# The Role of Stathmin in the Regulation of the Cell Cycle

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**Abstract** Stathmin is the founding member of a family of proteins that play critically important roles in the regulation of the microtubule cytoskeleton. Stathmin regulates microtubule dynamics by promoting depolymerization of microtubules and/or preventing polymerization of tubulin heterodimers. Upon entry into mitosis, microtubules polymerize to form the mitotic spindle, a cellular structure that is essential for accurate chromosome segregation and cell division. The microtubule-depolymerizing activity of stathmin is switched off at the onset of mitosis by phosphorylation to allow microtubule polymerization and assembly of the mitotic spindle. Phosphorylated stathmin has to be reactivated by dephosphorylation before cells exit mitosis and enter a new interphase. Interfering with stathmin function by forced expression or inhibition of expression results in reduced cellular proliferation and accumulation of cells in the $G_2/M$ phases of the cell cycle. Forced expression of stathmin leads to abnormalities in or a total lack of mitotic spindle assembly and arrest of cells in the early stages of mitosis. On the other hand, inhibition of stathmin expression leads to accumulation of cells in the $G_2/M$ phases and is associated with severe mitotic spindle abnormalities and difficulty in the exit from mitosis. Thus, stathmin is critically important not only for the formation of a normal mitotic spindle upon entry into mitosis but also for the regulation of the function of the mitotic spindle in the later stages of mitosis and for the timely exit from mitosis. In this review, we summarize the early studies that led to the identification of the important mitotic function of stathmin and discuss the present understanding of its role in the regulation of microtubules dynamics during cell-cycle progression. We also describe briefly other less mature avenues of investigation which suggest that stathmin may participate in other important biological functions and speculate about the future directions that research in this rapidly developing field may take. J. Cell. Biochem. 93: 242–250, 2004.  © 2004 Wiley-Liss, Inc.

**Key words:** stathmin; microtubules; mitotic spindle; cell cycle

Stathmin is an important molecule that is known to play a critically important role in the process of mitosis, and possibly in a variety of other cellular processes. In spite of these important and well-documented functions, this molecule remains so obscure that few investigators even recognize its name! This might be in part a reflection of the fact that it was discovered independently in a number of different laboratories, and as a result, was called by different names (e.g., p17, p18, p19, 19K, metablastin, oncoprotein 18, LAP18, and Op18/stathmin). The major purpose of this review is to introduce stathmin to the uninitiated and to discuss in detail what is known about its important role in the cell cycle. We will also use this opportunity to briefly introduce other equally important but much less characterized cellular functions of this molecule that will require a great deal of additional investigation in the future. We hope that this will serve to bring well-deserved recognition to this relatively obscure protein that is now being discovered and rediscovered repeatedly as the expression microarray technology is being widely used to derive clues about molecules that may play important roles in a variety of biological processes.

## STATHMIN AND CELLULAR PROLIFERATION

As mentioned above, stathmin was discovered independently in several different laboratories based on its presumed involvement in a number of different cellular processes. Several observations have been made that suggested a close link between stathmin expression and/or phosphorylation and regulation of cellular proliferation. Stathmin was first identified as a 17-kDa cytosolic protein that is rapidly phosphorylated when HL60 leukemic cells are

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induced to undergo terminal differentiation and cease to proliferate [Feurestein and Cooper, 1983]. Studies in several other leukemic cell lines also showed that stathmin expression is drastically decreased when the cells ceased to proliferate upon exposure to a variety of differentiation agents [Luo et al., 1991]. Stathmin was also found to be expressed at very high levels in primary acute leukemia cells regardless of their lineage [Hanash et al., 1988]. In the same report, stathmin expression was shown to increase markedly when normal lymphocytes are induced to proliferate by exposure to mitogenic stimuli. Interestingly, the level of stathmin expression in leukocytes from patients with chronic myelogenous leukemia was also shown to increase significantly when the disease progresses into the more proliferative stage known as "blast crisis." This positive correlation between stathmin expression and cellular proliferation is not limited to cells of the hematopoietic lineage. Similar observations were made in undifferentiated multipotential embryonal carcinoma cell lines where stathmin expression was shown to decrease upon induction of differentiation and cessation of proliferation. In other solid tumors like breast and ovarian cancer, it was shown that poorly differentiated tumors with high proliferative potential generally express higher levels of stathmin than more differentiated and less proliferative tumors. Moreover, in normal rodent and human tissues, stathmin was shown to be expressed at higher levels in tissues with high cell turnover such as testis and hematopoietic cells than in non-proliferative tissues. Furthermore, in a given tissue such as epithelium, stathmin was shown to be expressed at higher levels in the proliferative compartment relative to adjacent more differentiated cells. Finally, neonatal tissues were shown to express much higher levels of stathmin relative to adult tissues. All these observations suggested a strong correlation between stathmin expression and cellular proliferation in both normal and malignant cells.

## STATHMIN AND THE REGULATION OF CELL-CYCLE PROGRESSION

The first hint that stathmin may play a role in the regulation of cell-cycle progression came from the observation that the level of phosphorylation of stathmin increases markedly when K562 erythroleukemia cells enter the mitotic phase of the cell cycle [Luo et al., 1994]. Brattsand et al. [1994] also showed that the level of stathmin phospohorylation peaks in mitosis in both Jurkat T cells and HeLa cells. In the same study, it was shown that the level of stathmin phosphorylation is significantly lower in cells blocked in the $G_1/S$ phases of the cell cycle compared to proliferating cells. Both groups also showed that stathmin is phosphorylated in vitro by $p34^{cdc2}$ kinase, the major protein kinase that regulates entry of eukaryotic cells into mitosis. All these observations provided circumstantial evidence that stathmin may play a role in the $p34^{cdc2}$-regulated pathway that controls entry into mitosis and progression through the rest of the cell cycle.

More direct evidence for the involvement of stathmin in the regulation of mitosis came from the same two groups. On one hand, our group demonstrated that antisense RNA inhibition of stathmin expression in K562 leukemic cells results in decreased cellular proliferation and accumulation of cells in the $G_2/M$ phases of the cell cycle [Luo et al., 1994]. The study by Marklund et al. [1994] confirmed these observations and extended them by showing that overexpression of wild-type or $p34^{cdc2}$-target deficient mutant of stathmin in K562 cells also results in growth suppression and accumulation of cells in the $G_2/M$ phases of the cell cycle. The fact that both overexpression and inhibition of stathmin expression results in mitotic arrest generated a paradox that was resolved two years later by the independent identification of stathmin as a cellular factor involved in the regulation of microtubule dynamics [Belmont and Mitchison, 1996].

## STATHMIN AND THE REGULATION OF MICROTUBULE DYNAMICS

Microtubules consist of $\alpha/\beta$ tubulin heterodimers that exist in a state of continuous transition between phases of polymerization and depolymerization. This property, which is referred to as dynamic instability, is characterized by stochastic switching between phases of growth and phases of shrinkage. The transition from the phase of growth to the phase of shrinkage is known as "catastrophe" while the transition from the phase of shrinkage to the phase of growth is known as "rescue." In interphase, microtubules are long and relatively stable and

their dynamics of growth and shrinkage are relatively slow. In contrast, at the onset of mitosis, when the interphase arrays of microtubules depolymerize and then repolymerize to assemble the mitotic spindle, microtubules are highly dynamic as a result of a marked increase in their rate of catastrophe [Belmont et al., 1990]. While searching for cellular factors that might promote an increased catastrophe rate of mitotic microtubules, Belmont and Mitchison [1996] purified stathmin from *Xenopus* eggs extracts and characterized it as a protein that promotes microtubule depolymerization by increasing the rate of catastrophe. On that basis, Belmont and Mitchison [1996] proposed the first model to explain the mechanism by which stathmin exerts its mitotic effects through an increase in the rate of catastrophe. Subsequently, a different model was proposed by Jourdain et al. [1997] in which the microtubule-depolymerizing activity of stathmin is mediated through direct sequestration of tubulin. This model is based on the observation that stathmin binds two unpolymerized tubulin heterodimers and forms a ternary stathmin–tubulin complex (T2S). The tubulin-sequestering activity of stathmin prevents microtubule growth by diminishing the intracellular pool of tubulin that is available for polymerization. The differences between these two models were resolved by Howell et al. [1999] who proposed a third model in which the two previously described models apply under different pH conditions. These authors demonstrated that stathmin can have two distinct activities. The first is a catastrophe-promoting activity that requires the N-terminal region of the stathmin molecule and the second is the tubulin-sequestering activity that requires the C-terminal region.

The catastrophe-promoting activity is believed to occur at the ends of polymerized microtubules. Two separate studies showed that stathmin binds tubulin heterodimers at the microtubule ends and increases the rate of catastrophe by a GTP hydrolysis-dependent mechanism [Howell et al., 1999, Larsson et al., 1999]. Steinmetz et al. [2000] visualized the stathmin–tubulin complex by electron microscopy and showed, by digital image analysis, that stathmin binds to two longitudinally arranged α/β tubulin heterodimers and forms a complex with a curved protofilament-like shape. Gigant et al. [2000] analyzed the crystal structure of the complex of tubulin and the stathmin-like domain (SLD) of RB3, another member of the stathmin family. This analysis also showed that the tubulin subunits in the complex are associated head-to-tail in a curved conformation. The same group recently extended these observations by showing that the curved complex is capped by the amino-terminal region of the SLD domain. This prevents the incorporation of the complex into polymerized microtubules. In another report, Wallon et al. [2000] showed by mass spectroscopy that stathmin links two tubulin heterodimers together by binding to helix 10 of α-tubulin, which is known to be involved in longitudinal tubulin–tubulin interaction within microtubule protofilaments. Thus, by interacting with this region, stathmin may also prevent the incorporation of the stathmin–tubulin complexes in the microtubules, preventing further polymerization. In conclusion, these studies demonstrate that stathmin is capable of binding both polymerized and unpolymerized tubulin and can prevent polymerization of α/β heterodimers under some conditions and/or promote depolymerization of microtubules under others (Fig. 1).

## STATHMIN IN THE MITOTIC PHASE OF THE CELL CYCLE

Although the exact molecular mechanisms by which stathmin exerts its mitotic function are still being worked out, there is wide consensus that its microtubule-depolymerizing activity is essential for orderly progression through cell cycle. During prophase, the first phase of mitosis, chromatin condenses into chromosomes and interphase microtubules rapidly disassemble and reassemble to form the mitotic spindle. As the cell proceeds to metaphase, spindle microtubules elongate and eventually capture the chromosomes. Thus, at metaphase, the chromosomes are aligned in the metaphase plate and the normal mitotic spindle has a characteristic bipolar shape. During anaphase, microtubule depolymerization allows the segregation and the poleward movement of the chromosomes. As cells proceed through anaphase and telophase, fluctuations between microtubule polymerization and depolymerization lead to the structural reorganization and eventually the disassembly of the spindle, which is followed by exit from mitosis and cytokinesis. Microtubules then reorganize into a new interphase cytoskeleton upon entry into a new cell cycle.
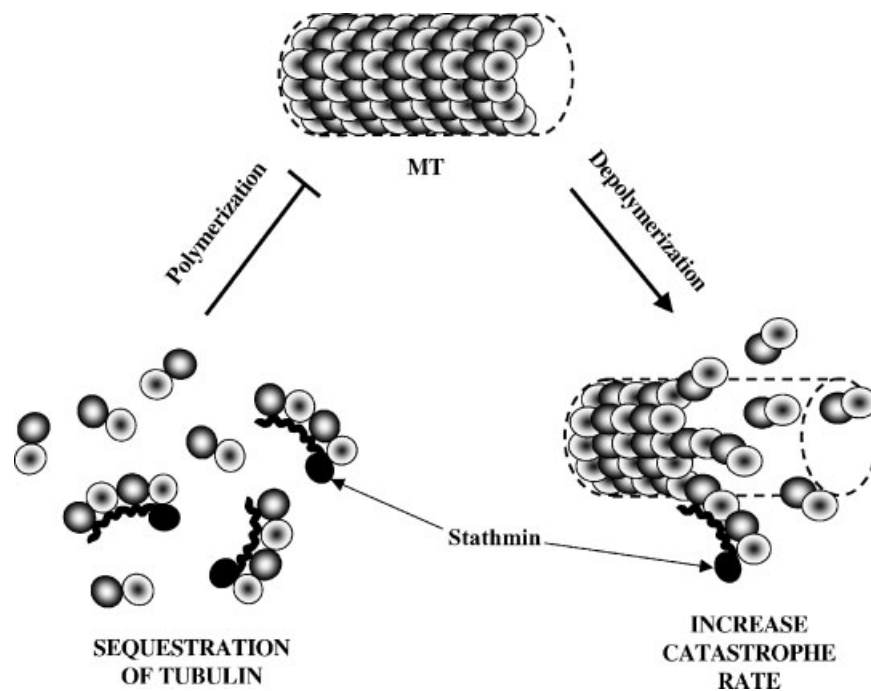
**Fig. 1.** Model for the role of stathmin in the regulation of microtubule dynamics. Microtubules (MT) continuously switch between phases of polymerization and depolymerization. Stathmin can sequester unpolymerized tubulin by binding two α/β-tubulin heterodimers (represented by light and dark shaded circles), thus diminishing the pool of tubulin heterodimers available for polymerization. Stathmin can also bind to the end of polymerized microtubules and increase the rate of catastrophe by inducing a conformational change that promotes microtubule depolymerization.

When cells enter mitosis, the microtubule-depolymerizing activity of stathmin is switched off by phosphorylation, allowing microtubules to polymerize and assemble into a mitotic spindle. This was originally demonstrated by Marklund et al. [1996] who studied the effect of overexpression of wild-type stathmin and p34$^{cdc2}$-target site phosphorylation deficient mutants on the mitotic phenotype of K562 cells. These studies showed that overexpression of wild-type stathmin depolymerizes interphase microtubules but does not interfere with the formation of the mitotic spindle. The authors suggested that this might be due to phosphorylation and inactivation of the ectopically expressed protein by mitotic kinases. This was confirmed by the observation that overexpression of p34$^{cdc2}$-target site mutants of stathmin that cannot be inactivated by phosphorylation results in arrest in the G$_2$/M phases of the cell cycle and inability to assemble a functional mitotic spindle [Marklund et al., 1996]. This mitotic phenotype is further accentuated when all four phosphorylation sites of stathmin are mutated [Larsson et al., 1997; our unpublished observations]. The mitotic cells that overex-

pressed the mutant protein had randomly distributed chromosomes, rather than chromosomes aligned at the metaphase plate. The cells were unable to form a functional mitotic spindle and displayed either bundles of short microtubules at each pole or had no detectable spindle altogether [Marklund et al., 1996; Larsson et al., 1997; our unpublished observations]. Chromosome segregation was not observed and the cells were arrested in the early stages of mitosis (i.e., prophase/prometaphase). Thus, the expression of a constitutively active form of stathmin arrests cells early in mitosis and prevents further progression through the cell cycle.

Studies from our laboratory showed that inhibition of stathmin expression in K562 leukemic cells does not affect their ability to enter mitosis [Iancu et al., 2001]. As mentioned above, like stathmin-overexpressing cells, stathmin-deficient cells also accumulate in the G$_2$/M phase of the cell cycle. However, analysis of the mitotic phenotype of these cells showed that they were capable of forming mitotic spindles, though the spindles were atypically organized. As a result, the cells had scattered or partially segregated chromosomes and had difficulty in completing

mitosis. Thus, although both overexpression and inhibition of stathmin expression in K562 cells results in accumulation of cells in mitosis, the cells are arrested at different points in mitosis. Whereas stathmin overexpression prevents mitotic spindle formation in early mitosis, stathmin inhibition seems to interfere with the function of the mitotic spindle in the later stages of mitosis. This is not surprising since spindle disassembly is required for the proper completion of mitosis. Using an antibody that specifically recognizes stathmin that is phosphorylated at Ser 16, Gavet et al. [1998] showed that while stathmin is phosphorylated (i.e., inactivated) when cells enter into mitosis, it becomes dephosphorylated (i.e., reactivated) when the cells are ready to exit mitosis and undergo cytokinesis. In other studies from our laboratory, okadaic acid treatment of K562 cells in which stathmin expression is inhibited resulted in arrest in post-metaphase stages of mitosis and severe mitotic abnormalities [Mistry and Atweh, 2001]. Taken together, these observations suggest that phosphorylation of stathmin by an okadaic acid-sensitive protein phosphatase(s) is crucial for the ability of cells to exit mitosis. In other words, the reactivation

of stathmin in the later stages of mitosis is necessary for the disassembly of the mitotic spindle and the exit from mitosis. Thus, stathmin is critically important not only for the formation of the mitotic spindle when cells enter mitosis but also for the regulation of post-metaphase events and proper exit from mitosis (Fig. 2).

## STATHMIN IN OTHER PHASES OF THE CELL CYCLE

At the end of mitosis, the separation between the new daughter cells is achieved by a process referred to as cytokinesis. Cross-talk between the mitotic spindle microtubules and the actin cytoskeleton is believed to be essential for the formation of the acto-myosin contractile ring that completes the process of cytokinesis. Studies by Johnson et al. [1999] suggested that stathmin may be involved in the microtubule-dependent events of cytokinesis. When cytokinesis was blocked by Bistratene A treatment of HL60 cells, the cells became polyploid and multinucleated [Johnson et al., 1999]. This was associated with an increase in the level of stathmin expression and its level of phosphorylation. In a different study, Daub et al. [2001]
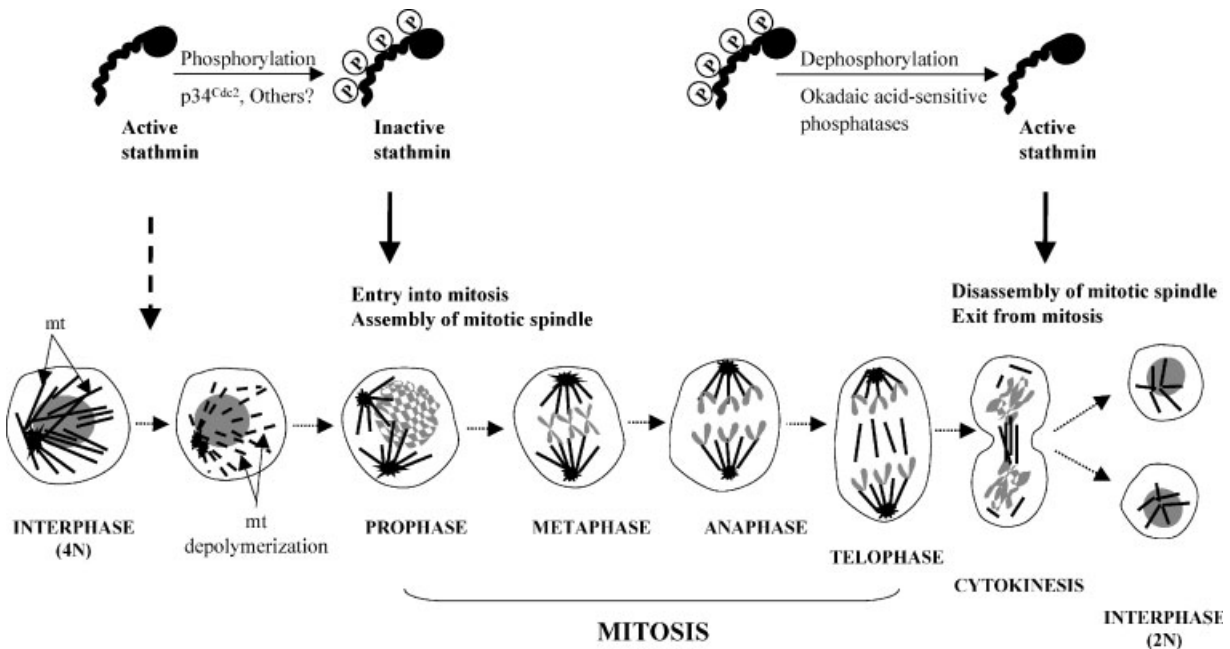


**Fig. 2.** Model for the role of stathmin in the mitotic phase of the cell cycle. Chromosomes (represented in grey) condense and segregate during the four phases of mitosis (prophase, metaphase, anaphase, and telophase) while cytoplasmic division occurs by cytokinesis. At the onset of mitosis, interphase microtubules (mt) depolymerize (illustrated by the interrupted lines) then repolymerize to assemble the mitotic spindle. The inactivation of stathmin by phosphorylation allows mitotic spindle assembly and entry into mitosis while its reactivation by dephosphorylation promotes mitotic spindle disassembly and exit from mitosis.

showed that stathmin may be a downstream target of Rac/Cdc42, which are Rho GTPase-related proteins that are involved in the regulation of the actin cytoskeleton and the initiation of cytokinesis. Taken together, these studies suggest that the microtubule regulatory function of stathmin may also be required for the morphological changes associated with cytokinesis and the entry into a new cell cycle.

As described above, the activity of stathmin during the mitotic phase of the cell cycle is regulated by phosphorylation, at least in part, by p34$^{cdc2}$. Interestingly, new lines of evidence suggest that the activity of stathmin may also be regulated at the transcriptional level by p53 and E2F, two transcription factors that play critically important roles in the regulation of cell-cycle progression. It was first demonstrated that induction of p53 by DNA-damaging agents results in a drastic decrease in the level of stathmin expression [Ahn et al., 1999]. It was later shown that the p53-induced downregulation of stathmin expression is associated with accumulation of glioblastoma cells in the G$_2$/M phase of the cell cycle [Johnsen et al., 2000]. In a different study, the G$_2$/M arrest that is induced by genotoxic stress in NIH3T3 was shown to be associated with E2F-mediated downregulation of stathmin expression [Polanger and Ginsberg, 2003]. These studies suggest that stathmin might be involved in checkpoints pathways that prevent cell-cycle progression following exposure to DNA-damaging agents.

## STATHMIN AND THE ENDOMITOTIC CELL CYCLE

In the vast majority of eukaryotic cells, the process of cell division includes a mitotic phase that is followed by cytokinesis. This gives rise to two daughter cells with a diploid DNA content. However, in certain cell types like megakaryocytes, hepatocytes, and vascular smooth muscle cells, an "atypical" mitotic pathway is utilized to achieve polyploidy (i.e., DNA content greater than 2N). Endomitosis is characterized by the failure of cells to complete the late stages of mitosis and cytokinesis after they duplicate their DNA content. At a certain stage during megakaryocyte maturation, the cells start acquiring high levels of ploidy (from 4N to 128N) by switching from a normal mitotic cycle to an endomitotic cycle. Immunofluorescence studies showed that maturing megakaryocytes enter

mitosis normally, proceed to late anaphase, skip telophase, and do not undergo cytokinesis [Nagata et al., 1997]. Since this process was associated with the presence of atypical mitotic spindles, it was suggested that proteins that are involved in the regulation of the mitotic spindle may play a key role in the process of polyploidization.

Since stathmin was shown to play an important role in regulating the mitotic spindle, we proposed that downregulation of stathmin expression in maturing megakaryocytes may be responsible for the abortive mitosis that leads to polyploidy [Iancu Rubin et al., 2003]. Studies from our laboratory and others showed that stathmin expression is downregulated during polyploidization of K562 and HEL cells that are induced to differentiate along the megakaryocytic lineage with phorbol ester. In addition, we showed that stathmin expression is much lower in primary murine megakaryocytes with high levels of ploidy compared to immature megakaryocytes with low levels of ploidy. More importantly, we showed that inhibition of stathmin expression increases the propensity of K562 cells to become polyploid upon induction of megakaryocytic differentiation. These data suggest that in an endomitotic cell cycle, the absence of stathmin expression may result in perturbations in the regulation of the microtubules of the mitotic spindle. This, in turn, may lead to the inability of the megakaryocytes to complete mitosis and undergo cytokinesis. Interestingly, a recently published report [Yoshie et al., 2004] described an inverse correlation between stathmin expression and the process of differentiation of stromal cells into decidual cells during pregnancy in rats. As in megakaryocytes, during the late stages of decidualization, cells switch to an endomitotic cycle and become polyploid. In agreement with our studies in megakaryocytes, stathmin expression was shown to be downregulated in late stage decidual cells compared to early stage cells. These findings support a role for the downregulation of stathmin expression in the physiological regulation of polyploidzation.

## STATHMIN IN OTHER CELLULAR PROCESSES

Stathmin is the prototype of a small family of phosphoproteins that include SCG10, SCLIP, and RB3. All these phosphoproteins share a common stathmin-like domain and also share

the functional activity of regulating microtubule dynamics [Cassimeris, 2002]. In addition to their well known role in mitosis, interphase microtubules are essential for a variety of other cellular processes that include, among others, intracellular transport, cell motility, cell polarity, and maintenance of cell shape. Thus, considering these non-mitotic functions of microtubules, it would not be surprising if stathmin turns out to play a key role in a variety of other biological processes in addition to its well established role in cellular proliferation.

One of the first functions to be attributed to stathmin was a potential role in the regulation of hormone secretion in rodent pituitary and insulinoma cell lines. Later studies showed that the high levels of stathmin in the testis are restricted to germ cells at certain developmental stages. This led to the suggestion that stathmin may play a role in spermatogenesis. Similarly, the abundance of stathmin in postmitotic neurons raised the possibility that it may have a distinct function in neurons that is not related to cell division. Interestingly, the level of stathmin expression was shown to be dramatically increased during neurite outgrowth and synapse formation, suggesting a role for stathmin in neuronal differentiation [Di Paolo et al., 1997]. Interestingly, the same group showed that inhibition of stathmin expression with antisense oligonucleotides prevents nerve growth factor (NGF)-induced differentiation of rat PC12 cells into sympathetic-like neurons. We described similar observations in a different model of cell differentiation in which antisense inhibition of stathmin expression prevented megakaryocytic differentiation of phorbol ester-induced K562 cells [Iancu Rubin et al., 2003]. These latter observations support a role for stathmin in the differentiation of hematopoietic cells. In fact, in every hematopoietic cell line studied, the level of stathmin expression is drastically decreased when the cells are induced to differentiate along different lineages. Finally, stathmin was found to be expressed at high levels in the migrating cells of the rat olfactive system, suggesting its possible involvement in cell migration [Camoletto et al., 1997]. This is supported by more recent studies that suggested that stathmin might be involved in the motility of *Xenopus* A6 epithelial cells [Niethammer et al., 2004]. It is still not clear, however, whether all these non-mitotic functions of stathmin are mediated exclusively through its microtubule depolymerization activity or through other activities that have yet to be defined.

Interestingly, despite this plethora of functions that have been attributed to stathmin, the stathmin knockout mice generated by Schubart et al. [1996] seemed to develop normally and did not show any phenotype upon initial examination. However, the same group recently reported that when stathmin-null mice age, they develop an axonopathy of the central and peripheral nervous system [Liedtke et al., 2002]. The same study showed increased expression of SCLIP, a stathmin-related protein, in the nervous system of the aging mice. In another line of investigation, the suppression of the only homologue of the vertebrate stathmin family in *Drosophila* led to dramatic impairment of germ cell migration and severe anomalies in the development of nervous system [Ozon et al., 2002]. The remarkable lack of phenotype in the stathmin null mice and the severe impairment of development in an organism with a single stathmin-like gene suggests a functional redundancy among stathmin family members in vertebrates. This redundancy is supported by a recent study that assessed the expression of stathmin and its other related proteins by quantitative RT-PCR analysis in a variety of human tissues [Bieche et al., 2003]. This study showed that the pattern of expression of the SCLIP member of the stathmin-like family, like the expression of stathmin itself, is ubiquitous, suggesting that stathmin and SCLIP may be functionally redundant.

## CONCLUDING REMARKS AND FUTURE PROSPECTS

There has been considerable progress during the last decade in the understanding of the role of stathmin in the regulation of mitosis. Although the role of stathmin in regulating microtubule dynamics and the mitotic spindle is firmly established, there are still many unanswered questions about its molecular mechanism(s) of action. However, in spite of recent progress in stathmin biology, there are many indications that we have merely scratched the surface of the many biological activities that this important molecule may be involved in. We predict that the rate of progress in this field will accelerate considerably during the next decade as more investigators start exploring the

non-mitotic functions of this protein. We also expect that the role of stathmin as a target in cancer therapy will receive considerably more attention as we learn more about its important role in the maintenance of the malignant phenotype [Mistry and Atweh, 2002]. We believe that the pharmaceutical industry will eventually appreciate the therapeutic potential of drugs that target the stathmin molecule and the race will begin for developing small molecule inhibitors that interfere with the interaction of stathmin with tubulin. One day this protein that existed in a state of relative anonymity for many years may develop a level of recognition that is commensurate with its many important biological functions.

## ACKNOWLEDGMENTS

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