or radiotherapy might improve some of the current therapeutic strategies (22). In order to target efficiently survivin, it is necessary the transcriptional and translational modulation of survivin to be well understood. Developing drugs that target survivin might initially seem difficult because survivin is not an enzyme nor it is a cell surface protein. However, advances in understanding of biology and function of this protein, have resulted in a wide spectrum of molecular inhibitors. Different strategies to counteract survivin in cancer cells have been proposed with the double aim to eliminate the tumor growth potential and to enhance tumor cell response to apoptosis-inducing anticancer agents. These approaches

conclude antisense oligonucleotides (AO), ribozymes and siRNA, gene therapy including transfecting with dominant negative mutants, synthetic small molecules inhibiting gene transcription, immunotherapy/vaccines (84-88). Moreover, nonsteroidal anti-inflammatory drugs, like indomethacin, have been mentioned to induce gastric cancer cells apoptosis by counteract survivin and Aurora-B kinase and the simultaneous treatment with siRNA can lead to higher cell injury (89,90).

Antisense oligonucleotides (AO)

AO are defined as those oligonucleotides that are 8-50 nucleotides in length that bind to RNA through Watson-Crick base pairing and subsequently modulate the function of the targeted RNA (91). The addition of AO against survivin resulted in decreased expression of survivin mRNA and protein, inhibition of proliferation and induction of apoptosis in a dose-dependent manner (92). Suppression of survivin through antisense oligo inhibits *in vivo* tumorigenicity and angiogenesis in gastric cancer cells (93). At first, a study by Yang *et al*. demonstrated that survivin antisense oligonoucleotide can inhibit the growth of gastric cancer cell line but cannot induce apoptosis by itself and proposed an AO that is complementary to the initiation codon and five downstream codons which accessed survivin mRNA more efficiently (94). However, a recent study showed that AO targeting survivin could significantly not only inhibit the growth of gastric cancer cells, but also induce their apoptosis and inhibit their telomerase activity (95). Furthermore, AO-mediated downregulation of survivin sensitizes tumors to chemotherapeutic agents as cisplatin (96,97), taxol (98), etoposide (99) and demcitabine (100). Increased sensitivity to radiation treatment has also been reported following AO-mediated downregulation of surviving (101). Nowadays, the second generation AO drug LY2181308 aims to enhance affinity target RNA and decrease toxicity. It has entered phase II of clinical trials.

SiRNA

SiRNA is a genetic interference technology that is effective for suppressing specific gene expression (102). It involves post-transcriptional gene silencing via a way in which double-stranded RNA (dsRNA) inhibits gene expression in a sequence-based manner through degradation of the corresponding mRNA (103).

In gastric cancer there are few reports of survivin targeting with siRNA since recently. SiRNA knockdown of the *survivin* gene can induce apoptosis and inhibit the growth of human gastric carcinoma cell (104,105). Li *et al*., have also shown that siRNA downregulation of survivin promotes gastric cancer cells death and inhibits cell proliferation through decrease in mitochondrial cytochrome C and cytoplasmic cytochrome C and caspase-3 (69). Their findings are consistent to earlier studies in gastric cancer MGC-803 cells and AGS cells (106,107). Moreover, reduction of survivin expression through siRNA leads to increased sensitivity to docetaxel therapy in gastric cancer cell (108). Likewise, studies in other type of cancer cells such as ovarian cancer cells confirmed that siRNA survivin induced high rates of apoptosis when it is combined with chemo-drugs (109). There are several studies on downregulation of survivin by RNAi in many types of cancer such as chondrosarcoma (46), breast (66), liver (110) and pancreatic cancer (54).

Small molecules inhibitor

YM155 is a small imidazolium-based molecule that inhibits specifically both mRNA and protein survivin expression and provokes tumour regression by activating caspases and inducing apoptosis. YM155 has been mentioned to suspend the growth of a significant number of human cancer cell lines including the cell lines derived from non-Hodgkin's lymphoma, hormone-refractory prostate cancer, ovarian cancer, sarcoma, non-small-cell lung cancer, breast cancer, leukemia and melanoma (111,112). The combination of YM155 plus various chemo-drugs such as platinum-based drugs, doxetaxel, etoposide, results in more effective inhibition of survivin, thus means greater tumor reduction in some cancer types like melanoma, neuroblastoma,non-small cell lung cancer, but not in breast cancer (68,70,113).

Tetra-o-methyl nordihydroguaiaretic acid also known as terameprocol, blocks cell cycle progression by inhibiting the expression of the *Cdk1* gene and simultaneously promotes apoptosis by inhibiting the expression of the *survivin* gene (50,114).

Fl118 can target multiple treatment resistant mechanisms. This new small molecule can inhibit not only IAPs but also antiapoptotic protein Mcl-1 and Bcl-2 (45).

Gene therapy/dominant negative mutants

The use of gene therapy seems to be effective at inhibition of survivin. A dominant negative mutant replacing the

cysteine residue at amino acid 84 with alanine (Cys84Ala) was transfected in gastric and colon cancer cells and provoked apoptosis and mitotic catastrophe and suppressed tumor growth and angiogenesis. Mice expressing dominant-negative survivin showed decreased probabilities of developing tumors or exhibiting tumor-associated angiogenesis. Moreover, survivin dominant-negative therapy increased sensitivity to cisplatin and 5-fluorouracil (43,86,115). A report by Nakamura *et al*. also revealed that inhibition of survivin function by transfection of a dominant-negative mutant of the *survivin* gene augmented susceptibility to cis-diamminedichloroplatinum induced apoptosis in gastric cancer patients (116). A different dominant negative mutation of survivin, characterized by alteration of threonine 34 to alanine was induced to gastric cancer cells by an adeno-associated virus inhibited cell proliferation and cancer growth, induced apoptosis and sensitized gastric cancer cells to 5-Fluorouracil both *in vitro* and *in vivo* (117). Various studies about survivin dominant mutant Thr34Ala in other type of cancers like melanoma, breast, cervical, lung and colorectal cancer cells have shown similar anti-tumor capacity (118).

Ribozymes

Ribozymes are small RNA molecules that have specific endonucleolytic activity and catalyse the hydrolysis of specific phosphodiester bonds, resulting in the cleavage of the RNA target sequences (119). Pennati *et al*. have 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 chemo-sensitization and radio-sensitization of human melanoma cells (84,120).

Immunotherapy

Cell-based cancer immunotherapy involves the use of immune cells such as the natural killer cells, dendritic cells, and cytotoxic T lymphocytes, which are isolated from the patient, activated *in vitro* and transfused back to the patient to target cancer cells (86). The main focus of immunotherapy has been on tumor-associated antigen recognition by T lymphocytes. Both CD8+ cytotoxic and CD4+ helper T cells can recognize antigens presented as small peptides in the grove of surface HLA molecules (71,93). The immunologic properties of survivin and the demonstration of HLA class I—restricted cytolytic T cells against survivin peptides in cancers suggested that survivin peptide-specific cytolytic T-cell immunotherapy might be a new therapeutic way (87,121). Survivin-directed immunotherapeutic strategies have been rapidly moved to the clinical setting: several phase I trials based on the administration of survivin-directed autologous cytotoxic T lymphocytes generated *ex vivo* or survivin peptides have been completed recently and the treatment was proved to be safe, without crucial adverse effects and associated with antigen-speific immunologic responses (84,88). Survivin-based vaccines to experimental animals have been found to induce tumor regression in several types of malignancy including lung cancer, pancreatic cancer, hormone refractory prostate cancer, lymphoma and neuroblastomas (101).

Conclusions

To summarize, survivin is undoubtedly a molecule that participates in tumorigenesis due to its ability to suppress apoptosis and its role to cell division. Survivin's overexpression in cancer but not in normal differentiated tissues shows the therapeutic potential of this molecule and makes it a promising cancer target. Survivin's inhibitor drugs seem to be the future of cancer treatment. Taking into account that gastric cancer is the second leading cause of cancer death, more studies are needed about its therapy. For more efficacy to cancer therapy, it is obliged to define the molecular pathway through which survivin provokes apoptosis and offer chemo-resistance to gastric cancer cells. Finally therapeutic application targeting this molecule, such as AO, ribozymes, siRNA, immunotherapy and gene therapy, could be an ideal solution to chemo and radio-resistance, but more clinical trials should be performed at various type of cancers concluding gastric cancer.

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