

Contributed Mini Review

Stathmin 1 in normal and malignant hematopoiesis

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Stathmin 1 is a microtubule destabilizer that plays an important role in cell cycle progression, segregation of chromosomes, clonogenicity, cell motility and survival. Stathmin 1 overexpression has been reported in malignant hematopoietic cells and Stathmin 1 inhibition reduces the highly proliferative potential of leukemia cell lines. However, during the differentiation of primary hematopoietic cells, Stathmin 1 expression decreases in parallel to decreases in the proliferative potential of early hematopoietic progenitors. The scope of the present review is to survey the current knowledge and highlight future perspectives for Stathmin 1 in normal and malignant hematopoiesis, with regard to the expression, function and clinical implications of this protein. [BMB Reports 2014; 47(12): 660-665]

STATHMIN 1 INTEGRATES MULTIPLE SIGNALING PATHWAYS

Stathmin 1 is a cytoplasmatic phosphoprotein of 18 kDa, also known as Oncoprotein 18 (OP18), Leukemia-associated phosphoprotein p18 (LAP18) or Metablastin, which belongs to the Stathmin family. All members of this family share a Stathmin-like domain that contains up to four serine phosphorylation sites (residues 16, 25, 38 and 68) at the N-terminal region and a tubulin-binding domain (1, 2). The schematic representation of Stathmin 1 is illustrated in Fig. 1. The main function of Stathmin 1 is based on the microtubule destabilizer activity of this protein, which enables the promotion of a microtubule catastrophe or the sequestration of alpha/beta-tubulin heterodimers, preventing the formation of microtubules (3-5). The name "Stathmin" derives from "Stathmos" which means "relay", the protein received this name due to its role in the signal transduction of multiple signaling pathways summarized

in Fig. 2 (6, 7).

Phosphorylation of Stathmin 1 at specific serine sites (16 and/or 63) reduces the affinity between Stathmin 1 and alpha/beta-tubulin heterodimers and represents an important mechanism of its regulation (8). During mitosis, accurate microtubule dynamics are necessary for the success of cell cycle progression and multiple signaling pathways participate in this process, targeting Stathmin 1 at serine sites. Aurora kinase B, Protein kinase A (PKA), P21 Protein (Cdc42/Rac)-Activated Kinase (PAK1) and Ca²⁺/calmodulin-dependent protein kinases (CamKs) may phosphorylate Stathmin 1 at serine 16 and/or 63, resulting in potent inactivation of tubulin binding capacity (9). Cyclin-dependent kinases (CDKs), Mitogen-activated protein kinases (MAPKs) and phosphoinositide 3-kinase (PI3K) induce Stathmin 1 phosphorylation at serine 25 and/or 38, which is not sufficient to inhibit the association between alpha/beta-tubulin and Stathmin 1. Stathmin 1 may be dephosphorylated by the phosphatase proteins, including Protein phosphatase 2A (PP2A), Protein phosphatase 2B (PP2B) and Phosphoprotein phosphatase 1 (PP1) (10-12). In addition to the functions of Stathmin 1 in cell cycle progression, this protein also participates in the correct segregation of chromosomes, clonogenicity and cell motility and survival of normal and cancer cells (8).

Noteworthy, many of the signaling pathways that modulate Stathmin 1 function have been implicated in hematopoiesis-related processes. The PI3K and MAPK signaling network regulates cell proliferation, survival and differentiation during normal and malignant hematopoiesis events (13, 14). CDKs regulation of cell cycle progression and transcription is well established in hematological malignancies and provides a ther-

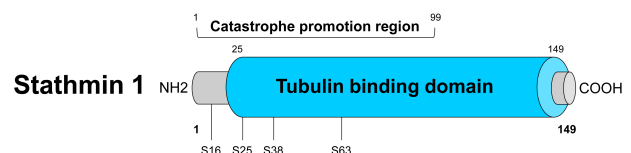


Fig. 1. Schematic structure of Stathmin 1 protein. The catastrophe promotion region at the N-terminal region, the tubulin binding domain at its C-terminal region and the four serine sites of phosphorylation (S16, S25, S38 and S63) are illustrated. The amino acid positions are indicated.

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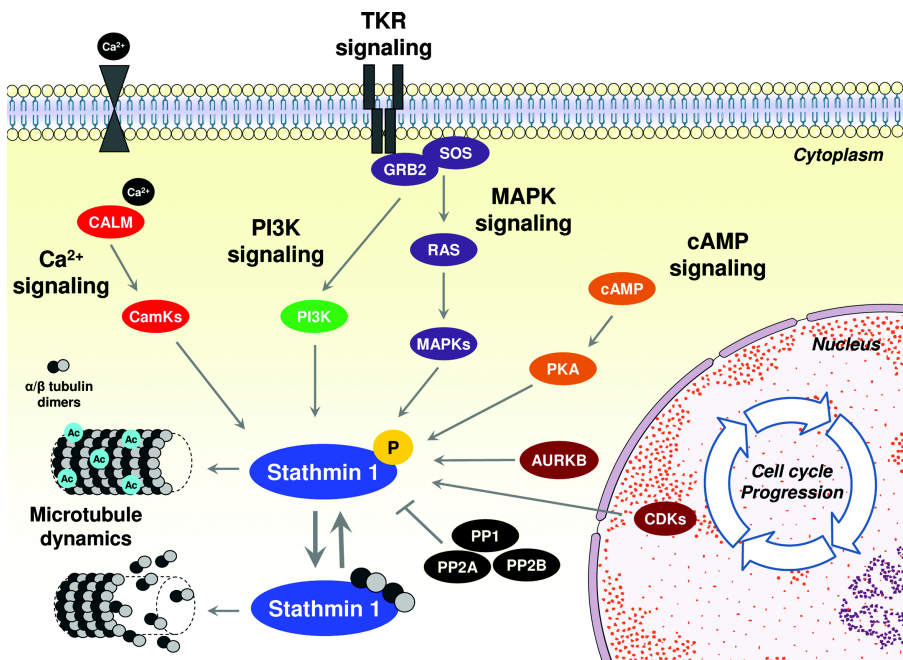


Fig. 2. Stathmin 1 signaling pathway. Cyclin-dependent kinases (CDKs), Mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase (PI3K), Aurora kinase B (AURKB), Protein kinase A (PKA), and Ca²⁺/calmodulin-dependent protein kinases (CamKs) phosphorylate Stathmin 1 at serine sites and modulate its association with alpha/beta-tubulin heterodimers. Protein phosphatase 2A (PP2A), Protein phosphatase 2B (PP2B) and Phosphoprotein phosphatase 1 (PP1) dephosphorylate Stathmin 1. The alternation in the phosphorylation and dephosphorylation status of Stathmin 1 contributes to the regulation of microtubule dynamics. Abbreviations: TKR, tyrosine kinase receptor; P, phosphorylation; Ac, acetylation.

apeutic opportunity (15, 16). Overexpression of Aurora kinase B has been associated with the progression of myelodysplastic syndromes (MDS) (17) and has been observed in acute myeloid leukemia (AML), chronic myeloid leukemia, acute lymphoblastic leukemia, multiple myeloma, aggressive non-Hodgkin lymphoma and Hodgkin lymphoma. Furthermore, Aurora kinase inhibitors appear to have a promising role in hematological malignancies (18).

STATHMIN 1 IN NORMAL HEMATOPOIESIS

The role of Stathmin 1 in hematopoiesis was initially addressed using myeloid leukemia cell lines. Stathmin 1 downregulation was reported during chemically-induced megakaryocytic differentiation of K562 and HEL cells and its inhibition resulted in higher differentiation ability and increased polyploidization (19). In addition, Stathmin 1 overexpression increased the endomitotic cycles, modulating the propensity for polyploidization (20). In contrast, Chang and colleagues (21) reported that high levels of unphosphorylated Stathmin 1 were required for efficient polyploidization during the megakaryocyte differentiation induced by PMA treatment. These findings may be explained by differences in the chemical inductor, drug concentration, time of treatment and limited ability of immortalized cell lines to finalize megakaryocytic differentiation. In murine hematopoietic cells, the expression of Stathmin 1 is high in immature megakaryocytes, low in mature megakaryocytes and undetectable in platelets, corroborating the hypothesis that Stathmin 1 is downregulated during megakaryocytic maturation (19). More recently, Iancu-Rubin

and colleagues (22) reported an elegant mechanistic study on Stathmin 1 in the human megakaryocytopoiesis using lentiviral-mediated Stathmin 1 overexpression in primary CD34⁺ cells, and Stathmin 1 overexpression reduced megakaryocyte polyploidization and platelet production (22).

Rabilloud and colleagues (23) described an increased Stathmin 1 expression during erythroid differentiation. Stathmin 1 was identified as highly expressed in murine and human erythroleukemia cells submitted to chemically-induced erythroid differentiation, *in vitro*, with erythropoietin. Interestingly, the highest level of Stathmin 1 was observed in primary proerythroblasts, compared with erythroblasts, and was not detectable in mature erythrocytes. These findings indicate that Stathmin 1 may be related to the higher proliferative ability of early erythroid progenitors (23).

There is little evidence of a role for Stathmin 1 in monocytic and granulocytic differentiation. Stathmin 1 was first identified as a rapidly phosphorylated protein in HL60 cells in response to PMA treatment for monocytic differentiation (24). Latterly, Johnson and colleagues (25) reported a gradual decrease in Stathmin 1 levels and phosphorylation during monocytic and granulocytic HL60 cell differentiation induced by physiological agents (D3 vitamin and ATRA plus G-CSF), in parallel with decreased cell proliferation.

Finally, stathmin 1-knockout mice present two human-like hematopoietic disorder phenotypes: megaloblastic anemia and thrombocytosis (26). These findings are in agreement with the previous evidence for Stathmin 1 function in megakaryocyto-

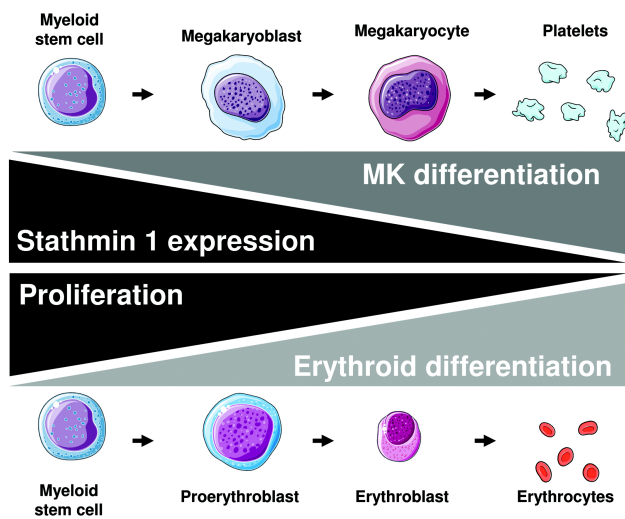


Fig. 3. Schematic representation of the role of Stathmin 1 in hematopoietic cell differentiation. This model is based on studies that evaluated Stathmin 1 during primary hematopoietic cell differentiation (22, 23), especially megakaryocytic (MK) and erythroid differentiation. Stathmin 1 expression is high in proliferating myeloid progenitors and is downregulated during cell differentiation.

poiesis and erythropoiesis (22, 23). A model of Stathmin 1 expression and relationship with hematopoietic cell differentiation, based on results using primary cells models, is illustrated in Fig. 3.

STATHMIN 1 IN MALIGNANT HEMATOPOIESIS

The early discoveries regarding Stathmin 1 were closely linked to the differential expression of this protein in acute leukemia, and Stathmin 1 was at that time named as leukemia-associated phosphoprotein p18 (27). As previously mentioned, Stathmin 1 was initially identified in HL60 leukemia cells during monocytic differentiation (24). Hanash and colleagues, using two-dimensional PAGE, identified a 18 kDa polypeptide overexpressed in primary acute leukemia cells, regardless of their lineage (28), and then cloned and sequenced the Stathmin 1 gene (29), and characterized the expression pattern in lymphocytes induced to proliferate with PHA, EBV-transformed lymphoid cells and Jurkat leukemia cells (30, 31). This group also reported that Stathmin 1 phosphorylation correlated with white blood cell counts and the percentage of cells in the S phase in a cohort of 177 childhood acute leukemia patients, by two-dimensional PAGE (32). Roos and colleagues (33) described an abnormal expression of Stathmin 1 in high grade lymphoma and acute leukemia, however no correlation with cells at S phase was found. Recently, Stathmin 1 was reported to be highly expressed in bone marrow hematopoietic cells in a cohort of 79 patients with acute leukemia, corroborating previous findings (34).

In MDS patients, Stathmin 1 expression was found to be highly expressed in bone marrow cells from high-risk disease individuals, compared to low-risk individuals, and Stathmin 1 expression positively correlated with bone marrow blast percentages in a cohort of 65 MDS patients (34). Another study, focused on the identification of biomarkers of human aging and aging-related diseases, reported Stathmin 1 to be a protein highly expressed in the plasma of MDS patients, compared to healthy donors (35). However, the biological functions of Stathmin 1 in the plasma have not yet been addressed.

Importantly, Stathmin 1 silencing resulted in a marked inhibition of tumorigenicity of the chronic myeloid leukemia cell line K562 *in vitro* and in a mouse model, suggesting that high levels of Stathmin 1 are necessary for the maintenance of the leukemia phenotype (36). Iancu-Rubin's group confirmed that knockdown of Stathmin 1 reduced K562 cell proliferation (37). Using lentiviral-mediated Stathmin 1 silencing, our group showed that Stathmin 1 inhibition reduced cell proliferation and clonogenicity capacity of acute myeloid leukemia U937 cells and acute lymphoid leukemia Namalwa cells (34).

With regard to lymphoid neoplasms, Stathmin 1 was found to be overexpressed in lymphoma cell lines compared with non-transformed lymphoblastoid cells (38), and in primary malignant lymphomas compared with normal lymphoid tissue (39). Using the microarray approach, Stathmin 1 was identified as one of the 15 most relevant genes for determining the outcome in myeloma multiple patients (41). Recently, Marafioti and colleagues (40), using high-throughput immunohistological screening, identified Stathmin 1 as a marker for follicular lymphoma. Stathmin 1 expression was absent or very low in normal lymphoid tissues, but it was highly expressed in 97% of the follicular lymphoma samples, including BCL-6 negative cases. Strong Stathmin 1 expression correlated with a high histological grade of the disease. The authors also suggested the use of Stathmin 1 expression as potentially useful for diagnosis of CD10 negative follicular lymphoma (40). Notably, studies using the expression of Stathmin 1 as a potential diagnostic tool are scarce in hematological malignancies and more studies in this research field are necessary.

FUTURE PERSPECTIVES FOR STATHMIN 1 IN HEMATOLOGY

Malignant hematological diseases are characterized by the deregulation of multiple signaling pathways, rendering the development of an efficient therapy difficult. In this sense, Stathmin 1 integrates several signaling pathways, many of them described to be altered in malignant hematopoietic cells, especially acute leukemia and myelodysplastic syndromes. Overexpression of Stathmin 1 activity may reduce the fidelity of chromosome segregation by interference in the metaphase-to-anaphase transition and causes chromosomal instability (42), a common finding in hematological malignancies. Stathmin 1 knockout mice present thrombocytosis, a typical clinical finding of some myeloprolifer-

ative disorders (26).

An important point to be clarified is whether Stathmin 1 is a “driver” or a “passenger” during the malignant transformation of hematopoietic cells. There is limited evidence of the transformation capacity of Stathmin 1 from normal to malignant cells. The expression of Stathmin 1 carrying Q18E mutation exerted transforming activity on 3T3 mouse fibroblasts, resulting *in vitro* foci formation and *in vivo* tumor growth in immunodeficient mice (43). Conversely, BCR/ABL-induced malignant transformation resulted in a marked increase of stathmin 1 expression in BaF3 cells, indicating that stathmin 1 may contribute to the transformed phenotype (44).

Focusing on Stathmin 1 as a potential therapeutic target, there is enough *in vitro* and *in vivo* evidence to indicate Stathmin 1 as a target for cancer treatment (8), however the translation from basic to clinical studies is lacking. Shi and colleagues (45) identified a novel small molecule compound (GDP366), with a dual inhibitor activity of Survivin and Stathmin 1, at mRNA levels. GDP366 was capable of inhibiting the growth of tumor cells *in vitro* and *in vivo*. Using a small hairpin RNA approach *in vivo*, Phadke and colleagues (46) tested the safety and antitumor efficacy of these molecules in rats and in a human tumor xenograft mouse model, respectively. Interestingly, the treatment with small hairpin RNA was able to reduce tumor growth in the model used and presented systemic safety at the therapeutic dose. These promising findings had potential for the development of more specific inhibitors of Stathmin 1 and are shielded the fact that of stathmin 1 knockout mice are viable and present few alterations, suggesting the possibility of low systemic toxicity.

CONCLUSION

Emerging findings regarding the function of Stathmin 1 in normal and malignant hematopoiesis are helping to understand relevant biological mechanisms. Recent basic science studies have shown that Stathmin 1 inhibition in cancer cells has been successful in reducing the proliferative phenotype of malignant cells. Therefore, strategies targeting Stathmin 1 in malignant hematopoietic cells represent an interesting field of investigation.

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