

Gene Section

Review

STMN1 (stathmin 1)

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Abstract

Stathmin 1 (STMN1) is a microtubule destabilizer protein with an important role in cell cycle progression, cell proliferation, migration and survival. The present review on STMN1 contains data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: C1orf215, LAP18, Lag, OP18, PP17, PP19, PR22, SMN

HGNC (Hugo): STMN1

Location: 1p36.11

DNA/RNA

Note

The entire STMN1 gene is about 22.8 kb and contains 5 exons (start: 26210672 bp and end: 26233482; orientation: minus strand).

The STMN1 gene encodes 2 isoforms, A and B. Isoform A contains 3 transcript variants that differ in the 5' UTR and have an alternate terminal exon, compared to isoform B, resulting in a shorter and distinct C-terminus. The isoform B represents the longest transcript variant.

Protein

Description

Stathmin 1 belongs to the Stathmin protein family, which is characterized by the presence of a Stathmin-like domain (also known as tubulin-binding domain) that participates in interactions/sequestering of alpha/beta-tubulin heterodimers (Figure 1).

Expression

Ubiquitous. Stathmin 1 is highly expressed during embryonic development. In adult cells, it is expressed during cell proliferation, and in nervous tissue and testis (revised in Curmi et al., 1999).

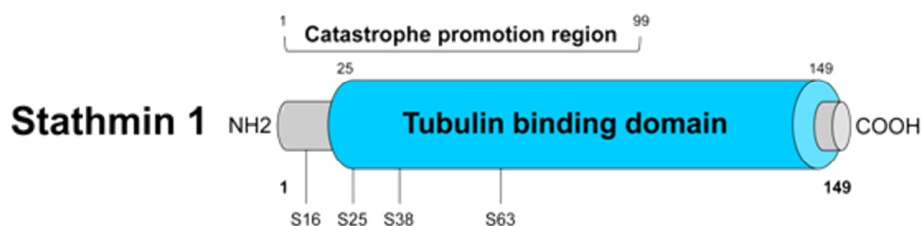


Figure 1. Representation of primary structure of Stathmin 1 protein. The catastrophe promotion region (aa 1 - 99) and the four serine phosphorylation sites (S16, S25, S38 and S63) at the N-terminal, and the tubulin binding domain (aa 25 - 149) at the C-terminal are illustrated in the figure. Reproduced with permission of the editor-in-chief of BMB reports from Machado-Neto et al., 2014b.

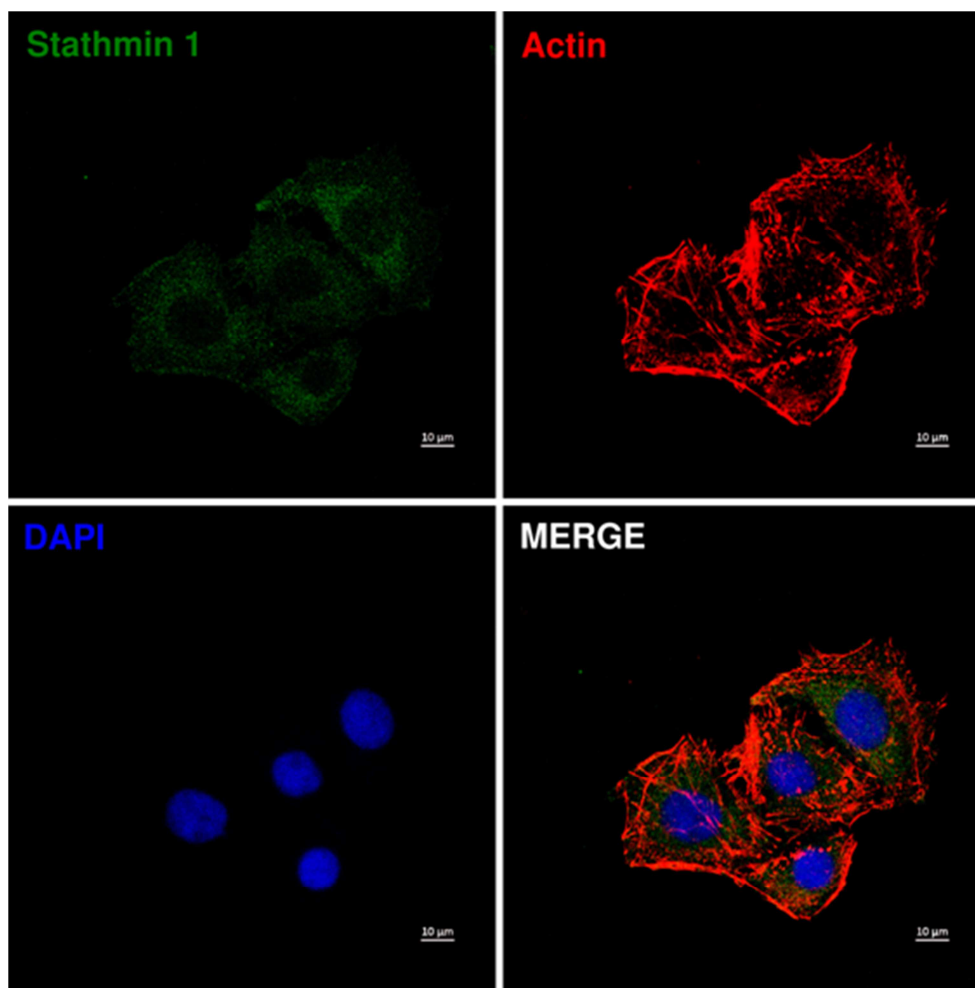


Figure 2. Intracellular localization of Stathmin 1 protein in HeLa cells. Confocal analysis of HeLa cells displaying Stathmin 1 (green), Actin (red) and DAPI (blue) staining; MERGE shows the overlapped images. Scale bar: 10 μm. Note the predominant cytoplasmic localization of Stathmin 1. Anti-Stathmin 1 (OP18; sc-55531) was from Santa Cruz Biotechnology, (Santa Cruz, CA, USA), Phalloidin (A12379) and DAPI (P-36931) were from Invitrogen (Carlsbad, CA, USA). Personal data.

Localisation

Stathmin 1 is predominantly found in the cytoplasm (Figure 2).

Function

Stathmin 1 is a phosphoprotein that participates in microtubule catastrophe and/or in the sequestering of alpha/beta-tubulin heterodimers, regulates microtubule dynamics, cell cycle progression, proliferation, motility and survival (Curmi et al., 1999; Belletti and Baldassarre, 2011). The main mechanism of regulation of Stathmin 1 activity is based in its phosphorylated and unphosphorylated status at serine sites (residues 16, 25, 38 and 68). Stathmin 1 phosphorylation at serine 16 and/or 63 reduces the affinity between Stathmin 1 and alpha/beta-tubulin heterodimers. The proteins that are able to phosphorylate Stathmin 1 at serine 16 and/or 63 are: aurora kinase B, protein kinase A (PKA), P21 protein (Cdc42/Rac)-activated kinase

(PAK1) and Ca^{2+} /calmodulin-dependent protein kinases (CamKs). Serine 25 and/or 38 may be phosphorylated by cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs) and phosphoinositide 3-kinase (PI3K) (Belletti and Baldassarre, 2011).

Phosphatase proteins that are able to dephosphorylate Stathmin 1 includes: protein phosphatase 1 (PP1), protein phosphatase 2A (PP2A) and protein phosphatase 2B (PP2B) (Guy et al., 1992; Tournebize et al., 1997; Mistry et al., 1998) (Figure 3).

Homology

Stathmin 1 shares high homology with the other members of the Stathmin protein family including Stathmin-like 2 (also named SCG10), Stathmin-like 3 (also named SCLIP) and Stathmin-like 4 (also named RB3). Stathmin 1 also shares high homology among different species (Table 1).

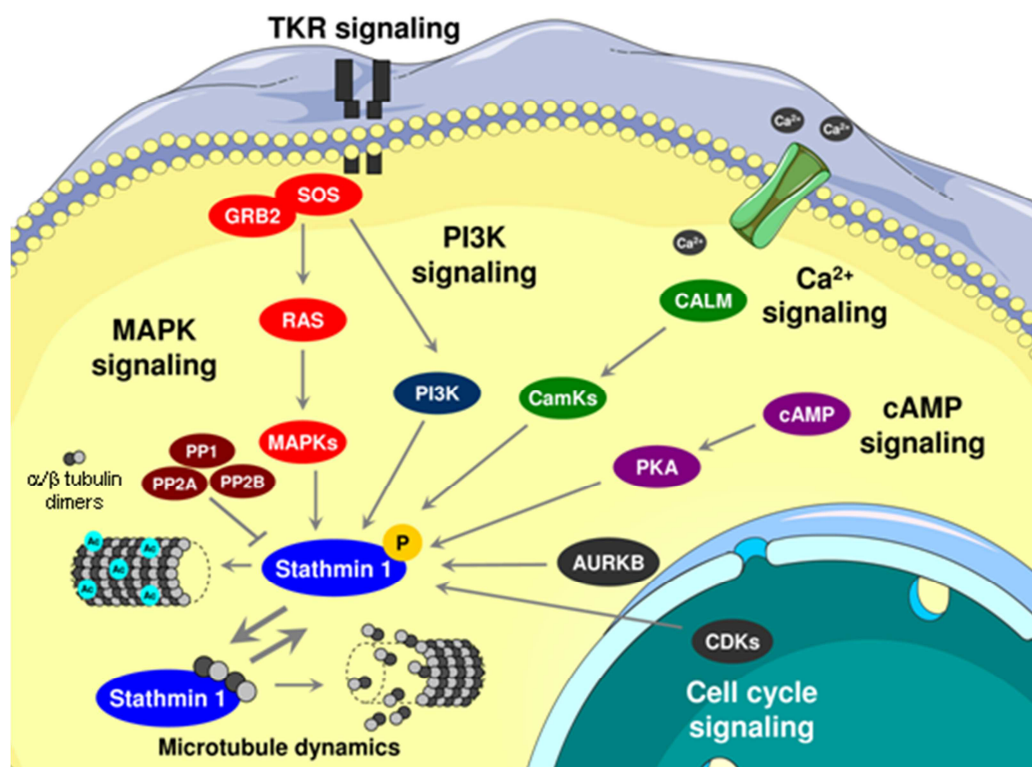


Figure 3. Stathmin 1 signaling. Stathmin 1 may be phosphorylated on serine sites by cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase (PI3K), aurora kinase B (AURKB), protein kinase A (PKA), and Ca²⁺/calmodulin-dependent protein kinases (CamKs), leading to microtubule stability. On the other hand, Stathmin 1 may be dephosphorylated by protein phosphatase 1 (PP1), protein phosphatase 2A (PP2A) and protein phosphatase 2B (PP2B), resulting in microtubule instability. Abbreviations: TKR: tyrosine kinase receptor; P: phosphorylation; Ac: acetylation. This figure was performed using Servier Medical Art tools (<http://www.servier.com/Powerpoint-image-bank>).

Mutations

Recurrent mutations in the STMN1 gene are rare, 10 missense, 8 nonsense, 1 nonstop extension and 3 coding silent mutations are reported at COSMIC (catalogue of somatic mutations in cancer; COSMIC). In human esophageal adenocarcinoma, STMN1 Q18E mutation was identified and presented transformation potential in vitro and in vivo in NIH3T3 cells (Misek et al., 2002).

Studies performed in leukemia cells indicate that the Q18E mutation results in Stathmin 1 hyperactivity and contributes to chromosomal instability (Holmfeldt et al., 2006).

Implicated in

Various cancers

Note

The role and clinical impact of Stathmin 1 has been extensively addressed in many types of human cancers. In general, the increased expression of Stathmin 1 is found in many cancers and confers a poor prognosis (revised in Belletti and Baldassarre, 2011 and Rana et al., 2008). Using cancer cell line

models, several groups have demonstrated that Stathmin 1 inhibition may partially reverse the malignant phenotype.

Hematopoietic neoplasms

Note

Stathmin 1 was initially identified by proteomics analysis of HL60 leukemia cells (Feuerstein and Cooper, 1983). In primary acute leukemia and lymphoma samples, and leukemia cell lines, several independent groups have showed that Stathmin 1 is highly expressed (Hanash et al., 1988; Melhem et al., 1991; Melhem et al., 1997; Roos et al., 1993; Machado-Neto et al., 2014a; Brattsand et al., 1993); however its impact on survival outcome remains unknown. A recent study of immunophenotypic and molecular features of a large series of follicular lymphomas indicated that Stathmin 1 represents an useful novel diagnostic marker for these diseases (Marafioti et al., 2013). Importantly, Stathmin 1 silencing resulted in marked inhibition of tumorigenicity, proliferation and clonogenicity in leukemia cell lines (K562, U937 and Namalwa cells) (Machado-Neto et al., 2014a; Jeha et al., 1996; Iancu et al., 2001).

| % Identity for: <i>Homo sapiens</i> STMN1 | Symbol | Protein | DNA |
|---|--------|---------|------|
| vs. <i>P. troglodytes</i> | STMN1 | 100 | 99.3 |
| vs. <i>M. mulatta</i> | STMN1 | 100 | 99.1 |
| vs. <i>C. lupus</i> | STMN1 | 100 | 93.5 |
| vs. <i>B. taurus</i> | STMN1 | 100 | 93.7 |
| vs. <i>M. musculus</i> | Stmn1 | 98.7 | 89.0 |
| vs. <i>R. norvegicus</i> | Stmn1 | 99.3 | 91.3 |
| vs. <i>G. gallus</i> | STMN1 | 95.1 | 87.3 |
| vs. <i>D. rerio</i> | stmn1a | 80.0 | 74.3 |
| vs. <i>D. rerio</i> | stmn1b | 76.6 | 75.4 |

Table 1. Comparative identity of human STMN1 with other species. Source: HomoloGene.

In a study that focused on the identification of biomarkers of human aging and aging-related diseases, Stathmin 1 was found upregulated in plasma samples from myelodysplastic patients (Jiang et al., 2008). Recently, increased levels of Stathmin 1 were reported in bone marrow and CD34⁺ cells from high-risk myelodysplastic syndromes patients and during disease progression (Machado-Neto et al., 2014a). Notably, higher Stathmin 1 expression was associated with high-risk disease and higher bone marrow blasts percentage (Machado-Neto et al., 2014a), but did not impacted survival.

Stathmin 1 was also identified as one of the 15 most relevant genes for determining the outcome in myeloma multiple patients by microarray approach (Decaux et al., 2008).

Breast cancer

Note

Using Western blot analysis, Brattsand (Brattsand, 2000) reported that Stathmin 1 expression positively correlated with proliferation status and aggressiveness in a panel of 151 primary breast carcinoma samples. Similar results were found by Curmi and colleagues (Curmi et al., 2000), who also reported that Stathmin 1 overexpression correlated with loss of steroid receptors, histopathological grade III and mitotic index. Importantly, Stathmin 1 expression was indicated as a potential tool for predicting the outcome of breast cancer patients with lymph node metastasis and its expression was increased in the group with poor prognosis (Oishi et al., 2007). By multivariate analysis, high Stathmin 1 expression predicted reduced disease-free survival (Saal et al., 2007; Golouh et al., 2008; Baquero et al., 2012) and overall survival (Baquero et al., 2012). Decreased Stathmin 1 phosphorylation at serine 16 (an inhibitory site) correlated with the more metastatic phenotype in breast cancers cell lines and primary

tumors (Li et al., 2011). Using breast cancer cell lines and gene therapy tools, Stathmin 1 inhibition, by adenovirus-mediated gene transfer of anti-Stathmin 1 ribozyme, resulted in a dose-dependent inhibition of proliferation, apoptosis induction and had an additive effect together low concentration of taxol treatment in vitro and in vivo (Miceli et al., 2013).

Ovarian cancer

Note

Stathmin 1 overexpression has been described in ovarian cancer patients (Alaiya et al., 1997; Price et al., 2000). Wei and colleagues (Wei et al., 2008) observed that Stathmin 1 was expressed in all ovarian cancer samples analyzed and higher levels were observed in the metastatic tumors and negatively impacted survival by univariate analysis. In agreement, Stathmin 1 overexpression was found in primary high-grade serous ovarian carcinomas and ovarian cancer cell lines (Karst et al., 2011). High levels of Stathmin 1 predicted an unfavorable prognosis in ovarian cancer patients under paclitaxel and/or platinum therapy (Su et al., 2009; Aoki et al., 2009) also by univariate analysis. In p53 mutated ovarian cancer cell lines, Stathmin 1 silencing caused cell cycle arrest and apoptosis in vivo and in vivo (Sonogo et al., 2013).

Head and neck cancer

Note

Using proteomics approach, Stathmin 1 was found to be differently expressed in oral squamous-cell carcinoma and laryngeal squamous-cell carcinoma (Koike et al., 2005; Sewell et al., 2007). Stathmin 1 expression was also found to be significantly increased in oral squamous-cell carcinoma cell lines and primary tumors and its high expression correlated with advanced stages of the disease and poor disease-free survival by univariate analysis (Kouzu et al., 2006). In head-neck squamous-cell

carcinoma, Stathmin 1 was expressed at low levels (76% cases) and did not impact recurrence (Canzonieri et al., 2012). Cheng and colleagues (Cheng et al., 2008) identified an upregulation of Stathmin 1 in primary nasopharyngeal carcinoma and its expression was associated with recurrence and advanced stages of the disease. In agreement, Hsu and colleagues (Hsu et al., 2014) reported that Stathmin 1 was overexpressed in approximately 50% of the nasopharyngeal carcinoma samples and was associated with advanced age, high-grade tumors and was an independent predictor of worse disease-free survival. Notably, knockdown of Stathmin 1 suppressed cell cycle progression, proliferation, migration, invasion, xenograft tumor growth, induced apoptosis and potentiated paclitaxel response in nasopharyngeal carcinoma cell lines (CNE1-LMP1 and HNE2 cells) (Wu et al., 2014).

Hepatocarcinoma

Note

Yuan and colleagues (Yuan et al., 2006) reported a high Stathmin 1 expression in 56% of 156 hepatocarcinoma patients and high Stathmin 1 expression was associated with increased tumor size, tumor grade, metastasis, p53 mutation status and negatively impacted survival in univariate analysis. In agreement, elevated Stathmin 1 levels were also reported by Singer and colleagues (Singer et al., 2007) and were associated with the presence of undifferentiated tumors. Other studies observed an increased Stathmin 1 expression in tumor tissue compared to matched normal tissue, and a positive association between Stathmin 1 overexpression and recurrence or poor prognosis in univariate analysis (Hsieh et al., 2010; Chen et al., 2013b). In hepatocarcinoma cell lines, Stathmin 1 silencing reduced cell proliferation, viability, migration and augmented the response to paclitaxel, vinblastine and cisplatin treatment (Singer et al., 2007; Hsieh et al., 2010; Gan et al., 2010).

Endometrial cancer

Note

In a multicenter study including 1076 endometrial patients, Stathmin 1 overexpression was detected in 37% of cases and correlated with high grade disease and aneuploidy, and was an independent predictor of metastasis and worse disease specific survival (Trovik et al., 2011). In another study from the same group (Trovik et al., 2010), high Stathmin 1 expression was associated with a higher probability of endometrial cancer recurrence and PI3K activation. Additionally, a study conducted by Salvesen and colleagues (Salvesen et al., 2009), investigating the impact of PI3K activation in endometrial cancer, identified that high Stathmin 1 expression was an independent predictor of

aggressive phenotype and worse survival. Of note, Wik and colleagues (Wik et al., 2013) reported that the levels of Stathmin 1 phosphorylation at serine 38 site were associated with poor prognosis, tumor cell proliferation, increased PIK3CA copy number and PI3K activation by multivariate analysis. Werner and colleagues (Werner et al., 2014), using endometrial cancer cell lines, showed that Stathmin 1 silencing potentiated the response to paclitaxel treatment. This finding was confirmed in vivo: endometrial cancer patients with high Stathmin 1 expression had a poor response to paclitaxel therapy (Werner et al., 2014).

Bladder cancer and urothelial carcinoma

Note

Using quantitative PCR targeting 110 relevant cancer genes, Dubosq and colleagues (Dubosq et al., 2012) detected Stathmin 1 as highly expressed in early recurrence, compared to late or null recurrence cancer in a cohort of 47 bladder cancer patients, suggesting a role for this protein in the time of recurrence. Bhagirath and colleagues (Bhagirath et al., 2012) reported elevated STMN1 mRNA levels in muscle invasive tumors. In agreement, patients with high Stathmin 1 expression under taxane therapy had decreased recurrence-free survival by univariate analysis (Wosnitzer et al., 2011). In a cohort of 58 urothelial carcinoma patients, multivariate analysis revealed that Stathmin 1 positivity was associated with high grade tumors, recurrence and negatively impacted survival (Lin et al., 2009).

Colorectal cancer

Note

In a cohort of 149 patients with colorectal cancer, high Stathmin 1 levels were an independent predictor of worse overall survival (Zheng et al., 2010). In addition, Stathmin 1 expression was associated with tumor differentiation, invasion and stage of the disease (Zheng et al., 2010). In contrast, Ogino and colleagues (Ogino et al., 2009) showed that, by multivariate analysis, Stathmin 1 positivity had a protective effect on survival in a cohort of 546 colorectal patients (stratified in obese and non-obese individuals). Interestingly, obesity had a negative impact on survival in Stathmin 1 positive patients, but not in Stathmin 1-negative patients (Ogino et al., 2009). A recent study conducted by Tan and colleagues (Tan et al., 2012) corroborated the findings from Zheng and colleagues (Zheng et al., 2010), indicating that high Stathmin 1 levels negatively impacted survival in a cohort of 324 colorectal cancer patients in univariate analysis. Tan and colleagues (Tan et al., 2012) also demonstrated functional evidences that Stathmin 1 is a positive regulator of cell proliferation,

clonogenicity, migration and invasion in colorectal cancer cell lines.

Gastric cancer

Note

Jeon and colleagues (Jeon et al., 2010) reported that a high expression of Stathmin 1 was an independent predictor of shorter recurrence-free survival, and associated with lymph node metastasis and high grade stages in a cohort of 226 gastric cancer patients. The authors, using two different gastric cancer cell lines (SNU638 and SNU16 cells), demonstrated that Stathmin 1 silencing decreased cell proliferation, migration, invasion and xenograft tumor growth (Jeon et al., 2010). Kang and colleagues (Kang et al., 2012), and Ke and colleagues (Ke et al., 2013), identified high Stathmin 1 expression in cell lines and primary cells from gastric cancer and predicted poor prognosis by univariate analysis. Interestingly, Kang and colleagues (Kang et al., 2012) also reported that Stathmin 1 silencing reduced the malignant phenotype *in vitro* and *in vivo*, and suggested that miR-223 is involved in the regulation of Stathmin 1 expression in gastric cancer cell lines (AGS and MKN7 cells). Another study, using lentivirus mediated RNAi delivery, also demonstrated that Stathmin 1 silencing reduced cell proliferation, migration and xenograft tumor growth in MKN-45 gastric cancer cells (Akhtar et al., 2013).

Prostate cancer

Note

Using high-throughput immunoblotting, elevated Stathmin 1 expression was found in metastatic prostate cancer protein extracts (Varambally et al., 2005). Another study reported that Stathmin 1 expression was higher in advanced prostate tumors (Ghosh et al., 2007). Stathmin 1 silencing resulted in cell cycle arrest, reduced clonogenicity and increased apoptosis in prostate cancer cell line (LNCaP cells) (Mistry et al., 2005). In contrast, Stathmin 1 inhibition augmented the epithelial-to-mesenchymal transition and metastasis potential in another prostate cancer cell line (DU145 cells) (Williams et al., 2012).

Pheochromocytomas

Note

In a study conducted by Sadow and colleagues (Sadow et al., 2008), among the endocrine tumors, high levels of Stathmin 1 were observed in malignant pheochromocytomas. These results were confirmed by two other groups, who reported an overexpression of Stathmin 1 in malignant/metastatic pheochromocytomas compared to benign tumors or normal tissues (Björklund et al., 2010; Lin et al., 2011).

Cervical cancer

Note

A higher Stathmin 1 expression was found in primary cells and cell lines from cervical carcinoma compared to normal cervical epithelial cells and also in tumor cells compared to matched adjacent non-carcinoma tissue (Xi et al., 2009). Increased Stathmin 1 expression correlated with a worse clinical stage and metastasis (Xi et al., 2009). Another study found Stathmin 1 overexpression in all cervical and rare expression of Stathmin 1 in benign samples; the authors suggest that the analysis of Stathmin 1 may be useful diagnostically in the identification of cervical cancer (Howitt et al., 2013).

Glioma

Note

In a cohort of 24 glioma patients, increased Stathmin 1 levels were associated with decreased recurrence-free survival in univariate analysis (Ngo et al., 2007). Similar results were observed in a xenograft glioma nitrosourea-treated model (Ngo et al., 2007). Dong and colleagues (Dong et al., 2012) observed that Stathmin 1 expression was aberrantly expressed in vascular endothelial cells from glioma, especially in high grade cases and the Stathmin 1 silencing reduced cell proliferation and invasion, and induced apoptosis in glioma-derived microvascular endothelial cells.

Lung cancer

Note

Chen and colleagues (Chen et al., 2003) reported a high expression of Stathmin 1 in a cohort of 93 lung adenocarcinoma patients and this expression was associated with poorly differentiated tumors. Stathmin 1 overexpression was also found in primary non-small cell lung tumors matched with normal tissues (Singer et al., 2009). Rosell and colleagues (Rosell et al., 2003) observed that high Stathmin 1 levels negatively affected the time to progression in non-small-cell lung cancer patients, by univariate analysis. Of note, Stathmin 1 inhibition decreased proliferation, migration and invasion in non-small cell lung cancer cell lines (Calu-1 and Calu-6 cells) (Singer et al., 2009).

Medulloblastoma

Note

Using a microarray approach, Stathmin 1 was identified as differentially expressed in primary medulloblastoma samples and it was associated with unfavorable overall survival (Neben et al., 2004). Accordingly, Kuo and colleagues (Kuo et al., 2009) reported that Stathmin 1 correlated with tumor dissemination and predicted decreased survival in medulloblastoma patients, by univariate analysis in both studies.

Pancreatic cancer

Note

Lu and colleagues (Lu et al., 2014) reported that Stathmin 1 was overexpressed in pancreatic cancer samples and that high Stathmin 1 levels were correlated with vascular emboli, tumor size, and negatively impacted overall survival in univariate analysis. In addition, Stathmin 1 silencing in pancreatic cancer cells resulted in reduced cell proliferation, clonogenicity and cell cycle arrest (Lu et al., 2014; Jiang et al., 2009).

Thyroid cancer

Note

Using cDNA microarray approach, Onda and colleagues (Onda et al., 2004) reported that Stathmin 1 was overexpressed in all anaplastic thyroid cancer cell lines analyzed and this was confirmed by immunohistochemical analyses in primary samples. Another study also observed that Stathmin 1 was highly expressed in anaplastic thyroid carcinomas (Sadow et al., 2008).

Cholangiocarcinoma

Note

In a cohort of 80 extrahepatic cholangiocarcinoma patients, high levels of Stathmin 1 correlated with invasion and shorter recurrence-free survival by multivariate analysis (Watanabe et al., 2014). The authors also demonstrated that Stathmin 1 silencing resulted in reduced cell proliferation capacity and increased sensitivity to paclitaxel treatment in a cholangiocarcinoma cell line (Watanabe et al., 2014).

Melanoma

Note

In primary melanoma samples, Stathmin 1 was highly expressed in two independent cohorts, but did not impact survival (Chen et al., 2013a). Stathmin 1 silencing reduced cell proliferation and migration. Furthermore, Stathmin 1 overexpression potentiated both these cell processes in melanoma cell lines (Malme-3M and A375 cells) (Chen et al., 2013a).

Mesothelioma

Note

Overexpression of Stathmin 1 was found in all mesothelioma cell lines tested (LRK1A, H2052, 211H, H290, MS1, H513 and H28 cells) and also in primary tumors compared to its matched normal tissue (Kim et al., 2007).

Pediatric brain cancer

Note

Using 2-dimensional differential in-gel electrophoresis, immunohistochemistry and quantitative PCR, Stathmin 1 was identified as

highly expressed in primary primitive neuroectodermal tumors compared to ependymomas samples (de Bont et al., 2007).

Renal cancer

Note

In Wilms tumors, Stathmin 1 was highly expressed in high grade compared to low grade tumors (Takahashi et al., 2002).

Sarcoma

Note

Belletti and colleagues (Belletti et al., 2008) reported that Stathmin 1 was increased in recurrent and metastatic sarcoma samples.

In addition, overexpression of the wild type Stathmin 1 or mutated Stathmin 1 (Q18E, gain-of-function mutation) potentiated the malignant phenotype in the sarcoma cell line HT1080 (Belletti et al., 2008).

Salivary cancer

Note

Using 2-dimensional differential in-gel electrophoresis, increased Stathmin 1 expression was found in adenoid cystic carcinoma (Nakashima et al., 2006).

To be noted

Note

Although Stathmin 1 regulates multiple important cellular functions, Schubart and colleagues (Schubart et al., 1996) initially reported that *Stmn1* knockout mice had normal growth, development, reproduction and did not show any aberrant phenotype. Later on, it was observed that *Stmn1* knockout mice developed an axonopathy of the central and peripheral nervous systems with aging (Liedtke et al., 2002). In addition, Shumyatsky and colleagues (Shumyatsky et al., 2005) reported that *Stmn1* knockout mice had reduced memory in amygdala-dependent fear conditioning, failed to recognize danger environments (Shumyatsky et al., 2005) and exhibited accelerated fear extinction (Martel et al., 2012). Using well-defined mouse models of carcinogenesis and *Stmn1* knockout mice, D'Andrea and colleagues (D'Andrea et al., 2012) demonstrated that *Stmn1* did not impact on cancer onset. Regarding hematopoietic-related processes, *Stmn1* knockout mice presented two human hematopoietic disease phenotypes: megaloblastic anemia and thrombocytosis (Ramlogan-Steel et al., 2012). Notably, *Stmn1* knockout mice did not have any that were alterations incompatible with life, and Stathmin 1 inhibition in several types of cancer cells reduced the malignant phenotype, making it an attractive target for anticancer therapies.

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