

A Review on Survivin as a Prognostic and Therapeutic Cancer Biomarker

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Abstract

Survivin is an antiapoptotic protein expressed in tumor cells that correlates with aggressiveness, prognosis and treatment. Objective: This review summarizes significance of survivin expression among different tumor types highlighting the potential value of survivin as an important biomarker that may have an impact on patient's response to therapy with prognostic implications.

Keywords

Survivin, Prognostic Biomarker, Cancer, Antiapoptotic

1. Introduction

The antiapoptotic survivin is a 16.5 kD wild-type protein consisting of 142 amino acids in length encoded by the BIRC5 gene at chromosome 17 [1] and it is expressed in fetal tissue and tumor cells [2]. The caspases (cysteine-aspartic proteases) are intracellular cysteine protease enzymes (such as caspase-3 and -7) that are involved in the regulation of programmed cell death (apoptosis) to maintain cellular homeostasis during development. Caspases are activated by initiator caspases, like caspase-9. Their activation will sequentially activate other executioner caspases which in turn result in enhanced cellular degradation and apoptotic morphological changes [3] [4]. Deregulation and inhibition of apoptosis is a known mechanism of cancerization and cancer progression. As survivin mainly functions as an anti-apoptotic protein, its expression in tumor cells was found to be correlated with aggressiveness and adverse clinical prognosis making it a promising biomarker or an indicator of tumor aggressiveness and/or response to therapy [5] [6].

Survivin down regulates p53 [7]. Overexpression of survivin may overcome checkpoints of the cell cycle and result in increased mitosis and lead to the trans-

formation to malignant cells [8] [9] [10].

2. Survivin and Bladder Cancer

studies relate survivin to survivin overexpression is strongly predictive of recurrence, progression specially mortality in bladder cancer and the malignant progression of urothelial carcinoma of the urinary bladder [11] [12]. Other studies showed that number of positive tumor cells increasing with the grade of the tumor [13]. other studies detect urine survivin sensitivity in comparison with the cystoscopy as a standard method but results showed less than 80% sensitivity [14] [15].

3. Survivin Breast Cancer

Positive expression of survivin in breast cancer predicted a significantly higher risk of disease recurrence and is shown to be associated with lymph node metastasis (P value = 0.01) [16]. The rate of survivin expression seems to correlate with the sensitivity of survivin detection methods. In one study using survivin immunohistochemistry, survivin was expressed in 65.3% (55.2% - 90.0%) of breast cancer samples while survivin mRNA detection using RT-PCR was identified in 93.6% (90% - 97%) of cases. The same study showed association of survivin expression with HER2 overexpression, vascular endothelial growth factor (VEGF) and, urokinase plasminogen activator (uPA)/PAI-1 [17].

A study from Egypt investigated the expression of survivin in correlation with the clinicopathological parameters, proliferation and molecular classification of breast carcinoma. In that study, survivin expression (detected in 78.5% of breast carcinomas) was related to tumor size, high histologic grade, lymph node metastases, advanced tumor stage, MIB-1 index and negative estrogen/progesterone receptor status. Notably, the subcellular localization of survivin significantly related to histologic grade, stage and lymph node involvement [18] [19]. In another study on 420 non-metastatic breast cancer tissue samples using the ELISA method, a high survivin expression was detected in 90% of cases and indicated a significantly poor prognosis on long term follow up [19].

4. Survivin Expression in Head and Neck Cancer

Different types of head and neck neoplasms have been studied for survivin expression in different studies. Expression of survivin and COX2 was related to the ability of invasion and cancerization in ameloblastoma [20] [21]. Overexpression of these 2 markers in oral mucosal premalignant lesions suggests a role in early stages of oral carcinogenesis [22]. Another study handled localization and prognostic value of nuclear and cytoplasmic survivin expression in the pre-therapeutic biopsies of 71 oral and oropharyngeal squamous cell carcinoma (OSCC) patients. Their results indicated that nuclear versus cytoplasmic survivin correlated with prognostic outcome. Cytoplasmic localization of survivin is also considered a potential therapeutic strategy [23]. Cases of oral SCC together with distant metastatic lesions were

analyzed for expression of survivin by immunohistochemistry and Western blotting. Out of the 91 cases (82.7%) of primary SCC and all metastases (seven cases, 100%) were positive for survivin expression, there was no significant correlation between survivin expression and age, sex, tumor size, and the presence of lymph node and distant metastases. Survivin expression was higher in less differentiated tumors and was prognostically significant ($P < 0.05$) [24].

Correlation between survivin mRNA expression and clinicopathologic features or prognosis of OSCC patients was analyzed. Small interfering RNA technology was used to detect and decrease cancerous cells expression of survivin and detect the effect on its sensitivity to chemotherapeutic drugs [25].

5. Survivin and Digestive Tract Tumors

The role of survivin in colonic tissue transformation of dysplasia low dysplasia to high dysplasia with P53 and B catenin was studied and results showed that positivity of survivin is raised by six to twelve folds in tumor cells [26] [27].

Regarding prognosis of recurrent colorectal carcinoma surviving considered as patients with negative survivin tumors had a five-year survival rate of 94.4% compared with 44.8% for patients with Survivin positive tumors [28].

(New Gene therapy for colon cancer by adeno-associated viral vector-mediated transfer of survivin Cys84Ala mutant gastro was studied and concluded that the use of AAV-mediated survivin mutant (Cys84Ala) is a promising strategy in colon cancer gene therapy) [29].

Other Studies aimed downregulation of survivin by induction of EPR-1 cDNA noticed a decrease in tumor growth and increased response to anticancer agents used for treatment of colon cancer [30]. Finally, the overall survival rate is decreased in those studied for showed positive survivin [31].

6. Survivin and Genital Tract Tumors

No survivin mRNA was expressed in all normal ovarian specimens, while it appeared in 73% of ovarian carcinomas, 47% of borderline ovarian carcinomas and 19% of benign ovarian tumors study suggest that survivin is associated with progression of ovarian carcinoma [32].

A retrospective review on Survivin status affects prognosis and chemosensitivity in epithelial ovarian was done on 90 patients with a median follow-up time of 51 months. The reverse transcription-polymerase chain reaction and flow cytometry were applied to detect survivin expression levels and cell apoptotic percentages. Results showed that cytoplasmic survivin protein expression is an independent molecular marker for prognosis. Sequence-specific shRNA targeting survivin can effectively suppress survivin expression, enhance apoptosis, and increase the sensitivity of ovarian cancer cells to paclitaxel but not to cisplatin [33].

Studies on endometrial carcinoma associated with PTEN abnormalities found that PTEN may interfere with the process of apoptosis and by promoting survivin expression [34]. Data indicate that a survivin-specific immune response may

be induced spontaneously in patients, further fortifying the eligibility of survivin as an immunotherapeutic target [35].

7. Survivin Expression in Lymph Nodes

Survivin over expression might be a poor prognostic factor for patients with NHL. However, more large-scale studies are needed to confirm these findings [36] [37]. Survivin suggested as an attractive target for new anti-cancer intervention of NHL and vector-based survivin-shRNA could clearly reduce the expression of survivin and induce cell apoptosis and growth inhibition of malignant cells [36].

8. Survivin and Renal Cell Carcinoma

Survivin was suggested as a prognostic marker in renal cell carcinoma. Expression was correlated with prognosis and clinicopathological features, and it could be used in the future as a biomarker for in therapy after more comprehensive studies [38].

9. Survivin and Hepatocellular Carcinoma

Survivin expression correlates with nuclear and histologic grade, microvascular invasion, increased mitotic figures, local recurrence, and poor prognosis. RT-PCR detection test for survivin along with immunohistochemistry of 20 cases of hepatocellular carcinoma and one case diagnosed as intrahepatic cholangiocarcinoma. Low levels of Survivin mRNA can be detected in normal and liver tissue [39]. Over-expression of the protein is associated with positive nuclear p53 nuclear staining [40]. The concentration of the protein may reflect the prognosis of the case but this is still needs more studies [41]. Two survivin scoring methods—topoisomerase II α nuclear labelling index (LI) and tumor differentiation—were analyzed by researchers for specificity results showed that Survivin nuclear LI correlated significantly with tumor cell proliferation [42].

10. Survivin in Pancreatic Cancer

A study correlated survivin mRNA, promoter's expression and radio sensitivity of the tumors showing a very promising result regarding radio-sensitivity and survivin inhibitors treatment usage and improvement of prognosis [43] [44] [45] [46].

Targeting survivin as an upstream regulator of mitochondrial dependent apoptosis, not only enhance apoptosis but also suppress angiogenesis [47].

11. Survivin in Head and Neck Tumors

Survivin expression in head and neck squamous cell carcinoma (HNSCC) as assessed by immunohistochemical staining and western blot and then compared with normal tissue was significantly associated with loss of differentiation in tumors and in that study, Bcl-XL was associated with nodal metastasis ($P < 0.001$) [48].

Furthermore, Oxaliplatin treatment for HNSCC was studied in radioresistant

cases with high survivin levels and found to be effective in reducing the resistant to radiation therapy [49].

12. Conclusion

Survivin is an important biomarker in diverse types of malignant neoplasms originating in different organs. Correlation of survivin expression with adverse tumor characteristics and less favorable patient's outcome indicates the importance of including survivin in the biomarker panel used to evaluate malignancies with therapeutic and prognostic implications.

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Abbreviations

BIRC5: Baculoviral inhibitor of apoptosis repeat-containing 5

HER2: Human epidermal growth factor receptor 2

VEGF: Vascular endothelial growth factor

PAI-1: Plasminogen activator inhibitor-1

MIB-1: Mindbomb E3 ubiquitin protein ligase 1

COX2: Cyclooxygenase 2

OSCC: Oral Squamous Cell Carcinoma

SCC: Squamous Cell Carcinoma

AAV: Adeno-associated virus

EPR-1 cDNA: Effector cell protease receptor 1 complementary DNA

PTEN: Phosphatase and tensin homolog

NHL: Non-Hodgkin lymphoma

Bcl-2: B cell lymphoma 2

Bcl-XL: B cell lymphoma extra large