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Linking the septin expression with carcinogenesis

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Abstract The septin is a conserved GTP binding protein family which is involved in multiple cellular processes. Many evidences have indicated that some septins were abnormally expressed in certain kinds of tumors and the altered expressions were related to the process of carcinogenesis. To better understand the relationship between septins and cancer, we compared the expression of 14 human septin family members in 35 kinds of tumor types with their normal counterparts using the publicly available ONCOMINE microarray database. We found altered expression of most septin members in many kinds of tumors. Significantly, SEPT2, SEPT8, SEPT9, SEPT11 were consistently up-regulated, and SEPT4, SEPT10 were down-regulated in most cancer types investigated. Furthermore, the abnormal expressions were also in accordance with the tumor malignances or prognosis of corresponding cancer patients. These findings have contributed to the view that septins may belong to a kind of cancer critical genes. More septins might act as potential oncogenes or tumor suppressor genes in cancer development.

Keywords Septin · Carcinogenesis · Expression · ONCOMINE

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Introduction

Septins are a conserved family of GTP binding proteins which are widely found in the eukaryotes except plants [1]. They were first found in Saccharomyces cerevisiae with cytokinesis deficiency. Yeast with septin deficiency or mutation could not perform normal cytokinesis [2]. All septins are composed of a central conserved GTPase domain, and the variable N terminal and C terminal domains [3]. So far, 14 septins have been identified in mammals [4]. In addition to cytokinesis, septins have been proved to play important roles in many cellular processes including vesicle trafficking [5], exocytosis [6], apoptosis [7], and tumorigenesis [8].

Growing evidences have linked septins with the development of certain human diseases, particularly in tumors [9]. SEPT5, SEPT6, SEPT9, SEPT11 were found to form in-frame fusion proteins with MLL in infant acute leukemia patients [10–13]. SEPT2 was widely expressed in brain tumor samples, and its expression level varies in different cell cycle phases. Expression of SEPT2 mutants could inhibit the cell division and cause multinucleated cells [14]. Enhanced expression of SEPT4 was found in human colorectal cancer. Specific cleavage of the endogenous SEPT4 mRNA could induce significant cell growth and G2 arrest in several colorectal cancer cell lines [15]. However, an alternative splicing variant of SEPT4 namely ARTS was reported to be a candidate tumor suppressing gene [16]. ARTS could promote the TGF-β mediated apoptosis through targeting XIAP [17]. And ARTS was lost in 70% of the acute lymphoblastic leukemia patients [18]. SEPT9 localizes at chromosome 17q25.3, which was identified as a common LOH site for sporadic ovarian cancer and breast cancer [19, 20]. A microarray analysis showed that SEPT9 was over-expressed in diverse human tumors including

breast, kidney, liver, lung, lymphoid ovary, pancreas etc. [21]. Recently, the over-expression of SEPT9 splicing variant 1 (SEPT9-v1) was found to be associated with the oncogenic phenotypes in breast cancer cells [22]. SEPT9-v1 could interact and stabilize the c-Jun-N-terminal kinase (JNK) and thus enhance the cell proliferation and survival in mammary epithelial cells [23].

According to the former studies, the abnormal expression of certain septins is usually closely related with tumorigenesis. This phenomenon indicated that the septin family might be a kind of cancer critical proteins, and more family members might be involved in the development of certain cancers. In order to get a comprehensive impression of the septin family in carcinogenesis, we studied the expression of all the human septin family members in 35 cancer types using the oncomine microarray database. Oncomine is an integrated bioinformatics platform which collects, standardizes, and analyzes the cancer transcriptome data based on thousands of independent microarray studies [24]. In this study, we found altered expression of many septin family members in different cancer types. Particularly, SEPT2, SEPT8, SEPT9, SEPT11 were over-expressed in most cancers, while SEPT4 and SEPT10 were down-regulated in most cancer types. Furthermore, the altered expressions of SEPT4, SEPT9 and SEPT10 were also significantly associated with tumor aggressiveness or prognosis. These findings provided new evidence for the importance of the septin family in carcinogenesis, and might be helpful to further identify new cancer related septins and their roles in cancer development.

Materials and methods

Database

The Oncomine microarray database (http://www.oncomine.org) was used to study the expression of the septin gene family in 35 cancer types as compared with their normal control tissues. The gene transcriptome data only from the same study and generated with the same methodology were used. All gene expression date were log transformed, median centered per array, and the standard deviation was normalized to one per array [25]. Student's t test was used for differential expression analysis, and only studies with P value less than 0.05 were considered.

Results

The gene expression of all 14 human septins in 35 kinds of cancer types were investigated using the oncomine microarray database. Most of the septin family members have altered expression in certain cancer types (Table 1).

SEPT2, SEPT8, SEPT9, SEPT11 are significantly up-regulated in most cancer types

SEPT2 has been found up-regulated in 11/35 tumors (Table 1), including brain tumors, breast cancer, cervix cancer, gastric cancer, head and neck cancer, liver cancer, melanoma, mesothelioma, myeloma, pancreas cancer, and salivary gland cancer (Supplementary Fig. S1). SEPT8 has been found up-regulated in 12/35 tumors (Table 1), including adrenal cancer, bladder cancer, leukemia, liver cancer, lung cancer, lymphoma, mesothelioma, myeloma, pancreas cancer, renal cancer, salivary gland cancer and seminoma (Supplementary Fig. S2). SEPT9 has been found up-regulated in 15/35 tumors (Table 1), including brain tumors, breast cancer, esophagus cancer, head and neck cancer, leukemia, liver cancer, lung cancer, lymphoma, melanoma, mesothelioma, myeloma, pancreas cancer, renal cancer, salivary gland cancer and seminoma (Supplementary Fig. S3). SEPT11 has been found up-regulated in 12/35 tumors (Table 1), including brain tumors, breast cancer, cervix cancer, esophagus cancer, head and neck cancer, leukemia, melanoma, ovarian cancer, pancreas cancer, prostate cancer, renal cancer and seminoma (Supplementary Fig. S4).

SEPT4 and SEPT10 are significantly down-regulated in most cancer types

SEPT4 has been found significantly down-regulated in 11/35 tumors (Table 1). Down-regulation of SEPT4 was found in adrenal cancer, in bladder cancer, in brain tumors, in breast cancer, in cervix cancer, in liver cancer, in lung cancer, in melanoma, in ovarian cancer, in pancreas cancer, in seminoma (Supplementary Fig. S5). SEPT10 has been found significantly down-regulated in 11/35 tumors (Table 1). Down-regulation of SEPT10 was found in bladder cancer, in breast cancer, in head and neck carcinoma, in liver cancer, in lung cancer, in melanoma, in ovarian, in pancreas, in prostate, in seminoma, in testis tumor (Supplementary Fig. S6).

The altered expression of SEPT4, SEPT9 and SEPT10 are associated with tumor grade, tumor stage, and prognosis

We further investigated whether the abnormal expression of the septins are associated with progression and clinical outcomes of patients with different cancer types.

We found out that SEPT4 was significantly down-regulated in astrocytoma grade IV compared to grade III ($P = 3.7E-6$) [26]; in patients with brain tumors dead at 3 years compared to patients alive at 3 years ($P = 0.036$)

Table 1 Expression of 14 septins in 35 kinds of human cancer types compared to their normal counterparts using the oncomine microarray database ("+" means the gene is up-regulated and "−" means the gene is down-regulated)

	SEPT1	SEPT2	SEPT3	SEPT4	SEPT5	SEPT6	SEPT7	SEPT8	SEPT9	SEPT10	SEPT11	SEPT12	SEPT13	SEPT14
Adrenal				−				+	−					
Bladder				−		−	−	+		−				
Blood														
Brain	−	+	−	−	−	−	+		+	+	+	−	−	
Breast		+	+	−	−	+	−		+	−	+	+	+	
Cervix		+		−	−	+	+		−	+	+	−	+	
Chondrosarcoma														
Colon					+		+	−						
Endocrine														
Endometrium														
Esophagus				+	−	−		−	+		+			
Gastric		+												
Head and neck		+			−	+		−	+	−	+	−	+	
Leukemia	−			+	−	+	+	+	+		+		+	
Liver	+	+	+	−		+	−	+	+	−	−	−		
Lung				−	+	+	−	+	+	−	−			
Lymphoma				+				+	+	+	−			
Melanoma		+		−	+	−	−	−	+	−	+			
Mesothelioma		+						+	+		−			
Myeloma		+	−		−	+	+	+	+		−		+	
Neuroblastoma														
Oral														
Ovarian		−		−	−	−	−	−		−	+			
Pancreas	+	+		−	+	+		+	+	−	+	−	−	
Prostate			+	+	+	+	−	−	−	−	+		+	
Rectum														
Renal		−	+	+	+	−	+	+	+	+	+			
Salivary gland		+						+	+		−			
Sarcoma														
Seminoma	+	−	+	−	+		−	+	+	−	+	−	−	
Skin														
Testis	−	−		+		+				−		−		
Tongue				−						+				
Thyroid														
Uterus														

[27]; in breast carcinoma grade 2 and grade 3 compared to grade 1 ($P = 9.8E-4$) [28]; in 5 year relapsing ER + breast carcinoma patients compared to patients with no relapse ($P = 0.023$) [29]; in patients with non-small cell lung cancer dead at 5 years compared to patients alive at 5 years ($P = 0.008$) [30]; in poorly differentiated hepatocellular carcinoma compared to moderately and well differentiated hepatocellular carcinoma ($P = 0.011$) [31]; in 5 year relapsing head and neck squamous cell carcinoma patients compared to patients with no relapse ($P = 0.004$) [32]; in patients with multiple myeloma dead at 1 year compared to patients alive at 1 year ($P = 0.008$) [33] (Fig. 1).

SEPT9 was significantly up-regulated in glioma grade 4 compared to grade 3 ($P = 2.5E-5$) [34]; in patients with glioma dead at 3 years compared to patients alive at 3 years ($P = 2.7E-4$) [34]; in follicular lymphoma stage III and stage IV compared to stage I and stage II ($P = 0.004$) [35]; in breast carcinoma grade 2 and grade 3 compared to grade 1 ($P = 1.5E-5$) [36]; in patients with breast carcinoma dead at 5 years compared to patients alive at 5 years ($P = 2.4E-4$) [29]; in 5 year relapsing squamous cell lung carcinoma patients compared to patients with no relapse ($P = 0.002$) [37]; in squamous cell lung carcinoma N stage1 and stage 2 compared to stage 0 ($P = 0.039$) [37] (Fig. 2).

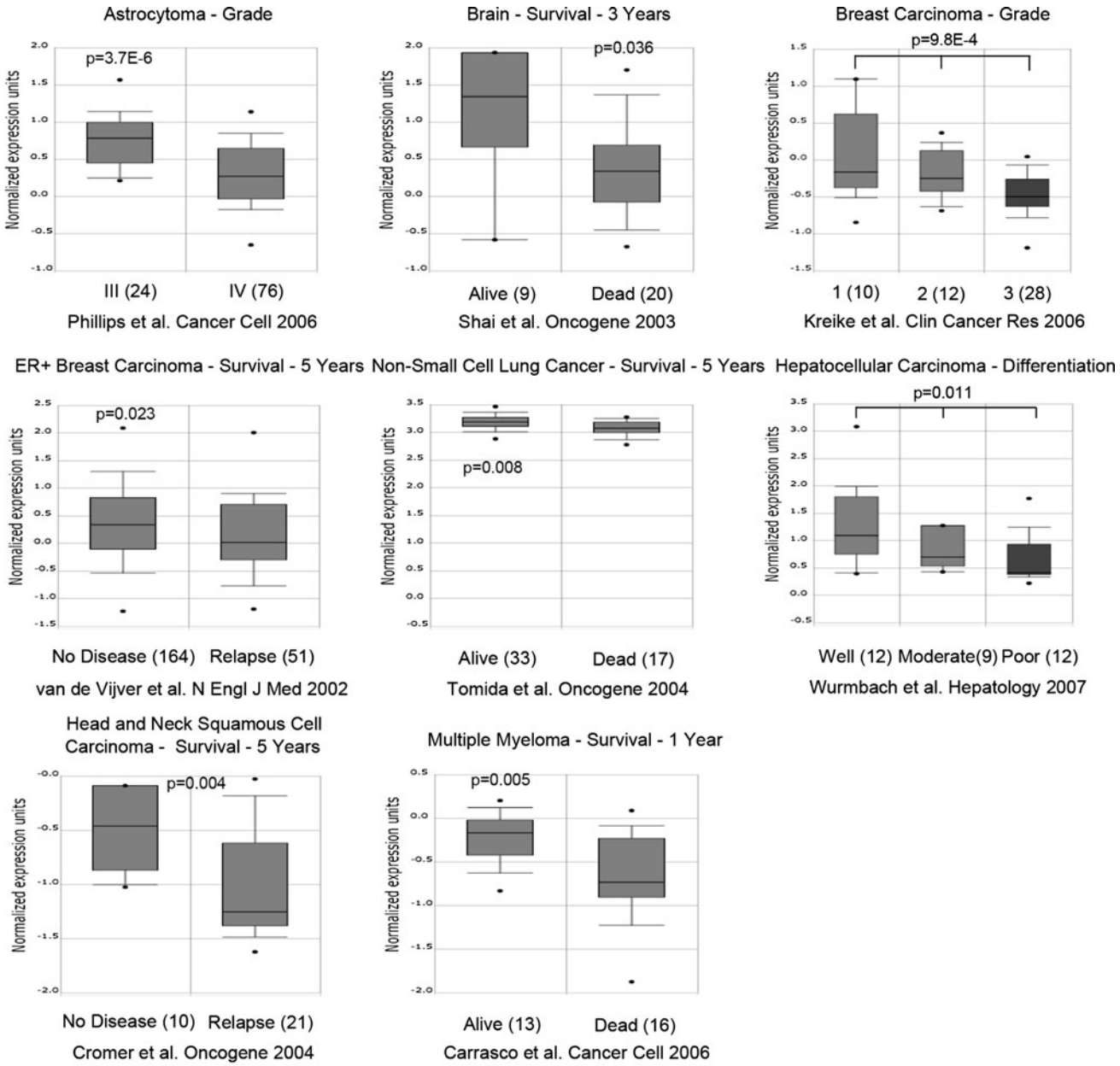

Fig. 1 Association of SEPT4 expression and tumor progression in various cancers. SEPT4 expression in astrocytoma grade IV and grade III [26]; in alive patients with and dead patients with brain tumors [27]; in breast carcinoma grade 1, grade 2 and grade 3 [28]; in ER+ breast carcinoma patients with relapse and with no relapse [29]; in alive patients with and dead patients with non-small cell lung cancer [30]; in poorly differentiated, moderately differentiated and well differentiated hepatocellular carcinoma [31]; in head and neck squamous cell carcinoma patients with relapse and with no relapse [32]; in alive patients with and dead patients with multiple myeloma [33]

SEPT10 was significantly down-regulated in bladder carcinoma grade 2 and grade 3 compared to grade 1 ($P = 6E\text{-}4$) [38]; in bladder carcinoma stage T4, T3, T2 and T1 compared to Ta ($P = 0.012$) [38]; in breast carcinoma grade 2 and grade 3 compared to grade 1 ($P = 5E\text{-}5$) [39]; in patients with breast carcinoma dead at 5 years compared to patients alive at 5 years ($P = 7.4E\text{-}4$) [29]; in ovarian adenocarcinoma grade 2 and grade 3 compared to grade 1 ($P = 0.011$) [40]; in prostate carcinoma gleason score 7–10 compared to 5–6 ($P = 3E\text{-}5$) [41]; in metastatic soft tissue cancer compared to primary soft tissue cancer ($P = 6.7E\text{-}4$) [42] (Fig. 3).

Discussion

Since first discovered in yeast, the septins have been proved to be not simply a kind of constitutional cytoskeletal

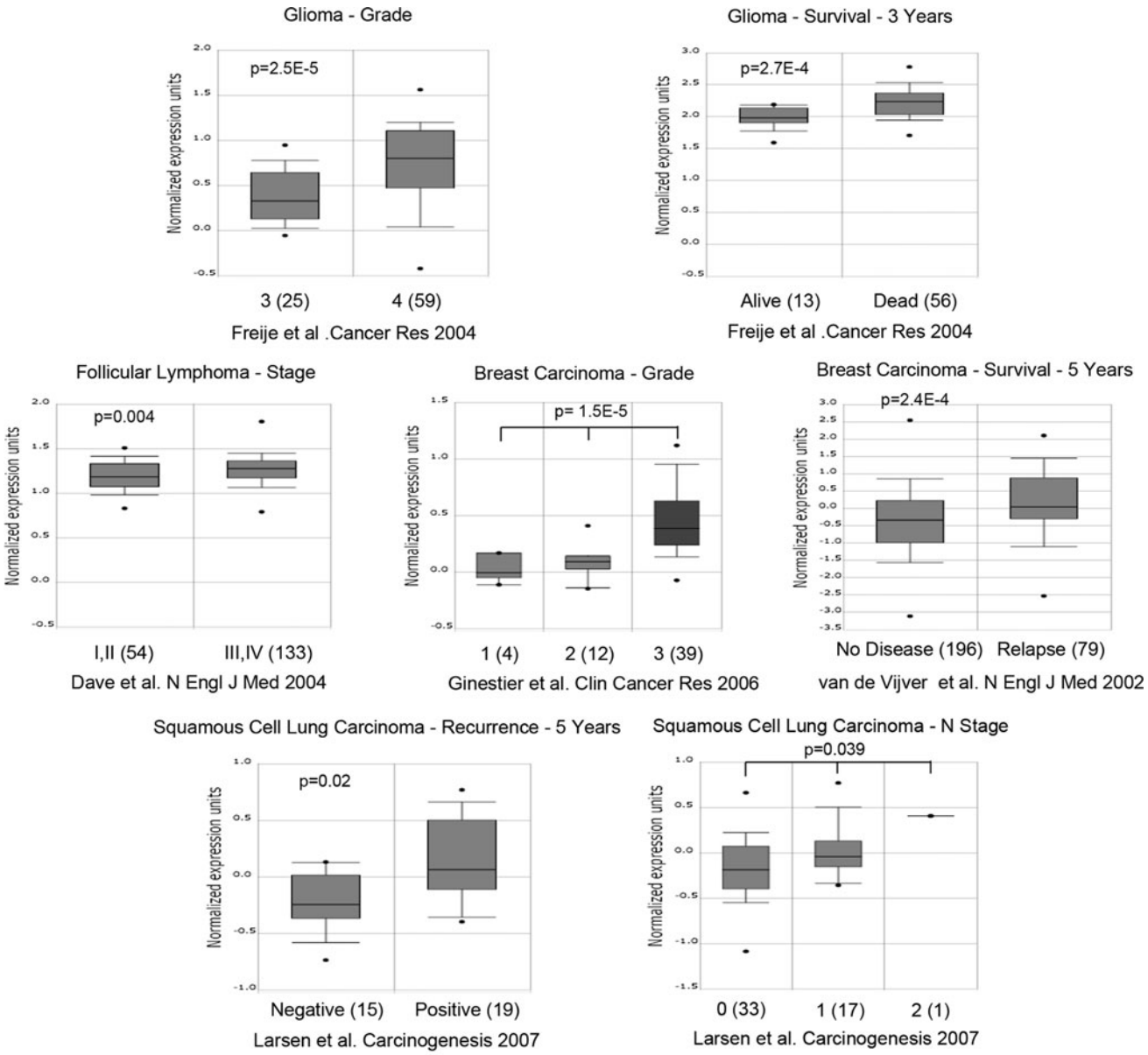

Fig. 2 Association of SEPT9 expression and tumor progression in various cancers. SEPT9 expression in glioma grade 4 and grade 3 [34]; in alive patients with and dead patients with glioma [34]; in follicular lymphoma stage I, stage II, stage III and stage IV [35]; in breast carcinoma grade 1, grade 2 and grade 3 [36]; in alive patients with and dead patients with breast carcinoma [29]; in squamous cell lung carcinoma patients with relapse and with no relapse [37]; in squamous cell lung carcinoma N stage 0, stage 1 and stage 2 [37]

proteins, but a huge protein family with diverse cellular functions. Septins usually act as the molecular depots which recruit or sequester important signaling proteins with remote functions [43]. This model might account for their critical roles in regulating different kinds of cellular signaling pathways and their associations with many human diseases. As abnormal expression of septins is often found in various cancer types, the relationship between septins and carcinogenesis is becoming a hot spot of the functional study of septin gene family.

In this study, we investigated the expression of 14 human septins in 35 kinds of human cancer types. The results showed that most of the septins had altered expression in various cancers. Obviously, SEPT2 was over-expressed in 11/35 cancer types; SEPT6 was over-expressed in 12/35 cancer types; SEPT9 was over-expressed in 15/35 cancer types; SEPT11 was over-expressed in 12/35 cancer types; SEPT4 was found significantly down-regulated in 11/35 cancer types; and SEPT10 was also down-regulated in 11/35 cancer types. Besides, other septin family members have shown varying degrees of altered expression in different kinds of tumors (Table 1). More importantly, the altered expressions of some septins are closely associated with tumor progression and clinical

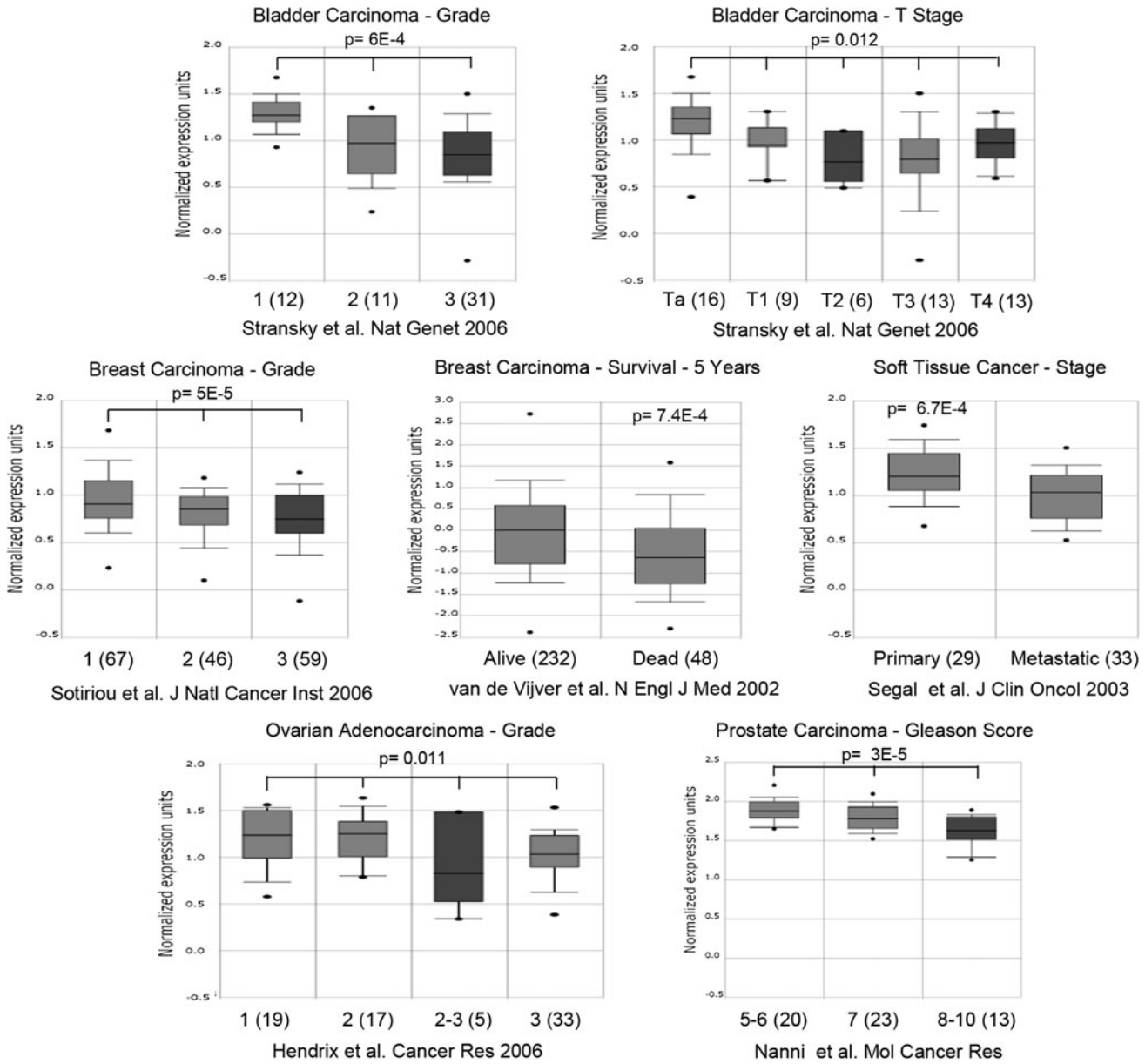

Fig. 3 Association of SEPT10 expression and tumor progression in various cancers. SEPT10 expression in bladder carcinoma grade 1, grade 2 and grade 3 [38]; in bladder carcinoma stage T4, T3, T2, T1 and Ta [38]; in breast carcinoma grade 1, grade 2 and grade 3 [39]; in alive patients with and dead patients with breast carcinoma [29]; in ovarian adenocarcinoma grade 1, grade 2, grade 2–3 and grade 3 [40]; in prostate carcinoma Gleason score 5–6, and Gleason score 7–10 [41]; in metastatic soft tissue cancer and primary soft tissue cancer [42]

outcomes including tumor grade, tumor stage and prognosis. The results are in accordance with previous reports, such as the well-studied SEPT9 which have been mentioned before. We have also found some new cancer related septins which have very limited reports about their relationship with cancer, for example, SEPT10 and SEPT11. SEPT10 was significantly down-regulated in many cancer types (Supplementary Fig. S6), and the down-regulation is closely related with the tumor progression and clinical outcomes of the patients (Fig. 3). SEPT11 was found over-expressed in many tumors (Supplementary Fig. S4). The over-expression of SEPT11 was also associated with tumor stage and prognosis (data not shown).

Above all, this report has linked the septin family with carcinogenesis. Some of the septins were found to be consistently up-regulated or down-regulated in many human tumors, and the altered expression is also correlated with tumor progression. The results indicated that some septins might act as potential oncogenes or tumor-suppressor genes in the development of certain kinds of

cancers. The report has provided new clues for further investigation of the relationship and inner mechanisms involved in this process.

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