Original Article

SE translation mRNA overexpression: a potential prognostic predictor in breast cancer

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Background: Patient SE translation (SET) belongs to histone chaperone nucleosome assembly protein family and has been confirmed that it is associated with carcinogenesis, tumor progression and patient outcome. In this study, we aim at assessing the prognostic value of SET mRNA, the function and pathway of SET and its related genes in breast cancer.

Methods: The clinicopathological and prognostic significance of SET was assessed by the molecular taxonomy of breast cancer international consortium (METABRIC) database (n=1,904). Additionally, based on the data and network of SET and its related genes from cBioPortal website, their function in the progression of breast cancer was also explored.

Results: SET mRNA overexpression was a significant predictor of a poor prognosis (P=0.0006). The two signaling pathways associated with SET were the facilitating function of condensin II on mitosis and the accelerated transportation of tumor cell mRNA towards the extranuclear position, and SET acted to suppress condensin II and stabilize mRNA.

Conclusions: Owing to the regulation of chromosome condensation and stabilization of tumor cell mRNA, overexpression of SET is correlated with aggressive phenotypes and facilitates tumor proliferation and deterioration. SET may act as a valuable prognosis biomarker in breast cancer.

Keywords: Breast cancer; mechanism; prognosis; SE translation mRNA (SET mRNA)

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Introduction

Breast cancer is one of the commonest tumors accounting for about 1 in 4 cancer cases among women (1). This disease is well known by its high morbidity and mortality. It was reported that the number of diagnosed patients ranked the top in all types of female tumors (1), among which one of six women died of this disease (2). Therefore, breast cancer has always been the focus issue for scientific researchers. In our previous studies, SE translation (SET) was found to be overexpressed both in mRNA and protein levels in paclitaxel-resistant breast cancer cells, implying that SET might be a potential biomarker of drug resistance (3).

SET gene was located on human chromosome 9, the protein of which was commonly expressed in various nucleuses of tissues (4) and took part in multiple vital physiological and pathological processes, such as cell cycle regulation, cell migration and metastasis, gene transcription, DNA repair, etc. (5). Numerous studies have demonstrated that abnormal expression of SET was related to different kinds of diseases like Alzheimer (6), polycystic ovarian syndrome and hormone-related tumors. SET overexpression was associated to tumor progression and metastasis, whereas its low expression could be linked to the inhibition of tumor cell proliferation (7,8). Moreover,

SET was associated with poor prognosis and Oxaliplatin resistance in metastatic colorectal cancer patients which indicates that SET may act as a potential oncogene (9). SET plays such an important role in cancer progression. However, whether SET can lead to poor prognosis in breast cancer is lack of recognition. In this study, we investigated the association among SET mRNA, clinicopathological parameters, and prognosis of breast cancer patients in a large cohort. In the meantime, we also explored the functions of SET and its related genes in the disease process.

Methods

Patients and materials

All the clinical data of breast cancer patients were obtained from molecular taxonomy of breast cancer international consortium (METABRIC) database, including SET mRNA expression, diagnosed age, tumor size, neoplasm histologic grade, tumor stage, ER status, PR status, HER-2 status, inferred menopausal state and overall survival (OS). Besides, the expression network of SET and its related genes were searched from cBioPortal website (http://www.cbioportal.org/) for the exploration of their function in the progression of breast cancer.

Cut-off score of SET mRNA expression

The cut-off score of SET mRNA expression was calculated by X-tile 3.6.1 software (Yale University, New Haven, CT, USA). We input OS and SET mRNA expression scores of breast cancer patients which were acquired from METABRIC database, then set the latter index as the marker. Finally we got the cut-off score, which divided mRNA expression into high and low expression.

Statistical analysis

Chi-square test was used to analyze the relationship between different clinicopathological characteristics and SET mRNA expression for breast cancer patients. This process was followed by multivariate logistic regression in order to figure out independent influence factors for SET mRNA expression. COX regression model was then applied to investigate the influence of relative factors for OS. Survival curves were generated using the Kaplan-Meier method to examine the prognostic value of SET. A two-tailed P value of <0.05 was considered statistically significant. All data were analyzed using SPSS statistics for Windows version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Data acquirement and classification

Among 2,509 breast cancer samples in the database, we selected 1,904 cases with complete information for analysis. After calculated by X-tile software, the cutoff score of SET mRNA was –0.05, which was used to divide breast cancer patients into high expression group (score ≥–0.05) and low expression group (score <–0.05).

Relationship between SET mRNA expression and clinicopathological characteristics

As *Figure 1* shows, we divided each clinicopathological characteristic into two types. Chi-square test was then conducted to assess the correlation between clinicopathological factors and SET mRNA expression level. The results are listed in *Table 1*. The expression level of SET mRNA was significantly related to diagnosed age (P=0.010), tumor size (P=0.021), neoplasm histologic grade (P<0.001), tumor stage (P=0.005), ER status (P<0.001), PR status (P<0.001), HER-2 status (P=0.044), and inferred menopausal status (P=0.041). Multivariate logistic regression indicated that tumor histological grade (P<0.001) and ER status (P<0.001) were independent influence factors of SET mRNA expression level for breast cancer patients (*Table 2*). The cases with poor tumor tissue differentiation or negative ER tended to overexpress SET mRNA.

Potential prognostic factors for breast cancer patients

The univariate COX analysis revealed that diagnosed age (P<0.001), tumor size (P<0.001), neoplasm histologic grade (P<0.001), tumor stage (P<0.001), ER status (P=0.022), PR status (P<0.001), HER-2 status (P<0.001), inferred menopausal status (P<0.001), and SET mRNA expression (P=0.001) influenced the OS of breast cancer patients.

Furthermore, the multivariate COX analysis demonstrated that diagnosed age (P<0.001), tumor histological grade (P=0.018), tumor stage (P<0.001), and HER-2 status (P<0.001) were independent prognostic factors for breast cancer patients (*Table 3*). The poor prognosis was related to higher ages, poorer tumor tissue differentiation, advanced

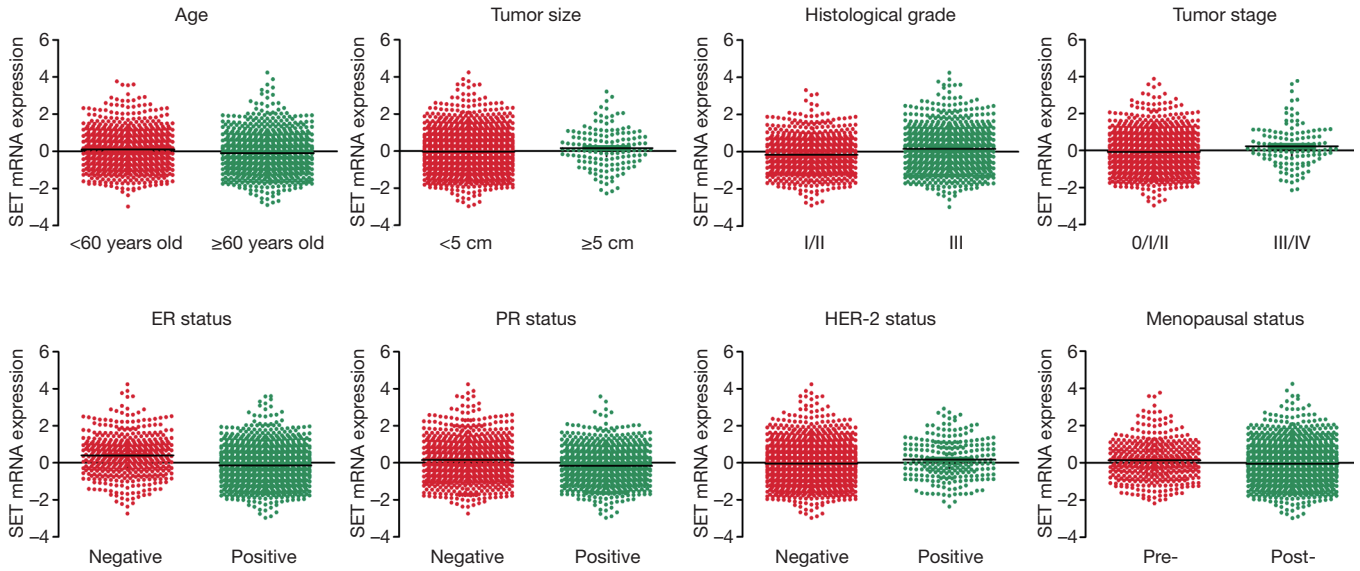

Figure 1 SET mRNA expression of different clinicopathological characteristics. SET, SE translation.

clinical stage, and positive HER-2 receptor status.

The effect of SET mRNA expression on the prognosis of breast cancer patients

According to Kaplan-Meier analysis, the OS of breast cancer patients with higher SET mRNA expression was significantly poorer than that of patients with lower SET mRNA expression (P=0.006). The result is showed in *Figure 2*.

Mechanism of SET and its related genes function in breast cancer

The network searched from cBioPortal website is showed in *Figure 3*. Total 12 genes related to SET were altered. The regulation of genes is showed in *Table 4*. Gene interaction types include "control state change of" and "in complex with".

We found that there were two main pathways affecting the progression of breast cancer and patients' prognosis by analyzing the network and searching literatures. The detail information of signaling pathways can be seen in *Figure 4*. One pathway was the regulating effect of condensin II on chromosome. As the data displayed, the five subunits – SMC2, SMC4, NCAPG2, NCAPH2, and NCAPD3 of condensin II were upregulated in most breast cancer patients. This complex could bind to chromosome to facilitate its condensation and sister chromatids separation (10). MCHP1 could specifically compete for condensin II binding site on chromosome using one of BRCA1 C-terminal (BRCT) domain which located in N terminus. As a result, condensin II would be suppressed and premature chromosome condensation (PCC) would be saved. When SET bounded to BRCT, the function of MCPH1 would be enhanced. Therefore, SET might be a negative regulator of mitosis entry (11,12) which can block G2/M transition, but it would dysfunction when the SET with mutated C-terminus was overexpressed in COS cells (13). We found MCPH1 was downregulated but SET was upregulated in most breast cancer patients. This phenomenon seemed to be paradoxical. However, there was no recording about mutate data of SET in the database. We hypothesized that if the mutation happened, SET wouldn't work and the function of MCPH1 was weak. Both of the two genes might not influence condensin II. This process could lead to the occurrence of mitosis entry and breast cancer cell proliferation. On the contrary, if SET was not mutated, the downregulation of MCPH1 and SET regulation effects in other pathways such as overcoming gene repression (5), modifying histone and activating PI3K-Akt pathway (3), would also contribute to breast cancer deterioration. This speculation needs to be further confirmed.

The second pathway was the transportation of tumor cells mRNA towards the extranuclear position. AU-rich elements mRNA (ARE-mRNA) was overexpressed in multiple tumor cells (14). Before ARE-mRNA being

Table 1 Relationship between clinicopathological characteristics and SET mRNA expression level

Characteristics	Cases	mRNA expression		P value
		Low	High	
Age				
<60	842	395	447	0.010*
≥60	1,062	561	501	
Tumor size (cm)				
<5	1,744	888	856	0.021*
≥5	142	58	84	
Histological grade				
I/II	905	509	396	<0.001***
III	927	403	524	
Tumor stage				
0/I/II	1,279	674	605	0.005**
III/IV	124	49	75	
ER status				
Negative	445	152	293	<0.001*
Positive	1,459	804	655	
PR status				
Negative	895	400	495	<0. 001***
Positive	1,009	556	453	
Her-2 status				
Negative	1,668	852	816	0.044*
Positive	236	104	132	
Menopausal status				
Pre-	411	188	223	0.041*
Post-	1,493	768	725	

*, P<0.05; **, P<0.01; ***, P<0.001. SET, SE translation.

transported, phosphorylated ELAVL1 (HuR) would bind to its A-U elements (15) to stabilize the complex together with nuclear phosphoprotein ligand pp32, APRIL, and SET (α, β). Then pp32 and APRIL would combine with the nuclear transport receptor XPO1 (CRM1) to mediate mRNA transportation out of nucleus (16,17). For the mRNA without A-U elements, its extranuclear transportation would be mediated by the evolutionarily conserved, heterodimeric transport factor complex NXF1·NXT1. On the cytoplasmic side of nuclear pore complex (NPC), NXF1·NXT1 would interact with the cytoplasmic filament nucleoporins Gle1, NUP42, and NUP214 to promote its separation with mRNA. These steps could guarantee the direction of mRNA exportation (18). In the process of mRNA nuclear transportation, SET acted to stabilize mRNA and to prevent it from degradation, therefore successful transportation would be guaranteed. According to the data, ELAVL1, SET, XPO1, and NUP214 were all upregulated. This could be beneficial to transport mRNA out of nucleus. Then the translation process of tumor cell and breast cancer development would be accelerated.

We also observed upregulation of ANP32A and

Table 2 Independent factors of SET mRNA expression level

Characteristics	P value	OR (95% CI)
Age (≥60 *vs.* <60)	0.611	1.067 (0.831–1.370)
Tumor size (≥5 *vs.* <5 cm)	0.090	1.550 (0.934–2.570)
Histological grade (III *vs.* I/II)	<0.001***	1.535 (1.208–1.950)
Tumor stage (III/IV *vs.* 0/I/II)	0.240	1.301 (0.839–2.019)
ER status (positive *vs.* negative)	<0.001***	0.484 (0.348–0.678)
PR status (positive *vs.* negative)	0.726	1.048 (0.807–1.362)
Her-2 status (positive *vs.* negative)	0.281	0.824 (0.579–1.172)
Menopausal status (post- *vs.* pre-)	0.959	0.992 (0.740–1.330)

***, P<0.001. SET, SE translation.

Table 3 Factors influencing prognosis of breast cancer patients

Characteristics	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Age (≥60 *vs.* <60)	<0.001***	2.120 (1.880–2.389)	<0.001***	2.138 (1.813–2.521)
Tumor size (≥5 *vs.* <5 cm)	<0.001***	1.832 (1.499–2.240)	0.101	1.292 (0.951–1.755)
Histological grade (III *vs.* I/II)	<0.001***	1.325 (1.174–1.496)	0.018*	1.210 (1.033–1.417)
Tumor stage (III/IV *vs.* 0/I/II)	<0.001***	2.390 (1.925–2.969)	<0.001***	1.877 (1.438–2.451)
ER status (positive *vs.* negative)	0.022*	0.848 (0.737–0.977)	0.589	0.944 (0.765–1.164)
PR status (positive *vs.* negative)	<0.001***	0.787 (0.700–0.886)	0.245	0.903 (0.761–1.072)
Her-2 status (positive *vs.* negative)	<0.001***	0.688 (0.579–0.819)	<0.001***	1.525 (1.224–1.899)
Menopausal status (post- *vs.* pre-)	<0.001***	1.686 (1.432–1.984)	0.226	1.143 (0.921–1.419)
mRNA expression (high *vs.* low)	0.001**	1.230 (1.092–1.386)	0.063	1.151 (0.992–1.335)

*, P<0.05; **, P<0.01; ***, P<0.001.

downregulation of ESR1. Although ANP32A could suppress solid tumor by preventing histone H3 from acetylation, it was also observed that ANP32A was overexpressed in some tumors. The deficiency of ANP32A would decrease acetylation of histone in tumor cells. Therefore, high expression of ANP32A would promote cell proliferation, survival and colony formation (19). This might be the reason why ANP32A upregulated for breast cancer patients. As a member of nuclear receptor family, ESR1 could bind to enhancers of DNA and then interacted with promoters to regulate the recruitment and activation of RNA polymerase II. Finally, the expression of regulated genes would be upregulated (20). For triple-negative breast cancer cells, other abnormally activated signaling pathway would recover cell proliferation and differentiation abilities to counteract the adverse impact of ESR1 deficiency on tumors. Meanwhile, lack of receptors would lead to deficiency of immunotherapy targets. It would be more difficult to treat breast cancer. All these defects could contribute to patients' poor prognosis (21).

Discussion

Since SET-CAN fusion gene was found in a case of acute undifferentiated leukemia in 1992 (22), the relationship between SET gene and tumor has gained more and more attention. Many studies have found SET overexpression both in RNA and protein levels in different types of tumors such as leukemia, non-Hodgkin lymphoma, hepatocellular carcinoma, pancreatic carcinoma, metastatic colorectal

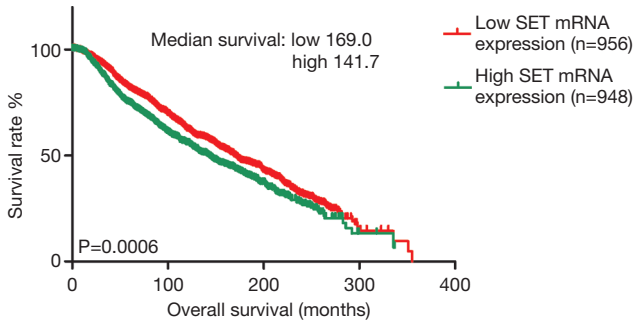

Figure 2 Survival curve of breast cancer patients with high and low SET mRNA expression. SET, SE translation.

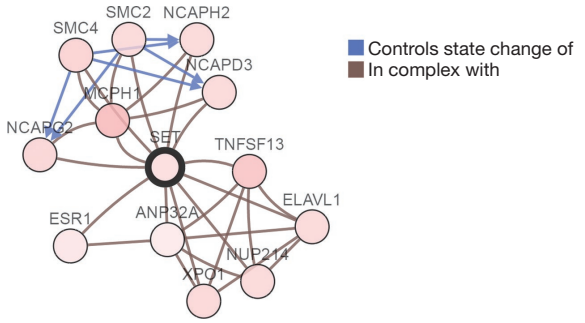

Figure 3 SET and its related genes network for breast cancer patients. SET, SE translation.

Table 4 Regulation of SET and its related genes for breast cancer patients

Gene nodes	Total alteration (%)	Up-regulation (%)	Down-regulation (%)
SET	3.5	2.6	1.0
SMC2	4.4	3.0	1.4
SMC4	5.2	4.3	1.0
NCAPG2	4.7	4.1	0.6
NCAPH2	4.4	2.9	1.6
NCAPD3	4.5	2.5	2.0
MCPH1	8.3	2.7	5.7
ESR1	2.5	0.0	2.5
TNFSF13	7.0	0.7	6.3
ANP32A	2.0	1.9	0.0
XPO1	4.6	3.1	1.5
NUP214	4.4	2.5	1.9
ELAVL1	4.1	3.4	0.7

SET, SE translation.

carcinoma, and breast carcinoma. They also found that the overexpression of SET protein was related to poor prognosis in leukemia (5). To the best of our knowledge, limited research has been done to evaluate the prognostic role of SET in breast cancer. Thus, the aim of the study was to determine biological and prognostic value of SET expression by using bioinformatics databases.

In our study, we found that SET mRNA was significantly associated with diagnosed age, tumor size, neoplasm histologic grade, tumor stage, ER status, PR status, HER-2 status, and inferred menopausal status. Among those characteristics, tumor histological grade and ER status were independent influence factors. Moreover, SET mRNA overexpression could act as a poor prognostic factor for breast cancer patients. These results are in agreement with previous studies (23-25).

There were two pathways involved in the process of breast cancer. They were the facilitation of condensin II on mitosis and the accelerated transportation of tumor cell mRNA towards the extranuclear position. In the first pathway, overexpressed-SET acted to suppress condensin II thereby inhibited mitosis, whereas mutated SET wouldn't influence condensin II. In the second pathway, SET acted to stabilize mRNA of breast cancer cells. These processes could be regarded as positive factor for tumor cell proliferation. All the conclusions above can be a

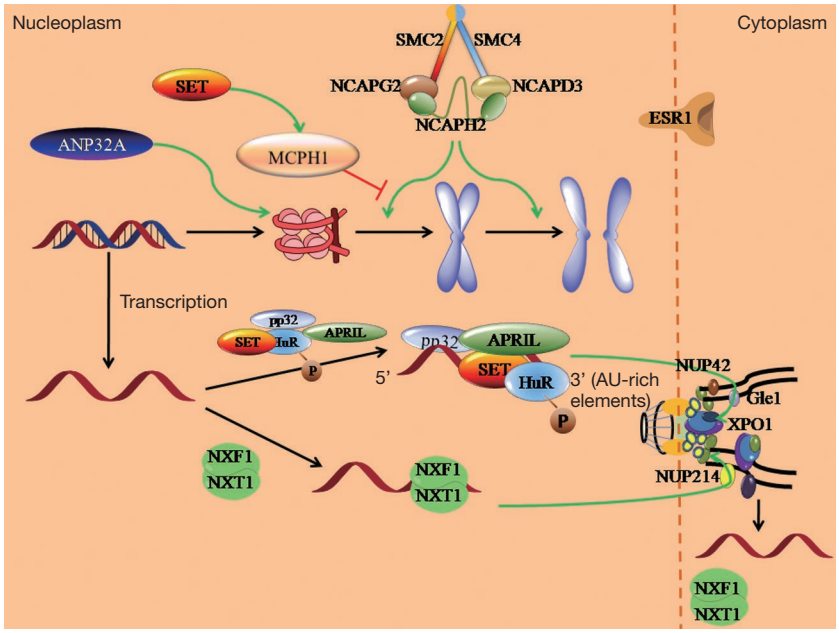

Figure 4 Pathways of SET and its related genes. SET, SE translation.

supplemental demonstration of previous researches (26-37).

Indeed, there are still some limitations in this study. We only analyzed SET mRNA expression for breast cancer patients due to the deficiency of protein expression and mutation data in METABRIC, and the sample size analyzed in this article was not large enough to generate the comprehensive results. These shortcomings can be overcome by conducting researches with more samples in other databases. Besides, further large-size animal experiments and clinical researches are needed to elucidate the role of SET in breast cancer. Finally, as the mechanism of SET was not clearly demonstrated (38-40), other regulating ways of SET can be deeply studied in the future.

Conclusions

SET mRNA tends to overexpress for breast cancer patients with poor tumor tissue differentiation and negative ER status. These patients might have a poorer prognosis. The same clinical outcome would also occur in those with higher ages, poorer tumor tissue differentiation, advanced clinical stage, or positive HER-2 receptor. For the progression of breast cancer, SET can regulate chromosome condensation and stabilize tumor cell mRNA thereby facilitating tumor proliferation and deterioration. These conclusions can be helpful in understanding SET function in breast cancer.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.09.11). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional ethical approval and individual informed consent were waived.

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