Review Article

The role of survivin in diagnosis, prognosis and treatment of breast cancer

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ABSTRACT Survivin is a cancer gene that is silenced in differentiated tissues, while overexpressed at high levels in vast majority of tumors. It has garnered great interests in recent years. Some essential properties characterizing it as an ideal target involve inhibiting apoptosis, promoting mitosis, stimulating vessel growth thus inducing chemo-resistance. These functions touch the full gamut of tumorigenesis, including proliferation, migration, and invasion, and collectively facilitate malignant behavior. In the case of breast cancer, survivin detection independent or combined in serum and/or urine has emerged as a measure for diagnosis. Moreover, many studies indicated aberrant expression of survivin is associated with poor prognosis and drug/radiation resistance. Strategies targeting survivin to treat breast cancer have got promising initial results. In this review, we summarize its role in breast cancer's diagnosis, prognosis, and treatment, with the intention to explain why this interesting molecule plays a conflicting role.

Key Words: survivin; diagnosis; prognosis; treatment; breast neoplasm

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Introduction

Breast cancer is by far the leading cause of cancer death in women throughout the world and its incidence continues to rise (1,2). The main reasons consist of high propensity to metastasize at an early stage and the acquired resistance to a wide range of anticancer agents (3). Once the cancer has spread beyond the breast and loco-regional lymph nodes, it is seemed to be incurable (4). In such cases, chemotherapy or radiotherapy considered to be the main treatment, but accompanied by various adverse effects. This fact emphasizes the importance of selecting sensitive diagnostic and prognostic markers in the early stage and more efficient targeted treatment for this disease.

Survivin is an inhibitor of apoptosis protein (IAP) and is overexpressed in a wide spectrum of tumors including breast cancer (5-7). Its primary functions comprise inhibiting apoptosis and regulating mitosis, which are associated with carcinogenesis (8). Considering of its differentiated expression between normal and cancerous tissues, it has become an attractive molecule for early detection and prognoses of breast cancer. Additionally, inhibition of survivin alone or in combination with other approaches has emerged as a promising therapeutic strategy.

Biologic function of survivin

Survivin as an inhibitor of apoptosis

Survivin inhibits apoptosis either directly or indirectly by interfering with the function of caspase-3, caspase-7 and caspase-9 (9-13). The effect of survivin on apoptosis may also in a caspase-independent way by interaction and cooperation with hepatitis B interacting protein (HBXIP) (14), Smac/diablo (15-17), AIF pathway (18), HSP90 (19), c-IAP-1 (20) HER-2/EGF (21,22) leptin/Stat3 (23) and progesterone/P53 (24).

Survivin as a promotor of mitosis

Current evidence suggests that survivin also plays a role in regulating mitotic progression. Which, rather than inhibiting apoptosis, is the primary function of survivin (25,26). In some cancer cells, survivin inhibition produces defects in chromosome segregation, cytokinesis and ultimately cell division, without measurable impact on apoptosis (27,28). The probable mechanisms include mediating mitosis by acting as an interphase between the

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centromere/central spindle and the CPC (chromosomal passenger complex) (29). The CPC is composed of the mitotic kinase aurora-B, borealin and INCENP and is involved in correcting attachment errors between chromosomes and the mitotic spindle, ensuring the correct completion of cytokinesis.

Survivin facilitating angiogenesis

In addition to its involvement in apoptosis and mitosis, there is growing evidence suggesting survivin has been implicated in angiogenesis. Transfection of endothelial cells (EC) with genes coding of survivin-specific siRNA (30), or antisense oligonucleotide (ASODN) (31), or phosphorylation-defective form of survivin (32) result in vascular regression during tumor angiogenesis. Adversely, survivin expression (both mRNA and protein) was increased in cultured vascular EC following exposure to angiogenic factors such as VEGF and bFGF (33-35). The mechanism by which survivin promotes angiogenesis is likely to attributed to its ability to preserve microtubule structure integrity, and inhibit apoptosis in EC, which may be required for EC viability and cytoprotection (35,36).

Diagnosis and detection of breast cancer

About 30-50% of patients with early-stage breast cancer, even those with negative lymph nodes, still develop a recurrent disease, which is metastatic in most cases (37-39). In patients who receive neoadjuvant chemotherapy (NACT), about 10%-35% (40,41) do not respond well because of chemoresistance and have a dismal prognosis of 10-20% 5-year survival (42). Breast cancer has been posing a great challenge with an overall poor long-term prognosis (43). There is increasing evidence that primary cancers begin releasing cancer cells into the circulation at an early stage (44-49). So peripheral blood of breast cancer patients was used for the detection of circulating tumor cells (CTCs) (50). At present, sampling of tumor markers such as cytokeratin 20, mammaglobin, c-Met, maspin, epidermal growth factor receptor (EGFR), Her2/neu, membrane association mucin1 (MUC1), CD44, have been detected with varying degrees of sensitivity and specificity (51-54). Most of these factors are less reliable for small tumors and further stratification of breast cancer patients remains a challenge (55). Since survivin is selectively expressed in malignant tissues, and can inhibit apoptosis, promote cell division and enhance angiogenesis (56), its detection in body fluids could serve as an ideal tumor marker for diagnosis and detection (tab1) (57-59). Such a study was carried out by Yie et al detected survivin-expressing circulating breast cancer cells in the peripheral blood using a RT-PCR ELISA technique (60). Survivin-expressing circulating cancer cells were detected in the peripheral blood samples from 34 (50.7%) out of 67 breast cancer patients, but not in the healthy women that were used as controls. The presence of survivin-expressing circulating breast cancer cells was found to be significantly associated with various clinicopathological parameters such as vessel infiltration, histological grade, tumor size, nodal involvement, ER/PgR status, Her-2 expression and clinical stages of the disease. The authors concluded that the detection of circulating cancer cells expressing survivin mRNA could provide valuable information for predicting metastasis and recurrence of breast cancer.

Similar to these findings, Chen et al studied the gene expression in a combined way using a membrane array technique (61). Survivin was shown to be one of the four marker genes detected in circulating tumor cells in the blood of Taiwanese women with breast cancer. The results revealed that tumor size, histologic grade, lymph node metastasis and TNM stage were significantly correlated with the positive detection of these genes, including survivin.

Guney N conducted a study to investigate the serum and urine levels of survivin in patients with breast cancer and the relationships with known prognostic parameters and therapy (62). Their results suggested that serum survivin level could be a sensitive marker for detecting metastases in lymph nodes from breast cancer patients. More recently, a research from China discussed that detection of survivin or other associated gene may serve as an important diagnostic test for breast cancer and provide an early biomarker of aggressive tumor behavior before the appearance of distant metastasis. Multiple marker assays may significantly improve the sensitivity of detecting heterogeneous tumor cells compared with single marker assay. Further clinical trials are needed to provide more convincing evidence.

Survivin and prognosis of breast cancer

The ultimate outcome of breast cancer relies on the initial stage of the cancer at diagnosis. The main prognostic factors associated with breast cancer are lymph node involvement, tumor size, histological grade, and hormone receptor status. However, tumor at the same stage can behave in a different manner, and the prognosis can vary (80). So it is important to find biomarkers that will predict the likelihood of recurrence and identify those patients who might benefit from therapy. Hence, low-risk patients can be spared unnecessary treatment, avoiding side effects and reducing the cost of treatment. Moreover, high-risk patients could be rapidly identified and offered more aggressive treatment. Recently, abundant survivin expression in human breast cancers have been found using

Tab 1: Survivin for breast cancer diagnosis and detection

Year/first author/reference	Alone or combined	Assay	Collection	Conclusions
2002/Nasu S (63)	alone	RT-PCR 37/41 (90.2%)	specimen	a useful diagnostic marker for breast cancer.
2002/Izawa A (64)	with c-erbB2 and PLU-1	RT-PCR 27/39 (69.2%)	specimen	useful as a marker for diagnosis
2006/Yie SM (60)	alone	RT-PCR ELISA	PB	PPV in vessel infiltration, histological grade, tumor size, nodal status, ER/PgR status, Her-2 status and clinical stages
2006/Chen CC (61)	with PTTG1, UbcH10 and TK1	membrane array technique	PB	PPV in tumor size, histologic grade, lymph node metastasis and TNM stage
2006/Guney N (62)	alone	EIA and ELISA	Serum and urine	serum survivin level could be a sensitive marker for detecting metastases in lymph nodes
2009/Shen C (65)	with hTERT and hMAM	real-time q PCR	PB	PPV in TNM stage, and lymph node metastasis

PPV: positive predictive value, NPV: negative predictive value, (q) RT-PCR, (quantitative) reverse transcriptase polymerase chain reaction, ELISA, enzyme linked immunosorbent assay, PB, peripheral blood.

RT-PCR (64,80,81). Several studies were carried out to assess the possibility of survivin as a prognostic molecule. For example, in a study of 275 patients with breast cancer (70), survivin mRNA was highly expressed in tissues from younger patients (<50) and in high-grade cancer tissues. High survivin concentrations were most strongly associated with ER- or PR-negative tumors. Survivin demonstrates a strong, independent association with poor prognosis. Survivin might be used as a new marker to stratify breast cancer patients for more optimal treatment modalities, or it could be a promising new target for therapy. In another study (66), survivin expression was examined in 167 cases of breast cancer and the results suggest that apoptosis inhibition by survivin, alone or in cooperation with bcl-2, is a significant prognostic parameter of worse outcome in breast carcinoma.

Consistent with these results at mRNA level, Ryan et al showed that survivin protein, as determined by ELISA, was also an independent prognostic factor in breast cancer (81). In this study, the prognostic impact of survivin was independent of patient age, tumor size, lymph node status, hormone receptor status, HER-2, VEGF, and urokinase plasminogen activator/plasminogen activator inhibitor type-1. Fuzhong et al reported that patients of low expression of survivin have high response rate after neoadjuvant chemotherapy and the results shows that survivin is an important predictive factor for effectiveness of neoadjuvant chemotherapy in locally advanced breast cancer (79). Another study analyzed the five survivin transcripts in 60 breast cancer patients treated with FEC (fluorouracil, epirubicin and cyclophosphamide) or TE (taxol and epirubicin) (82). They found that an imbalance in the alternative transcript ratios might make the cells resistant or sensitive to apoptosis. They also demonstrate for the first time that alternative survivin transcript expression levels may be predictive markers in FEC and TE treatment in breast carcinoma.Converse conclusions are also made in a few studies, for example, Kostadima et al quantitatively measured mRNA levels of survivin in 272 breast cancer patients but fail to correlate these levels with disease outcome (39). But the paper was questioned by Span et al for disproportionate groups and unfeasible multivariate analysis (83). Kennedy et al examined the expression of survivin protein in a series of 293 cases of invasive primary breast carcinoma (67), they found nucleus-localized survivin expression was a significant independent prognostic indicator of favorable outcome both in relapse-free and overall survival. This is a logical finding, as caspases are present and function in the cell cytoplasm (71). Although the black and white IHC images provided in the study do not permit appreciation of the nuclear or cytoplasmic staining of survivin, although the results could not be replicated in the 106 samples used for the RT-PCR study (68), their findings highlights that survivin has different functions by different forms with respective subcellular location. The above mentioned study firstly analyzed the expression of survivin and its two splice variants, survivin-DEx3 and survivin-2B in breast cancer (68). The results indicated that bcl-2 mRNA expression, but not survivin and its two splice variants, is a significant prognostic factor associated with favorable outcome, in terms of both RFS and OS, and correlating

Tab 2: Expression of survivin in breast cancer in relation to prognosis and outcome

Author/yr./ reference	Assay	Patient No. and positive rate	Outcome	- = +
Tanaka K/2000/ (66)	IHC	167/70.7%	With worse outcome in breast carcinoma.	-
Nasu S/2002/ (63)	RT-PCR	37/41 (90.2%)	No significant association with clinicopathological factors, survivin mRNA is a useful diagnostic marker for breast cancer.	-
Kennedy/2003/ (67)	pAb	293/60%	Nuclear staining of survivin is an independent prognostic indicator of good prognosis both in relapse-free and overall survival	+
O'Driscoll L/2003/ (68)	RT-PCR	72/106/68%	No significant association was found between the expression of wild-type or the splice variants and disease free or overall survival.	=
Chu JS/2004/ (69)	IHC	226/59.3%	Correlate with clinicopathologic parameters, It does not have significance as a marker in predicting overall or disease-free survival.	=
Span PN/2004 (70)	mRNA	275/100%	Poor prognosis，positive relationship with grade higher in ductal rather than in lobular breast cancers	-
Ryan B/2005/ (36)	sq RT-PCR	156/93.6%	Survivin andΔEx3 positively correlated with apoptosis	-
Barnes N/2006/ (71)	IHC	DCIS (n=161/73%) IBC (n=58 /74%)	Correlated to DCIS recurrence.	-
Ryan BM/2006/ (36)	ELISA	420/90%	Independent prognostic factor, with a significantly worse disease-free survival and overall survival	-
Kostadima L/2006/ (39)	RT-PCR	263/272 (90%)	Associated with adverse clinicopathologic and molecular characteristics of node-positive primary breast cancer but do not predict patient outcome.	=
Sohn DM /2006 (5)	IHC	52/80 (65%)	The expression of cytoplasmic survivin was common in breast cancer and could be both a useful diagnostic marker and an important source of prognostic information. with poor prognosis	-
Span PN/2006/ (72)	qRT-PCR	275	Total survivin, survivin 2alpha, and survivin-3B were associated with poor relapse-free survival	-
Hinnis AR/2007/ (73)	IHC	165	With shorter survival and adverse outcomes.	-
Al-Joudi FS/2007 (74)	IHC	260/382 (68.1%)	Aid in diagnosis, confirm malignancy, and assess the disease progress and response to therapy.	-
Al-Joudi FS/2007/ (75)	IHC	382	Tumor histological grades and tumor size and lymph node involvement.	-
Nassar A/2008 (76)	IHC	30/37 (80%)	Correlate with overall survival	-
Brennan DJ/2008/ (77)	IHC	102	Nuclear survivin is a poor prognostic marker in breast cancer.	-
Nassar A/2008/ (78)	IHC	91/84%	Correlate with poor prognostic parameters, but not with outcome	-
Tsai WC/2008/ (1)	IHC	290	Higher expressions of matriptase and survivin correlate significantly with clinicopathological parameters in breast cancer and the malignant potential in premalignant lesions. In addition, higher survivin expression had poorer prognosis of breast IDC cases.	-
Fuzhong T/2008/ (79)	SDS-PAGE, western-immunoblotting, IHC and mAb		The patients have high response rate of low expression of survivin survivin is an important predictive factor for effectiveness of neoadjuvant chemotherapy with TE regimen in locally advanced breast cancer	-

mAb, monoclonal antibody, pAb, polyclonal antibody, sq RT-PCR, semiquantitative reverse transcriptase polymerase chain reaction, IHC, immunohistochemistry, CNR, cytoplasmic to-nuclear ratio. – negative prognosis = irrespective + positive prognosis.

with ER positivity.

Survivin and treatment of breast cancer

Adjuvant chemotherapy or neoadjuvant chemotherapy

Growing evidence has indicated that survivin plays a crucial role in drug resistance, and modulation of survivin expression affects drug effectiveness. Mesri et al used a breast cancer line and delivered a recombinant adenovirus encoding survivin (T34A) into subcutaneous tumor nodules or into tumor-bearing peritoneum, striking antitumor activity was observed, parallel to taxol and more effective than adriamycin in induction of MCF-7 cell apoptosis and enhanced taxol-induced cell death (84). In three xenograft breast cancer models in immunodeficient mice, pAd-T34A suppressed de novo tumor formation, inhibited by approximately 40% the growth of established tumors, and reduced intraperitoneal tumor dissemination. Tumors injected with pAd-T34A exhibited loss of proliferating cells and massive apoptosis by in situ internucleosomal DNA fragmentation.

Many studies have demonstrated that some cancer prevention drugs may function by inhibiting survivin expression (85,86) and overexpression of survivin was related to chemoresistance of various drugs including adriamycin (87), cisplatin (88-90) and taxol (91). Upregulation of survivin by taxol per se appears to be an early event and independent of paclitaxel-mediated mitotic arrest in MCF-7 breast cancer cells (92). High survivin expression in turn results in resistance to taxol and may be a survival pathway in cancer cells (93). Retinoids, an inducer of apoptosis, have been shown to sensitize MCF-7 breast cancer cells to taxol by down regulating survivin (94). Similar outcome was got by several groups when they respectively investigated the potential role of prodigiosin (95), flavopiridol (96) , resveratrol (97), 3,3V-diindolylmethane (98) and Calcium sensing receptor (99) in the treatment of breast cancer. Moreover, PI-3K/Akt2 signal pathway (21, 100) and leptin/stat3 pathway (23) activation both played roles in acquired resistance to docetaxel in breast cancer cells. More recently, Lu et al found that the mechanism of Her-2 overexpression conferring on breast cancer cells resistance to taxol is via upregulation of survivin (101).

Radiotherapy

Evidence has also revealed an essential role for survivin in radiation therapy of breast cancer, i.e., survivin can be drastically down-regulated by radiation, with its high levels associated with resistance to radiotherapy. High expression of survivin in breast cancer associated fibroblasts in vitro shows resistance to ultraviolet (UV) light irradiation (105). Exposure of breast carcinoma MCF-7 cells to UVB, or fractionated radiation resulted in a significant increased survivin expression (96,106). Kim et al examined the effect of signal transducer and activator of transcription 3 (stat3) on survivin expression in irradiated breast cancer cells, and found inhibiting survivin and stat3 together could promote radiation sensitivity in MDA-MB-231 breast cancer cells (102). Consistently, combination of radiation and 17-AAG (an antitumor agent which blocks survivin's function)

Tab 3: Examples of altered sensitivity of cell lines to different cytotoxic drugs or radiation following manipulation of either survivin function or cellular levels

Cell line/tissue	Strategy/ survivin (down or up)	Therapy	Effect on therapy	Reference
MCF-7	mutant/down	taxol	enhanced	84
MCF-7	siRNA/down	taxol	enhanced	92
multiple breast cancer cell lines and patient samples	ASODN/down	taxol	enhanced	91
MCF-7	RA/down	taxol	enhanced	94
MCF-7, T-47D and MDA-MB-231	Prodigiosin/down	taxol	enhanced	95
MCF-7 xenograft model	flavopiridol/down	Adriamycin, Taxol, or UVB	enhanced	96
MCF-7 and MDA-MB-435	calcium sensing receptor/down	taxol	enhanced	99
MCF-7 tumor nodules or tumor-bearing peritoneum	mutant/down		=taxol, >adriamycin	84
MDA-MB-231	stat3inhibition/down	radiation	enhanced	102
BT-474	17-AAG/down	radiation	enhanced	103
MDA-MB-231	deguelin/down	radiation	enhanced	104

RA, retinoic acid.

in human BT-474 breast cancer cells resulted increased apoptotic indexes and cytotoxicity (103). A recent study from China shows that deguelin enhances radiosensitivity of breast cancer MDA-MB-231 cells by inhibiting pAkt and survivin expression (104). Similar outcome can be seen in other cancers, such as rectal cancer (107), pancreatic and gastric cancer (108,109).It is worthy of note that survivin can contribute to radiation resistance also by promoting the survival of tumor vascular endothelial cells (109,110,111). In fact, induction of vascular endothelial apoptosis was recently shown to be a major determinant of overall tumor response to radiotherapy (35).

Why survivin act as an absolutely different role?

We must notice that with the increased number of publications, inconsistent conclusions have been reported frequently in breast cancer (35), also in gastric cancer (112). Several reasons contribute to the opposing behavior of survivin.

There are all 5 splice variants (wide-type survivin, survivin2B, survivin2α, survivin3B and survivinΔEx3) with different structure and function (72, 112-114). For example, survivin-2a seems to strongly attenuate the antiapoptotic activity of survivin even without an apoptotic stimulus (115). survivin3B was more frequent in high grade breast carcinomas and correlated with the p53 gene mutation, suggesting a positive role of survivin-3B in apoptosis inhibition (116). Survivin2B might act as a proapoptotic factor in breast cancer (116), and its expression decreases in a tumor stage-dependent way, in small tumor size, its expression is significantly higher and is inversely associated with axillary node positive carcinomas (116). Theoretically, if survivin2B expresses predominantly, it will related to a good prognosis. A report confirmed the hypothesis by reporting that survivin-2B expression is toxic to cells (117). But its expression is at low levels in most malignant tissues, especially in late stage ones, so its function was hidden by other splice variants and this variation may play a role in cancer development (72, 116, 118,119). That may be the reason of some reports indicating a good or inconclusive prognostic role of survivin's expression in breast cancer (67,68). To regulate the balance between these splice variants, or selectively inhibit antiapoptotic variants, or enhance proapoptotic variants might lead to novel strategy for cancer prevention and therapeutics.

Besides different splicing forms, survivin also localized in different subcellular compartments. Wild type survivin and survivin2B preferentially localize in cytoplasm. Survivin 2a, almost equally between the cytoplasm and nucleus, While survivinΔEx3 localizes in both mitochondria and nucleus. However, in mitotic cells, survivin-ΔEx3 appeared to be translocated to and colocalized with the mitotic spindle. Dohi et al reported that mitochondrial survivin could be released into the cytoplasm, where it prevents caspase activation and inhibits apoptosis (120). Other studies found sending survivin into the nucleus (121) or lowered cytoplasmic-to-nuclear ratio of survivin (77) or nuclear export-deficient survivin mutants (122-124) failed to protect tumor cells against chemo- and radiotherapy-induced apoptosis. So exploiting the mechanism for the survivin's dynamic subcellular distribution and translocation will offer a new point of view.

Methylation and Phosphorylation. Several observations show that survivin is unmethylated in cancer but may be selectively methylated in normal tissues with individual variations (125,126). Methylation may play important a role in the p53 mediated suppression of survivin (127). Another critical requirement for survivin function was the phosphorylation on Thr34 (128). Treatment with a cyclin-dependent kinase inhibitor, flavopiridol, suppressed survivin phosphorylation on Thr34 and resulted in loss of survivin expression and induction of apoptosis in breast cancer cells (96).

Specificity and sensitivity of antibody or RT-PCR used in the research. Interestingly, some antibodies are specific to different domain of survivin, for example, an antibody specific to sequence Ala^{3}–Ile^{19}, recognizes survivin band from nuclear fraction. Another antibody, to sequence Cys^{57}–Trp^{67}, recognize survivin band from cytosol fraction (129). These immunohistochemical-based studies have failed to reach a consensus about how survivin staining should be interpreted (77). If the antibody used by the author could not react with the full survivin, or the tissues or images were inappropriately processed by the researchers, bias would occur. For example, different variants have same N-terminal sequence, which could be potentially recognized by survivin antibodies used currently, this observation raises a possibility that the nuclear survivin is survivin-ΔEx3 or both survivin and survivin-ΔEx3 (130). Which has been pointed out by Li et al according to their working experiences and the excellent images they offered (86). And this dilemma can be resolved by image analysis (85). Using RT-PCR to measure survivin mRNA is more accurate because survivin concentrations are largely controlled at the level of gene transcription (36, 131). Real-time RT-PCR has the advantages of being more quantitative than classical one (70). Although the primers and probes were designed specifically to pick only the intended variant, they would likely to react with each other (132). So more sensitive and special primers and probes are needed.

Conclusion

Because of its functions as a cancer gene/protein, survivin is currently extensively used in diagnosis, prognosis and treatment of breast cancer. The detection of serum/urinary survivin by immunochemistry or RT-PCR seems to be a promising assay to detect both newly diagnosed and recurrent breast cancer. Increased survivin expression in cancer patients is an unfavorable prognostic marker correlating with decreased overall survival in breast carcinomas. Survivin overexpression may be a predictive factor to determine response to chemotherapy and radiotherapy in patients with breast cancer. Survivin has been pursued as a cancer drug target by diverse strategies, such as immuno approaches and the application of small-molecule antagonists. Although some inconsistent reports exists, overwhelming reports support that measurement of survivin expression can help to make early diagnosis, predict prognosis and judge therapy effect of breast cancer. Targeting it for cancer treatment has less/ no toxicity to normal tissue and cells. These preliminary findings on the diagnostic, prognostic and predictive potential of survivin should now be confirmed in large prospective trials. Furthermore, assays for the measurement of survivin and its splice variants should be simplified, standardized and evaluated in external quality assurance schemes.

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