

Gelsolin, a Multifunctional Actin Regulatory Protein*

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The actin cytoskeleton is an essential scaffold for integrating membrane and intracellular functions. It is very dynamic and is remodeled in response to a variety of signals. Growth factor stimulation promotes actin assembly at the plasma membrane to generate movement, whereas apoptotic signals cause cytoskeletal destruction to elicit characteristic membrane blebbing and morphological changes. Gelsolin is a Ca^{2+} - and polyphosphoinositide 4,5-bisphosphate (PIP_2)¹-regulated actin filament severing and capping protein that is implicated in actin remodeling in growing and in apoptotic cells (reviewed in Refs. 1 and 2).

This review summarizes data supporting the role of gelsolin in cytoskeletal remodeling and phosphoinositide signaling and discusses the structural basis for the Ca^{2+} and PIP_2 regulation of severing and capping by gelsolin.

Overview about Severing, Capping, and Uncapping

Gelsolin is the most potent actin filament severing protein identified to date. Severing is the weakening of enough non-covalent bonds between actin molecules within a filament to break the filament in two. Gelsolin severs stoichiometrically and with close to 100% efficiency (3). Severing is initiated after gelsolin binds to the side of an actin filament. Gelsolin binds filaments rapidly but severs slowly (3); the delay may reflect the time required for structural rearrangement within gelsolin (see "Structural Basis for Ca^{2+} Regulation") and in the filament (4) prior to severing. Gelsolin changes actin conformation and kinks the actin filament (4), suggesting a mechanical basis for severing.

After severing, gelsolin remains attached to the barbed end of the filament as a cap. As a result, short actin filaments that cannot reanneal with each other or elongate at their barbed ends are generated. In this way, the actin network is disassembled. The importance of Ca^{2+} -mediated actin severing has been clearly documented during platelet activation (5), and gelsolin is the only known Ca^{2+} -dependent severing protein identified to date. Gelsolin severing can also have a constructive effect because it increases the number of filaments. Uncapping of gelsolin from these filaments generates many polymerization-competent ends from which actin can grow to rebuild the cytoskeleton to new specifications. Therefore, gelsolin can promote actin polymerization by severing followed by uncapping (mechanism B, as discussed in the Prologue (74) of this series).

Gelsolin Functions in Vivo

The Gelsolin Null Mouse Establishes the Importance of Gelsolin for Multiple Cell Functions—Cells from gelsolin null mice exhibit a variety of motility and actin defects. Gelsolin null fibroblasts have pronounced actin stress fibers (6), and this phenotype is consistent with an inability to sever and remodel actin filaments. They do not ruffle in response to growth factor (7), and they exhibit defective chemotaxis and wound healing. The rate of clotting is reduced (6),

as would be consistent with the requirement of actin severing for platelet activation (5). Neurite retraction is defective (8), and neurons are more susceptible to glutamate-induced excitotoxicity (9). Neutrophil extravasation is compromised (6). These findings establish the importance of gelsolin in maintaining motility and actin dynamics.

Despite multiple cellular pathology, the null animals (in a mixed strain background) are without gross phenotypic defects. This may reflect the existence of potent compensatory mechanisms. However, the compensation is incomplete and varies with the genetic background of the knockout animals. Gelsolin null animals in a pure strain mouse background are non-viable at perinatal and early postnatal stages (2), indicating that gelsolin is necessary for survival.

Membrane ruffling is a functional readout for a coordinated series of membrane and cytoskeletal events, and it is activated by the small GTPase, Rac. Gelsolin null fibroblasts have increased Rac expression (7), and Rac-GTP dissociates gelsolin-actin complexes (equivalent to uncapping) in cell extracts but not purified gelsolin-actin complexes (10). These results suggest that gelsolin is a downstream effector of Rac, but there are additional steps between Rac and gelsolin activation/inactivation. A number of studies suggest that linkage through the type I phosphatidylinositol 5-kinases (PIP5K s), the major enzymes that synthesize PIP_2 (reviewed in Refs. 11 and 12), is an attractive possibility.

The Role of PIP_2 in the Regulation of Cell Motility— PIP5K s coimmunoprecipitate with Rac (13) and also Rho (14), a small GTPase that promotes stress fiber formation. PIP5K s may thus be incorporated into signaling complexes that are targeted to the plasma membrane through Rac-GTP or Rho-GTP. This increases the local concentration of PIP_2 in membrane microdomains to selectively activate downstream cascades (reviewed in Refs. 12 and 15).

PIP_2 has a pivotal role in the phosphoinositide cycle that drives signaling, cytoskeletal organization, and membrane trafficking (reviewed in Ref. 15). Numerous cytoskeletal proteins are affected by PIP_2 *in vitro*. They include gelsolin family proteins (16), profilin (17), capping protein (18), ADF/cofilin (19), α -actinin (20), vinculin (21), ezrin/radixin/moesin (22), and WASp family proteins (23). The latter four proteins are activated by PIP_2 , whereas the first four are inactivated by PIP_2 . Ezrin/radixin/moesin, ADF/cofilin, and WASp are reviewed in this series (24–26). The challenge will be to identify cytoskeletal proteins that are physiologically regulated by PIP_2 and determine how they are differentially regulated.

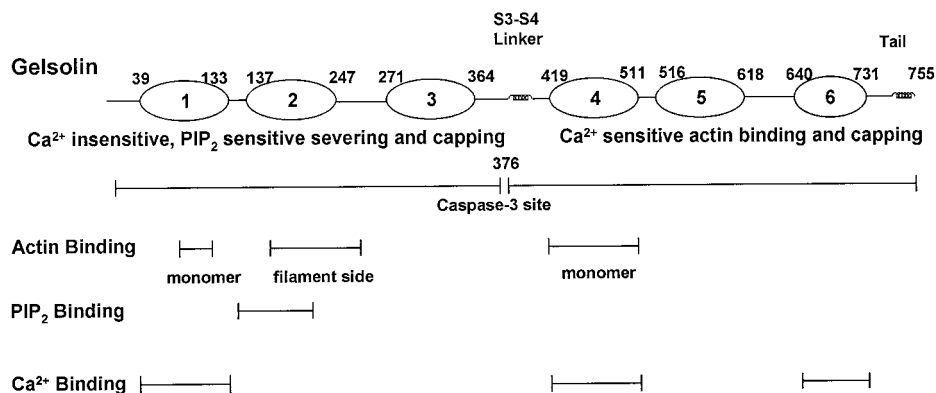
PIP_2 involvement in cytoskeletal regulation is supported by experiments that manipulate PIP_2 content in intact cells and in cell-free models. Microinjection of a monoclonal antibody to PIP_2 prevents stress fiber and focal adhesion formation (21). PIP5K overexpression induces the formation of short actin bundles (27) and increases the movement of dynamic actin spots containing a number of actin regulatory proteins (28). In contrast, overexpression of synaptojanin, the inositol polyphosphate 5-phosphatase that dephosphorylates PIP_2 , reduces actin stress fibers (29). Moreover, Hartwig *et al.* (30) were able to reconstitute the entire pathway between thrombin stimulation, Rac activation, PIP_2 synthesis, and barbed end nucleated actin assembly in permeabilized platelets. However, in neutrophils and other systems, the relation is less clear. Although Rac-GTP dissociates gelsolin-actin complexes (10) and stimulates PIP_2 synthesis, it does not promote actin assembly in lysates (31). Instead, Cdc42, which stimulates filopodia formation in cells, promotes *de novo* actin assembly *in vitro*, in a PIP_2 -dependent manner that is mediated through WASp and the Arp2/3 complex (32).

The range of responses and the contradictory effects of small GTPases and PIP_2 on nucleated actin assembly *in vivo* and *in vitro* and in different types of cells may be reconciled by postulating that there are multiple pathways for actin assembly. Plasma membrane

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‡ The abbreviations used are: PIP_2 , polyphosphoinositide 4,5-bisphosphate; PIP5K , phosphatidylinositol 5-kinase.

FIG. 1. **Gelsolin structure-function domains.** Residues are numbered as in human plasma gelsolin (43), and segmental boundaries are based on the structural definitions defined by the gelsolin crystal (44). Actin, PIP₂, and Ca²⁺-binding segments are shown.



lysis may disrupt the critical coupling between Rac and actin polymerization much more than that between Cdc42 and actin.

Effects of Gelsolin Overexpression on Cell Motility and Signaling—Gelsolin overexpression increases membrane ruffling and chemotaxis (33, 34), consistent with the role of gelsolin in dynamic actin remodeling. Surprisingly, CapG, a gelsolin relative that caps but does not sever actin, and the completely unrelated capping protein also increase cell motility when overexpressed (35, 36). *A priori*, pure capping proteins are expected to be less effective in promoting actin dynamics than severing/capping proteins, because they do not increase the number of actin filaments *per se* (compare mechanisms B (severing and uncapping) and C (uncapping only) in the Prologue to this minireview series (74)).

These results indicate that capping/uncapping may be sufficient to increase actin dynamics. More detailed study will be required to distinguish between the contributions of severing and capping.

Overexpression studies reveal that gelsolin may have other roles in addition to direct cytoskeletal regulation. Overexpressed gelsolin (34) and CapG (35) modulate phospholipase C γ and phospholipase C β activity in a biphasic manner both *in vivo* and *in vitro*. These effects depend on PIP₂ binding (34), suggesting that gelsolin enhances or competes with other PIP₂-binding proteins for their common substrate. This potent effect may be achieved by altering the packing of PIP₂ molecules within the membrane bilayer (37).

In conclusion, these results suggest that as PIP₂ content and availability change during signaling, cross-talk between PIP₂-regulated proteins provides a selective mechanism for positive as well as negative regulation of phosphoinositide signaling. This is particularly relevant as more PIP₂-regulated proteins are identified. Gelsolin coimmunoprecipitates with several PIP₂-interacting proteins, and it alters the activity of phosphatidylinositol 3-kinase and phospholipase D as well (reviewed in Refs. 1 and 2). Gelsolin is phosphorylated by c-Src *in vitro*, and phosphorylation is enhanced by PIP₂ (38). The physiological significance of these associations and phosphorylation has not been determined.

Gelsolin and Apoptosis—Gelsolin is a substrate for caspase-3 (39, 40), the effector caspase in both the death receptor and mitochondrial apoptotic pathways. Gelsolin cleaved by caspase-3 no longer requires Ca²⁺ to sever actin filaments (Fig. 1) (see also “Structural Basis for Ca²⁺ Regulation”), and it dismantles the membrane cytoskeleton to cause blebbing, a hallmark of apoptosis. Overexpression of the Ca²⁺-independent severing N-half induces apoptosis, whereas gelsolin null neutrophils have a delayed onset of apoptosis (39). These findings highlight the importance of inhibiting gelsolin severing to preserve the integrity of the cell and to selectively activate gelsolin under proliferative conditions.

The pro-apoptotic role of gelsolin is supported by the finding that most cancer cells (which usually have reduced apoptosis) have significantly lower gelsolin expression (41) (reviewed in Ref. 2). Furthermore, gelsolin overexpression, especially of a mutant form that is more sensitive to PIP₂, suppresses Ras transformation (42). Nevertheless, other data do not fit into this straightforward scheme. One group found that gelsolin overexpression protects against apoptosis (39). The relation between gelsolin, apoptosis, and tumorigenesis probably reflects a complex balance between the multiple effector functions of gelsolin.

Gelsolin Structure-Function

The structural basis for gelsolin regulation by Ca²⁺ is now beginning to be understood. Gelsolin has two tandem homologous halves, each of which contains a 3-fold segmental repeat (segments S1–S3 and S4–S6, respectively) (43, 44) (Fig. 1). The N- and C-halves are connected by a long linker, which is cleaved by caspase-3 (39, 40) *in vivo* and *in vitro*, and by many other proteases *in vitro*. The isolated C-half binds a single actin molecule only when Ca²⁺ is above 10^{−6} M.² The isolated N-half binds two actin molecules to sever and cap, even in the absence of Ca²⁺. Because severing by full-length gelsolin requires 10^{−6} M Ca²⁺, the C-half must act as a regulatory domain to inhibit severing by the N-half. In addition, the C-half potentiates severing by the N-half, possibly through cooperative binding to the filament (3).

There are two published high resolution structures of gelsolin, and a third is on its way. We will discuss results from the first two structures here and review results from the third structure later under “Structural Basis for Ca²⁺ Regulation.” The S1-actin-Ca²⁺ structure (46) shows how a single gelsolin segment binds actin. Because of the similarities between segments (43, 44), it can be used as a template for modeling how the other segments bind actin. The full-length gelsolin crystal formed in the absence of Ca²⁺ (gelsolin/EGTA) shows that inactive gelsolin has a compact quaternary structure in the absence of Ca²⁺ (44). Its two halves are held together by a C-terminal S6 tail, which latches onto S2 (Figs. 1 and 2A) (the tail latch, see “Structural Basis for Ca²⁺ Regulation.” Within each half, the first and third segments (S1 and S3, S4 and S6, respectively, for the N- and C-halves) are joined into a 10-strand β -sheet that is sterically incompatible with actin binding (Fig. 2B). This explains why neither S1 nor S4 binds actin in the absence of Ca²⁺. It also predicts that Ca²⁺ must induce major conformational changes in each half and in the relation between the halves to accommodate actin binding.

A recent cryoelectron microscopic study of a gelsolin construct missing S1 attached to an actin filament (4) hints at the extent of the change that is required. The reconstructed image shows that gelsolin S2–S6 binds to actin molecules in neighboring filament strands (via S2 and S4). The distances between the S2 and S4 and the S1 and S2 actin-binding sites on the filament indicate that there must be large scale conformational changes before S1, S2, and S4 can simultaneously bind actin. The convoluted linker probably unwinds, and parts of the S1 or S2 core domain may have to unravel to extend the linker between S1 and S2 (as proposed in Refs. 44 and 47). A model for how this sequence of events may occur is shown in Fig. 3.

Structural Basis for Ca²⁺ Regulation

The questions of how gelsolin is clamped in the inactive configuration under submicromolar Ca²⁺ conditions and how Ca²⁺ switches gelsolin on are clearly important because they pertain to proliferative and apoptotic signaling.

Multiple Ca²⁺-binding Sites—Although gelsolin was first identified as a Ca²⁺-regulated protein that binds two Ca²⁺ with 10^{−6} M

² K.-M. Lin, M. Mejillano, and H. L. Yin, submitted for publication.

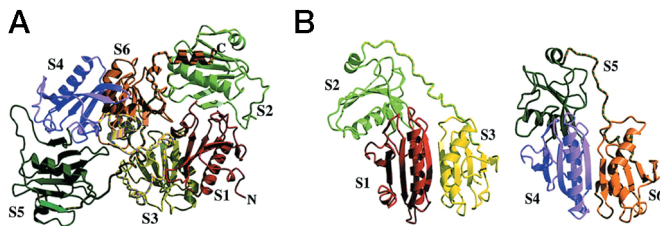


FIG. 2. **Structural model of gelsolin in the absence of Ca^{2+} .** A, full-length gelsolin; B, gelsolin N- and C-halves. Figure was provided by R. Robinson. S1–S6, gelsolin segments 1–6; N and C, N- and C-terminal half, respectively.

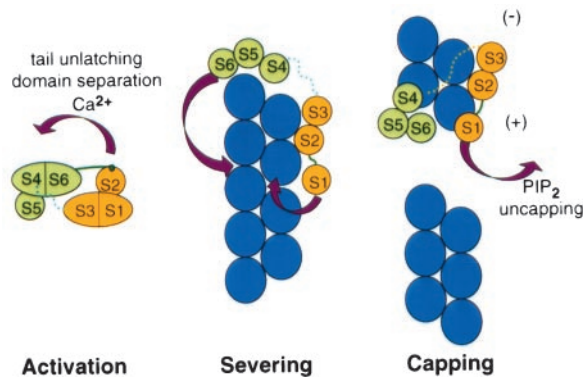


FIG. 3. **Schematic model for gelsolin binding, severing, and capping of an actin filament.** This figure is based on data found in Refs. 4 and 47 and Footnote 3. Actin molecules within a filament are shown as blue circles. (+), barbed end; (–), minus end. *Left*, gelsolin in the process of Ca^{2+} activation. This requires tail unlatching, domain separation within each half, and separation of the halves. *Middle*, S2–S3 binds to the side of an actin filament via S2. S1 wedges between two actins in the longitudinal axis. This step requires a rearrangement of the S1–S2 interface to lengthen the S1–S2 linker. S4–S6 reaches across the filament to bind actin at the other strand. This step would require, at a minimum, extension of the convoluted linker between S3 and S4. Severing occurs when sufficient actin-actin bonds are broken. *Right*, the terminal actin in each strand is capped by S1 and S4. PIP_2 induces gelsolin to dissociate from the ends in a process called uncapping.

K_d (48), subsequent studies find that gelsolin interaction with Ca^{2+} is considerably more complex. Isolated gelsolin domains have at least three Ca^{2+} -binding sites, with submicromolar and micromolar K_d values (49). On binding actin, intermolecular and intramolecular Ca^{2+} -binding sites are created (46, 50),³ so gelsolin can potentially bind even more Ca^{2+} ions. Paradoxically, a recent study finds that gelsolin binds only two Ca^{2+} ions in the presence of actin, and they bind cooperatively (52). The challenge will be to determine which of the currently identified Ca^{2+} -binding sites are physiologically relevant and how their occupancy alters gelsolin conformation.

At 37 °C, half-maximal severing is observed at 2×10^{-6} M Ca^{2+} ,² which is well within the physiological range encountered during surface receptor stimulation. A small decrease in pH also reduces the Ca^{2+} requirement for severing significantly (53–55), suggesting that gelsolin can integrate these signals to generate fine-tuned responses in cells.

The C-half Talks to the N-half through the Tail Latch Mechanism—Biochemical and physical studies indicate that Ca^{2+} opens up gelsolin by inducing a conformational change in the C-half to expose actin-binding sites on the N-half. The gelsolin/EGTA crystal structure shows that the C terminus of gelsolin has a tail extension that contains an unstructured strand capped with a short terminal helix (Fig. 1). The tail helix is in close contact with the actin binding helix of S2 (Fig. 2A) and may act as a latch to inhibit actin binding by the N-half in the absence of Ca^{2+} . This is called the tail latch hypothesis.

The importance of the S6 tail in Ca^{2+} regulation is now supported by deletion studies. Deletion of the tail helix decreases the Ca^{2+} concentration for half-maximal activation of severing from 2×10^{-6} M to 10^{-7} M,² whereas deletion of the entire tail abolishes

the Ca^{2+} requirement for severing altogether (57).² Furthermore, tail helix deletion abolishes the change in intrinsic tryptophan fluorescence observed at 10^{-6} M Ca^{2+} but not that at submicromolar Ca^{2+} (53, 56).² Therefore, the tail latch is the major switch that releases the final constraint on the N-half to initiate the severing cascade.

Gelsolin is unique among the gelsolin family proteins (see “The Gelsolin Superfamily”) in relegating Ca^{2+} regulation of its N-half to the C-half through its tail. It may have evolved the unique tail latch mechanism to achieve stringent regulation of severing and capping and to permit dispensing with Ca^{2+} regulation entirely during apoptosis simply by cleaving the severing half from the regulatory half.

Ca^{2+} Activation of the Gelsolin C-half—S4–S6 has remained a black box for many years, even though it is the primary Ca^{2+} -activated switch for gelsolin. The Ca^{2+} activation model can now be refined considerably because a crystal structure of the C-half complexed with actin and Ca^{2+} has just become available.³ As discussed above, in the absence of Ca^{2+} , S4 and S6 are melded together into an extended β -sheet (44) (Fig. 2B). In the presence of Ca^{2+} , the β -sheet is broken; S4 and S6 are completely separated along their interface. S6 swings away from S4 and forms new contacts with S5. Actin inserts into the space vacated by S6 and creates an intermolecular Ca^{2+} -binding site coordinated by S4 and actin. These results confirm that there are large scale domain rearrangements during Ca^{2+} activation.

Structural Basis for PIP_2 Regulation

Although there is ample evidence for reversible gelsolin-actin association in cells (reviewed in Ref. 1), gelsolin uncapping after severing cannot be achieved simply by reducing Ca^{2+} . This is because a Ca^{2+} molecule is trapped between gelsolin S1 and actin, and it is inaccessible to EGTA (46). Phosphoinositides, particularly PIP_2 (16, 58), are the only known agents that inhibit gelsolin severing and dissociate gelsolin from actin *in vitro* (59).

Gelsolin binds PIP_2 with micromolar affinity (55). Binding is enhanced by Ca^{2+} and by low pH (55). Gelsolin prefers PIP_2 to phosphatidylinositol-3,4,5- P_3 (58, 60, 61) and does not bind inositol trisphosphate (17). Therefore, gelsolin binding is stereoselective and enhanced by the diacylglycerol chain. This requirement is unlike the situation with many pleckstrin homology proteins, which bind phosphoinositides and the equivalent inositol phosphates with similar affinity (62).

Gelsolin can simultaneously bind between one and three PIP_2 molecules within lipid vesicles, and binding is highly dependent on the physical characteristics of the bilayer (63). Therefore, gelsolin regulation by PIP_2 does not depend simply on the absolute PIP_2 mass but is rather dictated by a complex relation between lipid bilayer composition and geometry. This, together with the ability of gelsolin to change its affinity for PIP_2 in response to Ca^{2+} and pH (55) and to induce changes in PIP_2 packing within the membrane (37), hints at the large number of signals that are sensed and integrated by gelsolin to carry out its functions. In addition, we are just beginning to appreciate the active role gelsolin may have in modulating phosphoinositide signaling (see “Effects of Gelsolin Overexpression on Cell Motility and Signaling”).

PIP_2 inhibits the gelsolin N-half, and the N-half PIP_2 binding sequences are mapped to a common flat, solvent-exposed surface in the linker between S1–S2 and the beginning of S2 in the gelsolin/EGTA crystal (Fig. 1). These sites have an acidic amino acid consensus that does not resemble the pleckstrin homology domain (64, 65). PIP_2 induces a conformational change (55, 66) that may interfere with the local rearrangements required to permit S2 and S1 to bind two actin molecules simultaneously (Fig. 3). Structural information about gelsolin complexed with PIP_2 will be required to determine whether this is how PIP_2 inhibits gelsolin and if PIP_2 binds to other gelsolin domains as well.

The Gelsolin Superfamily

Many members of the gelsolin family that have three or six gelsolin repeats have been identified (reviewed in Refs. 1 and 2). They have distinct as well as overlapping patterns of tissue expression, which is consistent with specialized function (67). Except for gelsolin, Ca^{2+} regulation and actin binding are not segregated into

³ R. C. Robinson, M. Mejillano, V. Le, L. D. Burtneck, H. L. Yin, and S. Choe, submitted for publication.

the two halves of the molecule. For example, villin, a six-domain protein, has a Ca^{2+} -dependent N-half (68), and CapG, a three-domain protein, has built-in Ca^{2+} regulation in its actin-binding segment (69).

Novel members with long N-terminal extensions have also been discovered. For example, flightless I has an N-terminal extension of 16 tandem leucine-rich repeats (70), which can potentially mediate heterologous protein-protein interactions. Its binding partners include a family of novel proteins with coiled coil repeats (71, 72) and possibly Ras (73). Through these interactions, flightless I may link the actin cytoskeleton to intracellular and membrane structures to integrate signaling responses.

Conclusions and Perspectives

This review has focused on the intracellular functions of gelsolin and emphasizes progress made to obtain a mechanistic model of how gelsolin regulates the actin cytoskeleton in response to Ca^{2+} and phosphoinositide signaling. With a clear understanding of how actin regulatory proteins work individually, we are now poised to delineate how they cooperate to orchestrate actin dynamics within living cells. Some progress has already been made. One study shows that gelsolin and capping protein coordinately cap barbed ends during platelet activation (73). Another study finds that filaments capped by gelsolin and Arp2/3 at the barbed and pointed ends, respectively, can still undergo rapid turnover in the presence of ADF/cofilin, and new uncapped barbed ends are generated (51). Therefore, gelsolin severing and capping can theoretically promote *de novo* nucleation by Arp2/3 by increasing the number of pointed filament ends and increasing the actin monomer pool (45). These findings extend the scope of the involvement of gelsolin in regulating actin dynamics.

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