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Survivin as a diagnostic and therapeutic marker for thyroid cancer

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ABSTRACT

Thyroid cancer (TC) is known as the most prevalent form of endocrine malignancy. With regard to high heterogeneity of the nodules, problem of discriminating between benign and malignant ones in terms of pathological characteristics, as well as lack of appropriate molecular markers; significant efforts are being made to identify molecular markers that able to detect tumorous lesions. Survivin, the newest member of the family of proteins inhibiting cell apoptosis, has been recently considered as a novel molecule marker for cancer. Studies on TC have also demonstrated distinctive expression of survivin and its splice variants in cancer cells compared to normal ones. Therefore, detection of survivin expression and its new splice variants can be utilized to identify tumor nodules and distinguish them from non-cancerous ones, along with other routine laboratory methods.

1. Introduction

Although only 1% of malignant cancers are of thyroid type, this is the most prevalent endocrine malignancy that accounts for 90% of cases [1]. The risk of TC in women is three times greater than that in men. The highest rates are also observed between the ages of 45 and 55 in women and between 55 and 65 in men [2]. High heterogeneity of thyroid tumors, problem in discriminating between benign and malignant nodules in terms of pathological characteristics, as well as lack of appropriate molecular markers can make it difficult to differentiate benign nodules from cancerous ones. In recent years, numerous efforts have been made to introduce a molecular marker able to predict the nature of thyroid tumors as an auxiliary diagnostic and prognostic factor along with other methods. Since programmed cell death (apoptosis) is taken into account as a natural mechanism of cell defense against cancers, any defects in its induction pathways can lead to abnormal cell proliferation and ultimately production of tumor glands. Therefore, apoptosis inhibitors are regarded as important markers involved in cancer incidence and progression [3]. In this respect, survivin is a newly-discovered member of the family of proteins that suppresses apoptosis. The given gene is expressed in abundance in embryonic tissues, but its expression in mature normal tissues is negligible and cannot be traced [4]. Moreover, the expression of this gene for a tumor is very specific and it has been introduced as the fourth transcriptome expressed in tumor cells [5]. The distinct expression of survivin and its splice variants in cancer cells compared to normal ones has also led to the expression of this gene as a key diagnostic marker for cancer [6]. Although earlier studies concerning the association between survivin and thyroid tumors have revealed a correlation between survivin expression and tumor nature, there is no comprehensive information on the expression pattern of survivin in thyroid tumors.

2. Survivin gene

The size of the survivin gene is 15 kb. It is also located on chromosome 17q25 and consists of four exons and three introns. The survivin gene product is a protein that is comprised of 142 amino acids and has a molecular weight of 16.2 kDa [7]. Human survivin protein has 84.3% homology with that of mice. Survivin is also recognized as a newly-discovered member of the inhibitor of apoptosis (IAP) family and is also the most potent inhibitor of apoptosis. Besides; survivin has complex activities including the inhibition of apoptosis, acceleration of cell transformation, participation in cell mitosis and angiogenesis, as well as drug-tolerance of tumor cells [8] (Fig. 1). Survivin similarly plays an important role in angiogenesis. In this regard, increasing survivin expression protects endothelial cells from apoptosis in vitro [9].

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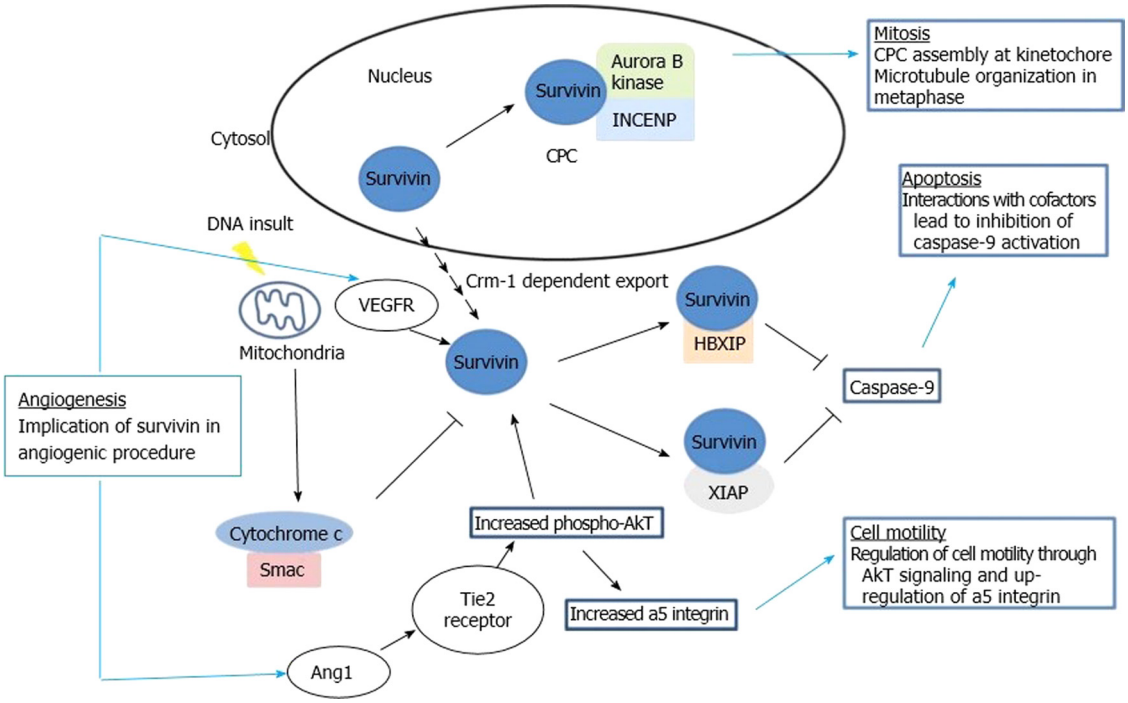

Fig. 1. Survivin activity contributing to tumor development and metastasis. Adapted from [13].
Survivin cell activity helps in developing tumors and metastasis. It is also considered as a multi-functional protein that interferes with the regulation of mitosis, apoptosis, and cellular mobility, and can even provide proliferative and metastatic benefits to tumor cells. Survivin also forms part of the chromosomal passenger complex (CPC) with aurora B kinase, and the inner centromere protein (INCEP) to regulate chromosomal alignment during mitosis. Survivin interaction with hepatitis B X-linked interacting protein (HBIXP) and X-linked IAP (XIAP) can also prevent and regulate the activation of caspase-9, as a molecule involved in cell death. Likewise, the anti-apoptotic effects of survivin can be regulated by the pro-apoptotic SMAC molecule; that is released from mitochondria as the pathway for apoptosis is introduced. Survivin can correspondingly accelerate cellular mobility via activating AKT and increasing the expression of α5 integrin [13].

As the angiogenesis of the tumor is critically dependent on the survival of the endothelial, survivin can indirectly lead to tumor growth through the protection of newly-formed blood vessels [10]. The given gene is also a bi-functional protein that acts as a suppressor of apoptosis and plays a key role in cell proliferation. Accordingly, survivin is strongly up-regulated in a variety of prevalent cancers [11]. Furthermore, it is known as the smallest member of the IAP family, expressed only in embryonic tissues and tumors. This gene is also strongly associated with differentiation, proliferation, infiltration, and metastasis processes within tumor cells. Furthermore, survivin acts directly on the caspase signaling, mainly through regulating caspase-3 and caspase-7 activity. It should be noted that caspase signaling may be indirectly inhibited by survivin via P21 [12].

3. Survivin in TC

Evaluation of survivin expression in papillary thyroid carcinoma (PTC) and anaplastic thyroid carcinoma (ATC) indicates a stepwise increase in survivin expression from the limited clinical stage of PTC to advanced stages of PTC to ATC [14]. With regard to apoptotic events in thyroid malignancy, it has been suggested that the transfer of well-differentiated carcinoma cells (PTCs) to undifferentiated ones (ATCs) is accompanied by a reduction in the expression of anti-apoptotic, galactine-3, and Bcl-2 molecules and consequently an augmented expression of the survivin. Possibly, at least part of the ability of the thyroid malignant cells to escape apoptosis may be facilitated [14]. Indeed, molecular studies have revealed that down-regulation of survivin in cancerous thyroid cells can result in intensified apoptosis and chemotherapy sensitivity [15]. In addition; it has been observed that survivin binds to the CDK4 cell cycle regulator, which activates CDK2/Cyclin-E and eventually leads to phosphorylation of ribosomal protein. This can initiate cells into the cell cycle following the phosphorylation of ribosomes to accelerate the transformation at the G1/S stage [16,17]. Natural thyroid follicles irregularly express survivin, while its expression is increased with the dedifferentiation of thyroid carcinoma [18]. According to thyroid studies, the rising trend in survivin expression is one of the first events in thyroid tumors. Expression of survivin is also associated with invasion, metastasis, and tumor progression [14,19,20]. In this regard, one study demonstrated a strong association between survivin expression and status of metastatic lymph nodes in patients with PTC, which might be correlated with the process of metastasis [21]. The high expression of survivin in medullary thyroid carcinoma (MTC) is also correlated with raised calcitonin basal blood levels, while this is not evident for XIAP. The observation that high serum calcitonin associates with up-regulation of survivin in MTC specimens has been also supported by the data published by Thomas and Shah [22]. This interdependency between survivin and calcitonin may be of unique significance in MTC, because para-follicular C cells as the sole producers of the peptide hormone calcitonin are the hosts from which MTC initiates. Thus, the association between autocrine and paracrine signaling, in which tumor cells secrete calcitonin and induce anti-apoptotic or promitotic signaling pathways upon binding to their receptor is of utmost importance for oncogenesis in MTC. This self-preserving cycle of autocrine secretion and self-stimulation may be considered as a key regulatory step, which warrants additional research in this field [23]. Several investigations have further shown that survivin has an augmented expression in ATC and is associated with more invasive [18,20]. Increasing the expression of survivin in the nucleus also represents anaplastic (AC). Similarly, survivin may play an important role in the pathogenesis of AC. Furthermore, the overexpression of survivin from benign to AC and the relationship between expression of survivin and the clinical stage has indicated that survivin is involved in AC progression [24]. Survivin can correspondingly lead to increased expression during thyroid carcinoma. Moreover, it can improve profiles in

advanced thyroid carcinoma such as pT3/T4 [19]. In this regard, reduced and increased expression of survivin may be a potentially useful prognostic marker for the classification of human thyroid carcinoma. So, decreasing survivin expression using siRNA does not cause death in a natural cell population due to lack of expression of survivin. This suggests that the use of survivin siRNA as a new therapeutic approach to TC requires further research [19]. In this regard, Eto et al. mostly observed survivin nuclear expression; while in another study, they only recognized cytoplasmic survivin. The survivin cytoplasmic presence has been even suggested to be related to the anti-apoptotic role and cellular survival, whereas the nucleus expression of survivin has been associated with increased activity and it is likely to be correlated with a more advanced stage of cancer although this hypothesis is still under discussion [25]. Previous studies have shown that survivin expression is strongly associated with dedifferentiated thyroid carcinoma and survivin has demonstrated mis-expression in normal thyroid tissues [18,19,21]. Therefore, survivin may be an attractive target molecule for the treatment of dedifferentiated thyroid carcinoma [26]. Molecular studies have also reported that reduction of survivin expression in TC cells leads to an increase in apoptosis and sensitivity to chemotherapy agents [27]. In this respect; reporting similar survivin expression levels in papillary microcarcinomas and large PTCs, Antonaci et al. [28] demonstrated that survivin gene up-regulation was an early event in PTC tumorigenesis. Survivin expression studies, analyzed for a wide range of thyroid tumors, have also found increased levels of expression from well-differentiated to anaplastic carcinoma as well as its association with disease progression and invasive behaviors. Additionally; expression of survivin has been investigated by immunohistochemical methods in thyroid tumors, nevertheless it shows low expression than other malignancies in humans. Published results in this field have further revealed a stepwise increasing trend in survivin staining along the spectrum of thyroid sores from well-differentiated to anaplastic carcinoma, suggesting that expression of survivin may contribute to disease progression of thyroid carcinoma and may be also associated with aggressive behaviors and dedifferentiation [18,19,29]. The over-expression and the sub-cellular localization of survivin may also identify a cohort of tumors with aggressive biological and clinical behaviors, rapid progression towards a poorly differentiated phenotype, and poor prognosis. It should be noted that survivin shows significant functional implications in the oncogenesis of follicular thyroid carcinoma (FTC) and thus proves to be a viable target in patients with advanced FTC [30]. Accordingly; since precise determination of prognostic factors remains an essential step in evaluation of TC patients, further investigations should be carried out on larger and more heterogeneous populations to validate and extend the results.

4. Survivin splice variants in TC

Differential expression of diverse survivin splice variants in malignant and non-malignant tumors makes it valuable as a tumor marker for the diagnosis and prognosis of TC. In this regard, studies have suggested a relationship between survivin variants and different tumors, and an anti-apoptotic role has been also suggested for such varieties [31]. Recent research studies have similarly demonstrated a high expression level of survivin and survivin-ΔEx3 in malignant thyroid tumors compared to benign and non-cancerous nodules [12]. In this respect, Vandghanooni et al. evaluated survivin expression using RT-PCR and found that survivin-DEx3 had increased expression in malignant TC cells (approximately 10-fold) compared to normal tissues [12]. Thus, expression of the survivin gene and the survivin-DEx3 splice variant can be assumed as a potential candidate for a reliable biomarker for PTC detection [12]. Interestingly, the growth in expression of survivin DEx3 in the nucleus is more commonly seen in poorly differentiated and anaplastic carcinomas, which are usually radiotherapy-resistant. To assess whether positive nuclear staining for survivin can be used as a biomarker for predicting radioactive resistance in poorly differentiated thyroid, more studies are needed; i.e. radiotherapy-resistant patients are currently selected only on the basis of clinical parameters [32]. It should be noted that two types of survivin splice variants; 2B and DEx3, have different biological properties. In this regard, survivin 2B is involved in the activation of apoptosis. In contrast, survivin DEx3 is suggested, along with tumor invasion, to play a role in advanced tumor stage and poor prognosis in many types of cancers [33]. Accordingly, further studies are required on the probability of the diagnosis and the prognosis of different survivin variants within the cell as well as the relationship between different survivin variants with patients' outcomes and their responses to radiotherapy.

5. Chemotherapy and survivin in TC

The level of survivin protein in PTC cells is significantly reduced following treatment with AUY922 (Luminespib). This implies that apoptosis induced by AUY922 is due to reduced expression of survivin. The molecular mechanism of the inhibitory effect of AUY922 is also probably caused by the degradation of the molecular complex of HSP90/survivin, which moderates survivin expression [34]. The results of one study in this domain showed that survivin inhibitor (YM155) could significantly reduce cell proliferation in anaplastic thyroid carcinoma cell lines, inhibit in vivo proliferation and metastasis, and consequently prolong survival time. Moreover, YM155 can have potent anti-cancer activity in ATC cells, inducing dose- and time-dependent growth inhibition associated with the suppression of survivin and claspin expression. Despite the fact a specific and precise mechanism reducing the expression of survivin by YM155 is unclear; it seems that targeting the promoter region of the survivin gene suppresses expression at the level of mRNA and protein [35]. Another study on hyperoside also showed that hyperoside-induced apoptosis may be induced by the inhibition of survivin protein expression and Fas/FasL regulation [36]. Therefore; c-IAP1, survivin, and SMAC are proteins that contribute to TC resistance to CDDP, doxorubicin, and taxol. In addition, the findings have indicated that c-IAP1 and survivin are directly involved in achieving permanent resistance of the TC cells in chemotherapy. These results have suggested that c-IAP1 and survivin are potential targets for treatment interventions aimed at restoring the sensitivity of poorly-differentiated thyroid carcinomas (PDTC) and anaplastic thyroid carcinoma (ATC) that are chemically resistant. Targeting c-IAP1 and survivin with RNAi or immunological approaches (monoclonal antibodies) as short polypeptides that regulate their negative performance can be potentially an appropriate treatment approach for patients with PDTC or ATC who do not respond to chemotherapy. IAP1, survivin, and their negative regulator SMAC can also directly contribute to the development of resistance to chemotherapy in PDTC and ATC cells [27]. Exposure to short-term (48 h) TC cells with cisplatin (CDDP), doxorubicin, or taxol has also revealed that tumor cells can tolerate adverse conditions when there is increasing expression of c-IAP1 or survivin or decreasing expression of SMAC. In addition; it should be noted that cancerous thyroid cells exposed to chemotherapy are alive although the release of SMAC from their mitochondria is very limited. Silencing survivin expression can thus immediately increase CDDP or doxorubicin cell mortality. Likewise, increased expression of SMAC can significantly improve the cytotoxic effect of taxol. Furthermore, cancerous thyroid cells, which have permanent resistance to various chemotherapy drugs and actively grow in the presence of antiblastic compounds, express a high level of IAPs. In particular, CDDP-resistant cells with survivin expression levels are higher, while doxorubicin-resistant cells can increase the expression of c-IAP1. As a whole, turning off this IAP via siRNA can repair cellular sensitivity to chemotherapy agents [27].

6. Polymorphism survivin in TC

Several single-nucleotide polymorphisms (SNPs) are detected within

the promoter region of the survivin gene. In this regard, a polymorphism at position -31, which contains the substitution of G for C (rs 9904341), has been most commonly documented in previous studies. This polymorphism is placed at the cell-cycle-dependent elements (CDE) and cell-cycle homology region (CHR) repressor-binding motif of the promoter [37]. This mutation (G/C) seems to be associated with up-regulation of survivin at both transcription and translation levels [38]. The survivin − 31 G > C (rs 9904341) polymorphism is correspondingly associated with a risk of PTC in the Iranian population, and the presence of C alleles is significantly associated with the presence of clinical manifestations, including lymph node involvement, vascular involvement, and multifocality [39]. In a study, it was found that A9194 G SNP in survivin had a significant effect on PTC sensitivity in the Chinese population [8]. These findings suggested that the persistence of research on survivin polymorphisms had provided an important source of information on the pathogenesis and prediction of clinical behaviors associated with TC.

7. Diagnostic value of survivin in TC

Evaluating survivin expression is clinically of utmost importance in terms of providing predictions of metastatic potentials of TC and also making significant decisions regarding treatment procedures as well as follow-up of affected patients [40]. In this domain, survivin DEx3 has demonstrated higher expression in comparison with survivin and survivin 2B. Such findings have even advocated the potential clinical effectiveness of survivin DEx3 up-regulation for the distinction between benign and malignant types of thyroid tumor [41]. In this regard, screening survivin gene mutation might be similarly a suitable diagnostic criterion for PTC [7]. Therefore, gradual growth of survivin expression from benign tissues to anaplastic carcinoma together with a correlation between survivin expression and clinical stages imply that survivin is concerned with progression of thyroid carcinoma and the given gene is likely to independently contribute to different phases of thyroid carcinogenesis [24]. Moreover, higher expression of survivin in tumor tissues than that in normal ones can result in detecting single-cell transformation and it would be certainly a useful tool in fine needle aspiration (FNA) samples to meet the purpose of an early diagnosis of TC. Furthermore, evaluation of survivin expression in FNA samples can be presumed as a valuable tool for identification of patients affected with TC requiring more surgeries, having thorough follow-ups, and adopting therapeutic strategies in this domain [28]. As well, over-expression of survivin can be associated with clinicopathological parameters of high aggressiveness. In this respect, a correlation between high survivin expression and aggressive behaviors hints a role in the progression of malignant thyroid tumors and indicates that survivin can be an appropriate tool for predicting aggressiveness of a sub-set of PTCs [14]. The over-expression and the sub-cellular localization of survivin may also identify a cohort of tumors with aggressive biological and clinical behaviors, rapid progression towards a poorly differentiated phenotype, and poor prognosis. This might be even beneficial in improving patient management and consequently provide innovative prognostic tools to differentiate among various thyroid neoplastic entities [20]. Thus, investigations conducted on survivin polymorphisms can be taken into account as important sources of information on pathogenesis and prediction of clinical behaviors related to TC [8]. In this regard, nuclear expression of survivin is common as a characteristic of anaplastic, which may include survivin as a leading role-player in ATC pathogenesis. Furthermore, a gradual rise of survivin expression from benign tissues to ATC as well as a correlation between survivin expression and clinical stages implies that survivin can be correspondingly engaged in the disease progression of thyroid carcinoma.

8. Positive correlation between molecular biomarkers and survivin

COX-2 expression may be associated with the pathogenesis of thyroid carcinoma during the early stages that might be validated through papillary microcarcinomas and node negative cancers indicating significantly higher COX-2 expressions than later-stage cancers. Survivin and COX2 may independently influence various phases of thyroid carcinogenesis [24]. In this regard, cyclin D1 and survivin have been expressed at very high rates and almost to the same extent in large papillary thyroid carcinoma (LPTC) and papillary thyroid microcarcinoma (PTM), both in tumoral masses and in nodal metastases. Cyclin D1 and survivin over-expression are probably considered as early events in tumorigenesis of thyroid papillary carcinoma [28]. Accordingly, higher expression of cyclin D1 and survivin in tumor tissues than that in normal ones results in detecting single-cell transformation and it would be regarded as a valuable tool in FNA samples for an early diagnosis of papillary cancer [28]. So, up-regulation of proliferating cell nuclear antigen (PCNA) in TC has been previously observed. In a study, a strong positive correlation between survivin DEx3 and PCNA expressions was reported at the protein level in thyroid lesions. In comparison with PCNA, it was found that survivin DEx3 expression had shown higher specificity with similar sensitivity [41]. In another investigation, the significant roles of survivin and VEGF expression along with their positive correlation in TC having potential predictive values for poor prognosis of this disease were demonstrated [29]. In an additional study, a strong association was found between concomitant high expression of survivin and VEGF-C and the metastatic status of lymph nodes in PTC patients, indicating the possibility of their contribution to the metastatic process. Therefore, evaluation of survivin and VEGF-C expression could be clinically of great significance in terms of predicting the metastatic potential of PTC and making decisions about interventions and follow-ups of these patients [40]. In another investigation, the important roles of survivin and VEGF expression as well as their positive correlation in TC evolution with potential predictive values for poor prognosis of the given disease were highlighted [29]. It should be noted that nicotinamide phosphoribosyl transferase (NAMPT) expression can be up-regulated in thyroid malignancies. Thus, improved expression of NAMPT is associated with more advanced tumor stages and metastatic diseases. NAMPT expression is also correlated with survivin and survivin splicing variant DEx3 expressions [42]. In this respect; YM155 is recognized as an active agent in ATC cells since it exhibits strong anti-tumor activities against human ATC cells in vitro and consequently validates its anti-tumor activity in vivo, using a metastasis mouse model that recapitulates ATC clinical features. Moreover, it has been found that survivin can be over-expressed in ATC [43].

9. Potential of survivin as a biomarker circulating in blood

It has been confirmed that survivin is located in cytoplasm, mitochondria, and nucleus of the cell. Moreover, survivin has been recently demonstrated to be released from cancer cells to the tumor microenvironment via small membrane-bound vesicles called exosomes. However, recent investigations have indicated that survivin can also exist in exosomes released from cells to extra-cellular space through the exocytosis of multi-vesicular bodies [44]. Thus far, serum survivin has been examined in some studies in order to determine its use as a screening, follow-up, or early diagnostic test and to shed light on its effects on prognosis. It has been reported that both histopathological expression and high serum levels of survivin can be associated with poor prognosis in patients with prostate cancer, serious ovarian cancer, acute lymphoblastic leukemia, as well as breast cancer [44–49]. As a biomarker, the serum level of survivin that is measurable prior to surgical interventions may be also helpful. In some studies, conducted on several types of cancer, relationship between serum survivin levels and

Table 1
Main characteristics of related studies on TC and surviving.

Types of thyroid cancer	Number of patients	Main result	Clinically significant	Ref
PTC	75	Concomitant high expression of survivin is closely associated with LNM status of PTC patients.	Predicting the metastatic potential, treatment, and follow-up of survivin	[40]
SW579 cells	In vitro	Hyperoside can induce the apoptosis of the SW579 cell line, by downregulating the expression of survivin in the process of apoptosis.	Theoretical basis for the therapeutic effect of hyperoside by targeting survivin	[36]
PTC, MTC FTC	22	Survivin DEx3 expression has high specificity and sensitivity for discrimination between benign thyroid lesions and cancers.	Survivin DEx3 may be considered a biological marker of thyroid malignancy	[41]
MTC	79	High survivin expression was associated with an advanced T-stage and metastatic disease, Survivin demonstrate distinct expression patterns in MTCs.	Survivin might serve as viable target in patients with MTC	[23]
PTC	60	The findings reported that survivin is highly expressed in PTC.	Survivin play a role in the occurrence, lymph node metastasis, and clinical staging of PTC	[7]
PTC, MTC FTC	40	NAMPT expression in thyroid cancers significantly correlated with survivin and with survivin splice variant DEx3 expression	Further studies are needed to explain the role of NAMPT in thyroid cancer biology	[42]
ATC	Cell lines	YM155 treatment inhibited survivin expression in ATC cells.	Survivin attractive target for ATC therapy	[43]
Thyroid nodules	77	Survivin 2α expression is the highest in non-neoplastic surgical margin rather than other samples and the lowest expression was that of malignancy.	Survivin 2α protein may be has a vital protective effect throw survivin quenching	[51]
AG, FA, PC, AC	338			[24]
PTC, FTC	90	Downregulation of survivin expression by use of siRNA to block survivin mRNA and protein expression.	Survivin can be used as a diagnostic and therapeutic marker for thyroid carcinoma and target in the strategy of thyroid cancer therapy.	[19]
Thyroid nodules	61	Survivin-deltaEx3 is significantly up-regulated from normal to malignant thyroid carcinoma tissues.	Survivin-deltaEx3, can be potential new markers in diagnosis of PTC	[12]
PTC	67	The higher expression of survivin in tumor tissues than in normal tissue.	Survivin over-expression are probably early events in tumorigenesis of PTC	[28]
[a]Cell lines, primary cultures	In vitro Cell line	Silencing of survivin by RNA interference restored sensitivity to doxorubicin and cisplatin.	Increased expression of survivin contributes to the acquisition of permanent resistance to cytotoxic compounds	[27]
PTC	Cell lines K1 and IHH4	AUY922 induced apoptosis by downregulating the expression of survivin protein in PTC cells.	Survivin attractive target for AUY922	[34]
PTC, ATC	99	Correlation of high survivin expression with aggressive behavior implies its role in progression of thyroid tumor malignancy.	Survivin could be a useful tool in the prediction of aggressiveness of a subset of PTC and a possible target for molecular therapy for ATC patients	[14]
PTC	104	These results indicate that survivin is an unfavorable molecule for PTC prognosis, and that its high expression may indicate a subset of PTC patients with a more aggressive disease course.	Evaluation of survivin expression in FNA could be a useful tool for the identification of those PTC patients who require more extensive surgery, careful follow-up and therapeutic strategy	[21]
PTC, AC	56	Upregulation of survivin expression may be a molecular marker of dedifferentiation in thyroid epithelial carcinomas.	Upregulation of survivin, favoring progression toward a poorly differentiated phenotype	[20]
PTC	126	Survivin (A9194 G) polymorphism was found to play a protective role in the susceptibility to PTC.	These findings are important source of information on the pathogenesis and prediction of clinical behavior of thyroid cancers	[8]
PTC	123	The presence of **C** allele was significantly associated with the presence of more profound manifestations, including lymph node involvement, vascular involvement and multifocality.	Identifying genetic markers might be helpful in early diagnosis and decreasing disease mortality	[39]
TC, TA	68	Showed a higher positive frequency of immunohistochemical expression with a higher mRNA expression for survivin and VEGF in contrast to TA and NT.	Survivin expression and positive correlation in TC evolution with potential predictive values for poor prognosis of TC	[29]
TC	41	Potential value of survivin in discrimination between follicular thyroid adenoma and follicular thyroid carcinoma.	Survivin is a potential candidate for further investigation in the proper histologic diagnosis of thyroid cancers	[52]
FTC, PTC, ATC	129	In anaplastic carcinoma, survivin positivity was observed in 84% of the cases, which was in significantly higher incidence than in papillary or follicular carcinoma	Survivin is strongly related to the dedifferentiation of thyroid carcinoma	[18]
TL	6	Survivin mRNA levels were greater in thyroid lymphoma than in Hashimoto's thyroiditis.	Thyroid lymphoma expressing high levels of survivin may also require prompt and aggressive treatment.	[53]

human thyroid squamous cell carcinoma cell line (SW579), Fine needle aspiration (FNA), papillary thyroid carcinoma(PTC), Follicular thyroid cancer(FTC), Medullary thyroid cancer(MTC), Anaplastic thyroid cancer (ATC), thyroid lymphoma (TL), Hashimoto's thyroiditis, Nicotinamide phosphorybosiltransferase (NAMPT), lymph node metastasis (LNM), thyroid adenoma (TA), normal thyroid tissue (NT).

[a] Human thyroid cancer cells ONCODG1, BC-PAP (derived from papillary carcinomas), WRO, FTC-133 (derived from follicular carcinomas), and KAT-4 (derived from anaplastic carcinomas), SW-1736 and 8305C (immortalized from anaplastic carcinomas).

prognosis has been also investigated. In this domain, the detection of serum survivin via immunochemistry or RT-PCR seems to be a promising assay to detect newly-diagnosed cancers. Accordingly, these preliminary findings on diagnostic, prognostic, and predictive potentials of serum survivin should be confirmed in large-scale prospective trials. Furthermore, assays for the measurement of serum survivin and its splice variants need to be simplified, standardized, and evaluated in external quality assurance schemes. Despite the fact that survivin and its splice variants have been differentially expressed in TC tissues and they have been correlated with aggressiveness, there has been no concentration on their serum existence yet [50].

10. Conclusion

The study of survivin and its biological functions can contribute to the understanding of the mechanisms of thyroid tumorigenesis. Findings from various studies have indicated that survivin may be assumed as a potential target in therapeutic approaches to TC. Thus, screening survivin gene mutations may be a good diagnostic criterion for TC occurrence, lymph node metastasis, and clinical staging of TC. In addition, survivin in thyroid carcinoma is considered as an attractive target for the treatment of TC in clinical trials. Furthermore, over-expression of survivin in tumor tissues compared to normal ones allows for detecting single-cell alterations and it is also known as a beneficial tool for fine-needle aspiration (FNA) to meet the early detection of thyroid carcinoma. Moreover, survivin signaling is deemed as a potential molecular therapy targeting anaplastic thyroid carcinoma, in the function of a deadly malignant tumor that does not respond to radioiodine therapies. Accordingly, further studies to examine more patients affected with different types of thyroid carcinoma may shed light on the role of survivin in the development and prognosis of different types of thyroid carcinoma. As a result, evaluating survivin and its splice variants can significantly contribute to the detection of tumor nodules and consequently differentiate them from non-cancerous ones, together with other laboratory methods that are frequently employed in this domain. As a whole, research studies have suggested that differential expression of survivin and its splice variants may perhaps act as a diagnostic marker in patients suffering from TC. Therefore, there is a need to look into the prognostic value of survivin and its variants on a larger size of primary TC patients in a setting in which clinical outcomes can be further explored (Table 1).

Conflict of interest

The authors declare that they have no competing interests.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

References

[1] E.L. Mazzaferri, Management of a solitary thyroid nodule, N. Engl. J. Med. 328 (8) (1993) 553–559.

[2] B. Larijani, M.A. Mohagheghi, M.H. Bastanhagh, A.R. Mosavi-Jarrahi, V. Haghpanah, S.M. Tavangar, et al., Primary thyroid malignancies in Tehran, Iran, Med. Principles Pract. 14 (6) (2005) 396–400.

[3] B. Nachmias, Y. Ashhab, D. Ben-Yehuda, The inhibitor of apoptosis protein family (IAPs): an emerging therapeutic target in cancer, Semin. Cancer Biol. 14 (4) (2004) 231–243.

[4] O.M. Tirado, S. Mateo-Lozano, V. Notario, Roscovitine is an effective inducer of apoptosis of Ewing's sarcoma family tumor cells in vitro and in vivo, Cancer Res. 65 (20) (2005) 9320–9327.

[5] D.C. Altieri, Survivin, versatile modulation of cell division and apoptosis in cancer, Oncogene. 22 (53) (2003) 8581–8589.

[6] F. Li, Role of survivin and its splice variants in tumorigenesis, Br. J. Cancer 92 (2) (2005) 212–216.

[7] J.Y. Li, J. Shi, J.F. Sang, Y.Z. Yao, X.C. Wang, L. Su, Role of survivin in the pathogenesis of papillary thyroid carcinoma, Genet. Mol. Res.: GMR 14 (4) (2015) 15102–15111.

[8] Y.X. Wang, M.L. Li, Liu C.M. Yu SG, Y. Han, X.Y. Wang, The association between the Survivin A9194G exon polymorphisms and papillary thyroid carcinoma risk in the Han Chinese population, Pathol. Res. Pract. 209 (3) (2013) 151–154.

[9] D.S. O'Connor, J.S. Schechner, C. Adida, M. Mesri, A.L. Rothermel, F. Li, et al., Control of apoptosis during angiogenesis by survivin expression in endothelial cells, Am. J. Pathol. 156 (2) (2000) 393–398.

[10] D.C. Altieri, The molecular basis and potential role of survivin in cancer diagnosis and therapy, Trends Mol. Med. 7 (12) (2001) 542–547.

[11] M.J. Duffy, N. O'Donovan, D.J. Brennan, W.M. Gallagher, B.M. Ryan, Survivin: a promising tumor biomarker, Cancer Lett. 249 (1) (2007) 49–60.

[12] S. Vandghanooni, M. Eskandani, V. Montazeri, M. Halimi, E. Babaei, M.A. Feizi, Survivin-deltaEx3: a novel biomarker for diagnosis of papillary thyroid carcinoma, J. Cancer Res. Ther. 7 (3) (2011) 325–330.

[13] A. Pavlidou, C. Kroupis, K. Dimas, Association of survivin splice variants with prognosis and treatment of breast cancer, World J. Clin. Oncol. 5 (5) (2014) 883–894.

[14] S.A. Selemetjev, S.B. Savin, I.R. Paunovic, S.B. Tatic, D. Cvejic, Changes in the expression pattern of apoptotic molecules (galectin-3, Bcl-2, Bax, survivin) during progression of thyroid malignancy and their clinical significance, Wien. Klin. Wochenschr. 127 (9–10) (2015) 337–344.

[15] E. Tirrò, M.L. Consoli, M. Massimino, L. Manzella, F. Frasca, L. Sciacca, et al., Altered expression of c-IAP1, survivin, and Smac contributes to chemotherapy resistance in thyroid cancer cells, Cancer Res. 66 (8) (2006) 4263–4272.

[16] E. Aynaci, E. Coskunpinar, A. Eren, O. Kum, Y.M. Oltulu, N. Akkaya, et al., Association between survivin gene promoter -31G/C and -644C/T polymorphisms and non-small cell lung cancer, Genet. Mol. Res. 12 (3) (2013) 3975–3982.

[17] E. Liarmakopoulos, G. Theodoropoulos, A. Vaiopoulou, S. Rizos, G. Aravantinos, G. Kouraklis, et al., Effects of stromal cell-derived factor-1 and survivin gene polymorphisms on gastric cancer risk, Mol. Med. Rep. 7 (3) (2013) 887–892.

[18] Y. Ito, H. Yoshida, T. Uruno, K. Nakano, A. Miya, K. Kobayashi, et al., Survivin expression is significantly linked to the dedifferentiation of thyroid carcinoma, Oncol. Rep. 10 (5) (2003) 1337–1340.

[19] Z. Chen, N. Liu, G. Zhu, H. Dralle, C. Hoang-Vu, Targeting of the anti-apoptotic gene survivin in human thyroid carcinoma, Int. J. Mol. Med. 30 (3) (2012) 465–472.

[20] G. Pannone, A. Santoro, D. Pasquali, R. Zamparese, M. Mattoni, G. Russo, et al., The role of survivin in thyroid tumors: differences of expression in well-differentiated, non-well-differentiated, and anaplastic thyroid cancers, Thyroid 24 (3) (2014) 511–519.

[21] S. Selemetjev, T.I. Dencic, I. Marecko, J. Jankovic, I. Paunovic, S. Savin, et al., Evaluation of survivin expression and its prognostic value in papillary thyroid carcinoma, Pathol. Res. Pract. 210 (1) (2014) 30–34.

[22] S. Thomas, G. Shah, Calcitonin induces apoptosis resistance in prostate cancer cell lines against cytotoxic drugs via the Akt/survivin pathway, Cancer Biol. Ther. 4 (11) (2005) 1226–1233.

[23] T.A. Werner, Y. Tamkan-Olcek, L. Dizdar, J.C. Riemer, A. Wolf, K. Cupisti, et al., Survivin and XIAP: two valuable biomarkers in medullary thyroid carcinoma, Br. J. Cancer 114 (4) (2016) 427–434.

[24] Y.A. Kim, M. Chang, Y.J. Park, J.E. Kim, Detection of survivin and COX-2 in thyroid carcinoma: anaplastic carcinoma shows overexpression of nuclear survivin and low COX-2 expression, Korean J. Pathol. 46 (1) (2012) 55–60.

[25] R.H. Stauber, W. Mann, S.K. Knauer, Nuclear and cytoplasmic survivin: molecular mechanism, prognostic, and therapeutic potential, Cancer Res. 67 (13) (2007) 5999–6002.

[26] H. Garg, P. Suri, J.C. Gupta, G.P. Talwar, S. Dubey, Survivin: a unique target for tumor therapy, Cancer Cell Int. 16 (2016) 49.

[27] E. Tirro, M.L. Consoli, M. Massimino, L. Manzella, F. Frasca, L. Sciacca, et al., Altered expression of c-IAP1, survivin, and Smac contributes to chemotherapy resistance in thyroid cancer cells, Cancer Res. 66 (8) (2006) 4263–4372.

[28] A. Antonaci, F. Consorti, S. Mardente, S. Natalizi, G. Giovannone, C. Della Rocca, Survivin and cyclin D1 are jointly expressed in thyroid papillary carcinoma and microcarcinoma, Oncol. Rep. 20 (1) (2008) 63–67.

[29] H.Y. Zhang, X. Meng, Fang C.Q. Du ZX, G.L. Liu, H.Q. Wang, et al., Significance of survivin, caspase-3, and VEGF expression in thyroid carcinoma, Clin. Exp. Med. 9 (3) (2009) 207–213.

[30] T.A. Werner, L. Dizdar, I. Nolten, J.C. Riemer, S. Mersch, S.C. Schutte, et al., Survivin and XIAP - two potential biological targets in follicular thyroid carcinoma, Sci. Rep. 7 (1) (2017) 11383.

[31] J. Waligorska-Stachura, M. Andrusiewicz, N. Sawicka-Gutaj, M. Biczysko, A. Jankowska, M. Kubiczak, et al., Survivin delta Ex3 overexpression in thyroid malignancies, PLoS One 9 (6) (2014) e100534.

[32] L. Pace, M. Klain, C. Albanese, B. Salvatore, G. Storto, A. Soricelli, et al., Short-term outcome of differentiated thyroid cancer patients receiving a second iodine-131 therapy on the basis of a detectable serum thyroglobulin level after initial treatment, Eur. J. Nucl. Med. Mol. Imaging 33 (2) (2006) 179–183.

[33] J. Waligórska-Stachura, A. Jankowska, R. Waśko, W. Liebert, M. Biczysko, A. Czarnywojtek, et al., Survivin–prognostic tumor biomarker in human neoplasms–review, Ginekol. Pol. 83 (7) (2012).

[34] J. Liu, W. Sun, W. Dong, Z. Wang, Y. Qin, T. Zhang, et al., HSP90 inhibitor NVP-AUY922 induces cell apoptosis by disruption of the survivin in papillary thyroid carcinoma cells, Biochem. Biophys. Res. Commun. 487 (2) (2017) 313–319.

[35] T. Nakahara, A. Kita, K. Yamanaka, M. Mori, N. Amino, M. Takeuchi, et al., YM155, a novel small-molecule survivin suppressant, induces regression of established human hormone-refractory prostate tumor xenografts, Cancer Res. 67 (17) (2007) 8014–8021.

[36] Z. Liu, G. Liu, X. Liu, S. Li, The effects of hyperoside on apoptosis and the expression of Fas/FasL and survivin in SW579 human thyroid squamous cell carcinoma cell line, Oncol. Lett. 14 (2) (2017) 2310–2314.
[37] F. Ma, H. Zhang, Y. Zhai, W. Huang, C. Zhao, S. Ou, et al., Functional polymorphism -31C/G in the promoter of BIRC5 gene and risk of nasopharyngeal carcinoma among chinese, PLoS One 6 (2) (2011) e16748.
[38] M. Wagner, K. Schmelz, B. Dorken, I. Tamm, Epigenetic and genetic analysis of the survivin promoter in acute myeloid leukemia, Leuk. Res. 32 (7) (2008) 1054–1060.
[39] N. Yazdani, F.A. Sayahpour, V. Haghpanah, P. Amiri, M. Shahrabi-Farahani, M. Moradi, et al., Survivin gene polymorphism association with papillary thyroid carcinoma, Pathol. Res. Pract. 208 (2) (2012) 100–103.
[40] S. Selemetjev, S. Savin, I. Paunovic, S. Tatic, D. Cvejic, Concomitant high expression of survivin and vascular endothelial growth factor-C is strongly associated with metastatic status of lymph nodes in papillary thyroid carcinoma, J. Cancer Res. Ther. 14 (2018) S114–S119 Supplement.
[41] J. Waligorska-Stachura, N. Sawicka-Gutaj, M. Zabel, M. Andrusiewicz, P. Gut, A. Czarnywojtek, et al., Survivin DEx3 as a biomarker of thyroid cancers: a study at the mRNA and protein level, Oncol. Lett. 13 (4) (2017) 2437–2441.
[42] N. Sawicka-Gutaj, J. Waligorska-Stachura, M. Andrusiewicz, M. Biczysko, J. Sowinski, J. Skrobisz, et al., Nicotinamide phosphoribosiltransferase over-expression in thyroid malignancies and its correlation with tumor stage and with survivin/survivin DEx3 expression, Tumour Biol. 36 (10) (2015) 7859–7863.
[43] A. Mehta, L. Zhang, M. Boufraqech, Y. Liu-Chittenden, Y. Zhang, D. Patel, et al., Inhibition of survivin with YM155 induces durable tumor response in anaplastic thyroid Cancer, Clin. Cancer Res. 21 (18) (2015) 4123–4132.
[44] S. Khan, J.M. Jutzy, M.M. Valenzuela, D. Turay, J.R. Aspe, A. Ashok, et al., Plasma-derived exosomal survivin, a plausible biomarker for early detection of prostate cancer, PLoS One 7 (10) (2012) e46737.
[45] H.A. El-Attar, M.H. Kandil, Y.M. El-Kerm, M.K. El-Ghandour, Comparison of serum survivin and alpha fetoprotein in Egyptian patients with hepatocellular carcinoma associated with hepatitis C viral infection, Asian Pac. J. Cancer Prev. 11 (4) (2010) 897–903.
[46] Y.G. Lv, F. Yu, Q. Yao, J.H. Chen, L. Wang, The role of survivin in diagnosis, prognosis and treatment of breast cancer, J. Thorac. Dis. 2 (2) (2010) 100–110.
[47] W. Naumnik, W. Nilklinska, M. Ossolinska, E. Chyczewska, Serum levels of HMGB1, survivin, and VEGF in patients with advanced non-small cell lung cancer during chemotherapy, Folia Histochem. Cytobiol. 47 (4) (2009) 703–709.
[48] B. Dobrzycka, B. Mackowiak-Matejczyk, K.M. Terlikowska, B. Kulesza-Bronczyk, M. Kinalski, S.J. Terlikowski, Prognostic significance of pretreatment VEGF, survivin, and Smac/DIABLO serum levels in patients with serous ovarian carcinoma, Tumour Biol. 36 (6) (2015) 4157–4165.
[49] M.B. Ahmed, H.H. Shehata, M. Moussa, T.M. Ibrahim, Prognostic significance of survivin and tumor necrosis factor-alpha in adult acute lymphoblastic leukemia, Clin. Biochem. 45 (1-2) (2012) 112–116.
[50] S. Khan, J.M. Jutzy, J.R. Aspe, D.W. McGregor, J.W. Neidigh, N.R. Wall, Survivin is released from cancer cells via exosomes, Apoptosis 16 (1) (2011) 1–12.
[51] K. Kyani, E. Babaei, M.A. Feizi, S. Vandghanooni, V. Montazeri, M. Halimi, Detection of survivin 2alpha gene expression in thyroid nodules, J. Cancer Res. Ther. 10 (2) (2014) 312–316.
[52] V. Haghpanah, P. Shooshtarizadeh, R. Heshmat, B. Larijani, S.M. Tavangar, Immunohistochemical analysis of survivin expression in thyroid follicular adenoma and carcinoma, Appl. Immunohistochem. Mol. Morphol. 14 (4) (2006) 422–425.
[53] M. Sugawara, F. Matsuzuka, S. Fukata, K. Kuma, F. Moatamed, B.R. Haugen, Excessive survivin expression in thyroid lymphomas, Hum. Pathol. 33 (5) (2002) 524–527.