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Modulation of calcium signalling by the actin-binding protein cofilin

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Abstract

Cofilin is a small protein that belongs to the family of actin-depolymerizing factors (ADF). The main cellular function of cofilin is to change cytoskeletal dynamics and thus to modulate cell motility and cytokinesis. We have recently demonstrated that the actin cytoskeleton is involved in the modulation of Ca^{2+} signalling in starfish oocytes. To extend these observations, we have explored whether cofilin influences Ca^{2+} signalling in the oocytes. Here we show that microinjection of the functionally active cofilin alters the Ca^{2+} signalling mediated by the three major second messengers, $InsP_3$, NAADP, and cADPr. Cofilin intensifies the Ca^{2+} signals induced by $InsP_3$ and NAADP, and delays those induced by cADPr. Furthermore, the injection of cofilin increases the Ca^{2+} signals during hormone-induced oocyte maturation and fertilization. The results suggest that the dynamic regulation of F-actin by its binding proteins may play an important role in the modulation of intracellular Ca^{2+} signalling.

Keywords: Actin-depolymerising factor; Inositol 1,4,5-trisphosphate; Cyclic ADP-ribose; Nicotinic acid adenine dinucleotide phosphate; Phosphatidylinositol-4,5-bisphosphate; 1-Methyladenine; Latrunculin A

Starfish oocytes have been an excellent model system in the study of the generation and propagation of the Ca^{2+} signal in the living cell. Ca^{2+} released by three major second messengers, i.e., $InsP_3$, cADPr, and NAADP [1–6], is critical to the maturation and fertilization of the oocytes. The three major second messengers are believed to play distinct roles in generating Ca^{2+} signals during fertilization of starfish oocytes [7–9]. We have recently demonstrated that Ca^{2+} release from the $InsP_3$-sensitive stores is enhanced during oocyte maturation [10]. Since the increased Ca^{2+} response to the exogenously added $InsP_3$ nicely correlated with the dynamic rearrangement of F-actin [10], we have suggested that the asymmetrically distributed cytoskeleton may be involved in the enhanced Ca^{2+} response. Indeed, the addition of the actin-depolymerizing agent latrunculin A (LAT-A) induced a massive release of intracellular Ca^{2+} in mature oocytes, but not in immature oocytes [11]. Hence, the reorganization of F-actin during the maturation process [12] appeared to be somehow involved in the modulation of Ca^{2+} signalling.

Cofilin/ADF is an actin-binding protein that induces microfilament reorganization both *in vivo* [13,14] and *in vitro* [15–17]. The binding site for actin in the cofilin/ADF molecule overlaps the domain that binds PIP_2 [18,19]. This dual binding activity suggests the possible involvement of cofilin/ADF in the control of Ca^{2+} release. In the current communication we have explored this possibility. We have observed that exogenously added cofilin increased the intracellular Ca^{2+} release mediated by $InsP_3$ and NAADP in starfish oocytes. By contrast, it delayed cADPr-induced Ca^{2+} increase. Moreover, cofilin stimulated the intracellular Ca^{2+} release that occurs naturally during oocyte maturation and fertilization.

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Materials and methods

Preparation of oocytes. The Japanese (*Asterina pectinifera*) and Mediterranean (*Astropecten auranciacus*) species of starfish were acquired and maintained as previously described [9]. Fully grown immature oocytes arrested at the prophase of the first meiotic division were dissected from the gonads and processed in filtered artificial seawater (ASW: 460 mM NaCl, 10.1 mM KCl, 9.2 mM CaCl2, 35.9 mM $MgCl_2$, 17.5 mM $MgSO_4$, and 2.5 mM $NaHCO_3$, pH 8.0) as described previously [9]. For fertilization experiment, immature oocytes were first stimulated with 1-MA (10 μM) for 1 h, and then spermatozoa were added to the mature oocytes in ASW.

Actin depolymerization assay. Pyrene G-actin (monomer) was polymerized to fluorescent pyrene F-actin by using the Actin Polymerization Biochem kit BK003 (Cytoskeleton Inc., USA). Measurement of the fluorescence was performed in a spectrophotometer (Perkin-Elmer) with the excitation/emission wavelength at 365 and 407 nm, respectively.

Microinjection, photoactivation of caged compounds, and Ca^{2+} imaging. Fluorescent calcium dye (Oregon Green 488 BAPTA-1) was coupled to 10 kDa dextran (Molecular Probes, Eugene, OR) and co-injected with one of the caged compounds ($InsP_3$, cADPr, and NAADP purchased from Molecular Probes) after being dissolved in the injection buffer (450 mM KCl, 10 mM Hepes, pH 7.0). The pipette concentration of the Ca^{2+} dye was 5 mg/ml, and the concentration of each caged compound was specified in the figure legends. The actual concentration of the dye and compounds inside the oocyte is estimated about 100-fold lower than that in the injection pipette. Microinjection was performed with an air-pressure Transjector (Eppendorf). Human recombinant cofilin-1 purchased from Cytoskeleton Inc., USA (Cat. No. CF01, Lot No. 017) was injected in the same way (final concentration, 50 μg/ml). To activate caged second messengers, microinjected oocytes were irradiated with UV light (330 nm for 25 s) using the computer-controlled shutter system Lambda 10-2 (Sutter Instruments, Co., Novato, CA). Cytosolic Ca^{2+} changes were detected using a cooled CCD camera (MicroMax, Princeton Instruments, Inc., Trenton, NJ) mounted on a Zeiss Axiovert 200 microscope with a Plan-Neofluar 20×/0.50 objective. Fluorescent Ca^{2+} images were analyzed with the MetaMorph Imaging System software (Universal Imaging Corporation, West Chester, PA). The quantified Ca^{2+} signal was normalized to the baseline fluorescence (F_0) following the formula $F_{rel} = [F\text{-}F_0]/F_0$, where F represents the averaged fluorescence level of the entire oocyte at a given time point.

Western blot analysis. Protein was extracted from immature and mature oocytes of *A. auranciacus* and resolved in 15% SDS–PAGE. The blot was incubated in the PBS buffer containing 5% non-fat milk and 0.2% TWEEN. One hour later, the antibody against starfish cofilin/ADF (generous gift from Dr. I. Mabuchi, University of Tokyo) was added at the final concentration of 3 μg/ml. After 1 h incubation at room temperature, the antibody was extensively rinsed and the blot was incubated in the same binding buffer in the presence of HRP-conjugated anti-rabbit IgG. The blot was washed again with PBS and processed for ELC autofluorography, using a commercial kit (Amersham).

Results

Functional test of cofilin

To test if the recombinant human cofilin (Cytoskeleton Inc., USA) was biologically active, we performed *in vitro* actin depolymerization assay as described in the Materials and methods section. In this assay, pyrene G-actin had been assembled into fully fluorescent filamentous F-actin, and the progress of depolymerization was monitored by the decrease of fluorescence. When cofilin was added to the preassembled pyrene F-actin, the fluorescence decreased immediately to the basal level as expected, indicating that the actin filaments were quickly depolymerized (Fig. 1). The cofilin storage buffer used as a control only produced a modest depolymerization, the extent of which was three to four times lower than that induced by cofilin.

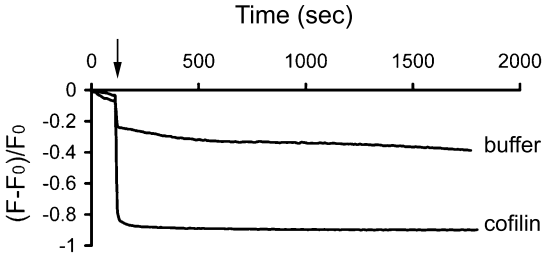

Fig. 1. Functional test of cofilin. Pyrene fluorescence assay of actin disassembly. Fluorescent pyrene F-actin (100 μg) was allowed to depolymerize into non-fluorescent pyrene G-actin in the presence of either cofilin (25 ng/μl, final concentration) or cofilin-storage buffer (reaction volume, 100 μl). Actin depolymerization was monitored by the change in fluorescence.

Cofilin enhances $InsP_3$-induced calcium release

Previously, we had demonstrated that the microfilament-disrupting agent LAT-A enhanced the $InsP_3$-dependent calcium release [10,11]. To extend this finding, we examined whether and how cofilin influences the dynamics of the InP_3-induced Ca^{2+} response. For this, immature oocytes were injected with caged $InsP_3$ (20 μM) and the Ca^{2+} indicator as described in the Materials and methods section. Five minutes later, when the Ca^{2+} indicator and caged $InsP_3$ had diffused uniformly inside the cell, $InsP_3$ was liberated by 25 s of continuous UV irradiation. As shown in Fig. 2A, $InsP_3$ promoted Ca^{2+} release from intracellular stores at the cell cortex. Then, the cortical Ca^{2+} signal began to spread centripetally until the entire cytoplasm was filled with Ca^{2+} (Fig. 2A). The quantification of the Ca^{2+} signal over the entire oocyte showed that the liberation of $InsP_3$ instantly released Ca^{2+}, with its peak reached by 9 s (Fig. 2B). In oocytes pre-injected with cofilin 15 min before the UV irradiation, the Ca^{2+} wave was generated more slowly, reaching the peak 5 s later (i.e., 14 s after $InsP_3$ photoactivation) in comparison to the control. However, the amplitude of the signal was greatly increased by cofilin, with the averaged peak value 62% higher than the control (Fig. 2B).

Cofilin enhances NAADP-induced Ca^{2+} signalling

We have recently demonstrated that the novel second messenger NAADP plays a distinct role in generating the Ca^{2+} signal in starfish oocytes. This signal typically initiates with a sharp Ca^{2+} increase in the cell cortex (cortical flash), which is due to the activation of an inwardly directed Ca^{2+} current across the plasma membrane [20]. To test if the effect of cofilin is restricted only to the modulation of the $InsP_3$-sensitive Ca^{2+} stores, we investigated whether cofilin can also influence the NAADP-mediated

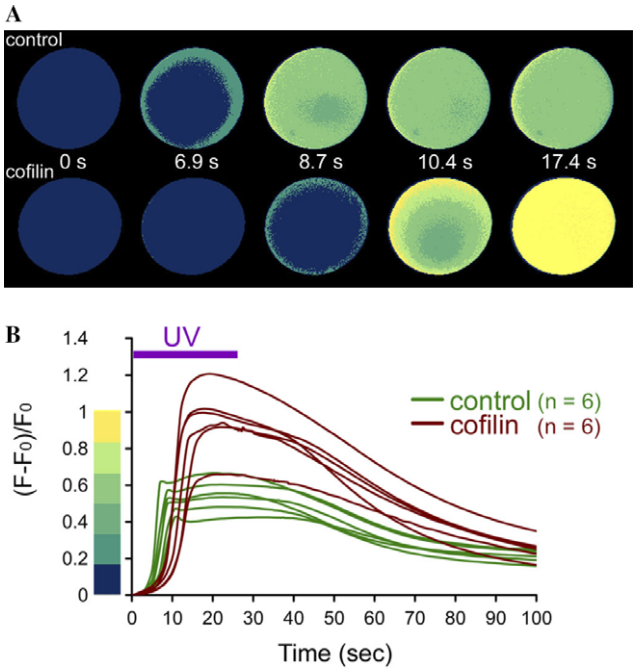

Fig. 2. Cofilin modulates Ca^{2+} release by $InsP_3$. (A) Effect of photoactivated $InsP_3$ (concentration in the injection pipette, 20 μM) on Ca^{2+} release inside starfish oocytes (*Asterina pectinifera*). Oocytes were coinjected with caged $InsP_3$ and the Ca^{2+} dye as described in the Materials and methods section. Relative fluorescence pseudo-colored images of the Ca^{2+} indicator provide the numerical equivalence of the Ca^{2+} signals in the absence or presence of cofilin. (B) The cytoplasmic Ca^{2+} signal was quantified and presented as a function of time in a graph. The duration of UV irradiation for the photoactivation of the caged compounds is indicated by a violet-colored bar.

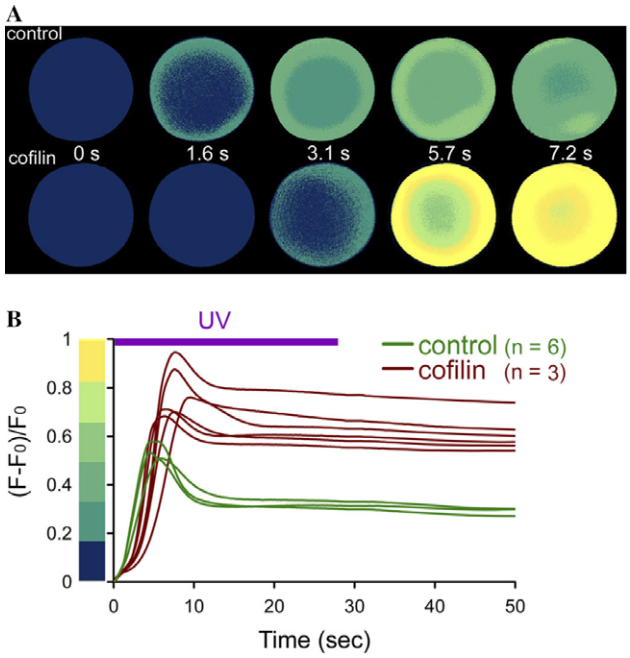

Fig. 3. Cofilin enhances NAADP-induced Ca^{2+} signalling. (A) Photoactivated NAADP (pipette concentration, 100 μM) induces a Ca^{2+} release in the cortical domain of the oocyte. (B) As was the case with $InsP_3$, the peak of the Ca^{2+} signal is substantially enhanced by pre-injected cofilin.

Ca^{2+} signal. For this, control or cofilin-preloaded oocytes were injected with caged NAADP. In the absence of pre-injected cofilin, the photoactivation of NAADP induced a Ca^{2+} increase which started in the cortical domain of the oocyte (Fig. 3A). Then the Ca^{2+} wave spread centripetally to the entire oocyte and reached its peak approximately 5 s after the beginning of UV irradiation. In the presence of cofilin, the Ca^{2+} increase was slightly delayed, as its peak occurred 8 s after the UV irradiation started. As was the case with $InsP_3$, the peak of the Ca^{2+} signal was substantially (44%) enhanced by cofilin injection (Fig. 3B).

Cofilin strongly delays the onset of the cADPr-dependent Ca^{2+} signalling

We then examined the effect of cofilin on the Ca^{2+} release induced by the third Ca^{2+}-linked second messenger, cADPr. In the absence of cofilin, the Ca^{2+} signal generated by uncaged cADPr initiated after 5 s in several distinct spots of the oocyte before spreading to the entire cytoplasm (Fig. 4A). This particular pattern confirmed the previous observation from our laboratory [21]. The peak of the global Ca^{2+} increase was reached between 10 and 15 s, which is considerably delayed in

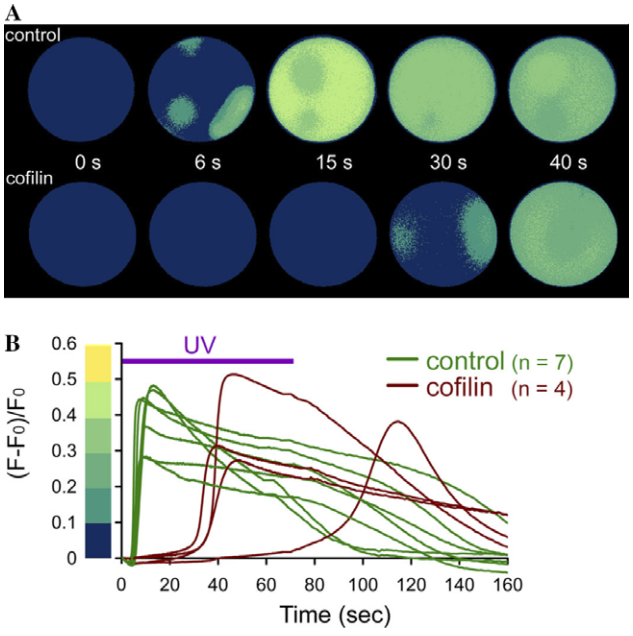

Fig. 4. Effect of the uncaging of cADPr (pipette concentration, 100 μM) on Ca^{2+} release inside starfish oocytes (*Astropecten auranciacus*). (A) The cADPr-induced Ca^{2+} signalling is strongly delayed in cofilin pre-injected oocytes. (B) In cofilin pre-injected oocytes, the amplitude of the Ca^{2+} signal is not changed, but the onset and development of Ca^{2+} increase is very much delayed.

comparison with $InsP_3$ (9 s) or NAADP (5 s). In the presence of pre-injected cofilin, the amplitude of the cytoplamic Ca^{2+} peak was not changed much, but the

onset and development of Ca^{2+} increase were very much delayed after cADPr uncaging. The peak was reached 30–60 s later than in the control oocytes (Fig. 4B). These results clearly indicate that cofilin, which reorganizes actin filaments, is able to influence the pattern and the amount of Ca^{2+} release in response to all three Ca^{2+}-related second messengers, i.e., $InsP_3$, NAADP, and cADPr.

The Ca^{2+} release during oocyte maturation is potentiated by cofilin

To test if cofilin also influences Ca^{2+} signalling during physiological process, control and cofilin-preloaded oocytes were stimulated with the maturation hormone 1-methyladenine. After 2 min of hormone incubation, control oocytes began to produce Ca^{2+} signal at the spot of the vegetal pole (Fig. 5A, arrow), from which it subsequently spread along the cortex toward the animal pole. This process was rather fast: 15–20 s after Ca^{2+} had first appeared in the oocyte, the Ca^{2+} signal swept through the entire cell.

In the presence of injected cofilin, the Ca^{2+} signal started nearly 10 s delayed but from a broad area of the cortex rather than from a single spot (Fig. 5A). As a result, the amount of Ca^{2+} release after hormonal stimulation was more than doubled in the presence of cofilin. When the global Ca^{2+} was quantified, the peak of the Ca^{2+} signal was 105% higher than that of the control oocytes (Fig. 5B). During the propagation of the signal, a gradient of Ca^{2+} concentration developed from the cortex to the cytoplasm, the highest level of Ca^{2+} being restricted to the cortical areas (Fig. 5A; and confocal microscopy observation, data not shown). However, it is important to emphasize that the hormone-induced Ca^{2+} signal arose entirely from the internal source, as it also occurred in oocytes bathed in calcium-free seawater (data not shown). In agreement with the experiments on the Ca^{2+}-related second messengers, the peak of Ca^{2+} release in the cofilin-injected oocytes was delayed by about 10 s in comparison with the control oocytes. Interestingly, when the Ca^{2+} signal subsided after 6 min, the basal level of cytoplasmic Ca^{2+} in the cofilin-injected cells was consistently lower than that of the controls (Fig. 5B). This result is in agreement with our observation that cofilin injection itself lowers the basal level of the Ca^{2+} in the cytoplasm of starfish oocyte (data not shown).

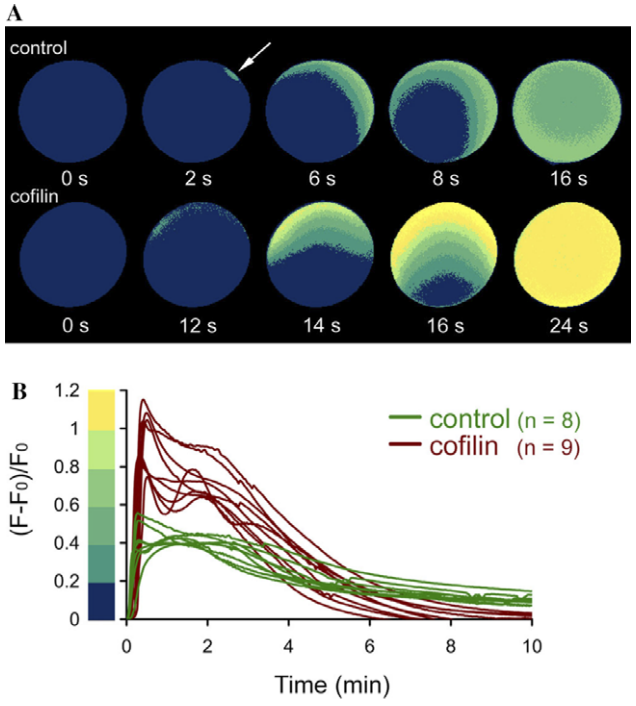

Fig. 5. Cofilin alters Ca^{2+} signalling patterns during maturation of starfish oocytes. (A) Cofilin potentiates the Ca^{2+} release during maturation of *Asterina pectinifera* oocytes. Two minutes after 1-MA stimulation, oocytes began to produce Ca^{2+} signals. The onset of the first detectable signal was taken as a reference point for timing ($t = 0$ s), and the subsequent changes of the released Ca^{2+} were visualized in the relative fluorescent pseudo-color images. Arrow: origin of the Ca^{2+} wave in the vegetal hemisphere. (B) Graph: Ca^{2+} signals quantified over the entire cytoplasm in the presence or absence of cofilin pre-injection.

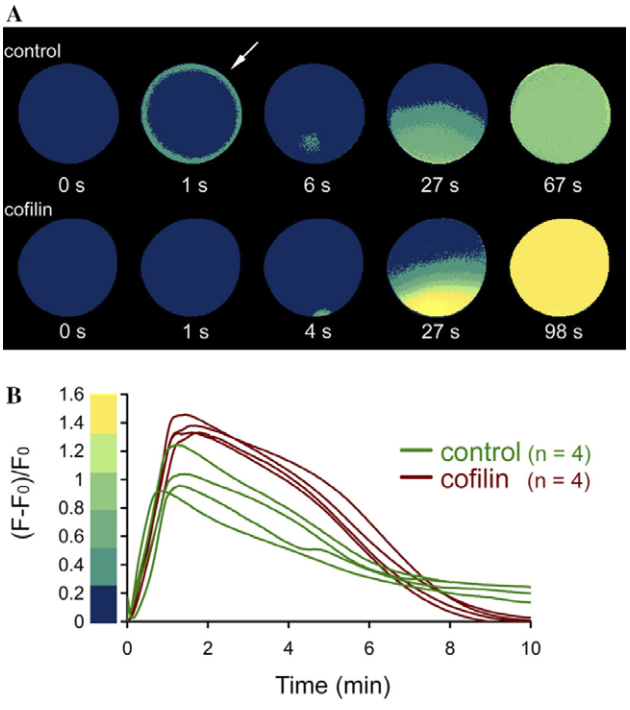

Fig. 6. Cofilin alters the sperm-induced Ca^{2+} response in *Asterina pectinifera* oocytes. (A) The oocytes were matured with 1-MA for 1 h and fertilized by spermatozoa. About 15 s after the sperm had interacted with the oocyte, Ca^{2+} began to be detected. Immediately after that, a strong cortical flash occurred and disappeared in the control oocytes (arrow). In the cofilin-injected oocytes, the cortical flash was abolished, but the pattern of the subsequent Ca^{2+} propagation was similar to that of the control except for the increased intensity of the signal. (B) Graph: Ca^{2+} signals quantified over the entire cytoplasm in the presence or absence of cofilin pre-injection.

Cofilin alters the sperm-induced Ca^{2+} response during fertilization

Ca^{2+} signalling during fertilization of starfish oocytes is characterized by an instant Ca^{2+} elevation that initiates just beneath the plasma membrane (cortical flash) and by the subsequent propagation of the Ca^{2+} wave to the entire cytoplasm [7–9]. In the absence of injected cofilin, the sharp cortical flash initiated after the sperm had contacted the oocyte (Fig. 6A). The cortical Ca^{2+} flash then disappeared very rapidly. Then, a wave of Ca^{2+} ensued from the sperm-oocyte interaction site and propagated to the opposite side of the oocyte (Fig. 6A).

In the presence of injected cofilin, the cortical flash was either abolished (12 cases out of 40) or significantly reduced (28 cases out of 40) in the fertilized oocytes (Fig. 6A). Despite the impairment of the cortical flash, cofilin substantially enhanced the propagation phase of the Ca^{2+} wave. When the increased Ca^{2+} was quantified over the entire cytoplasm, the peak of the signal in cofilin-preinjected oocytes was 32% higher than in the control (Fig. 6B). After the Ca^{2+} signal had subsided (>7 min), the basal level of cytoplasmic Ca^{2+} in the cofilin-injected oocytes was consistently lower than that of the control (Fig. 6B).

Discussion

Actin-binding protein cofilin/ADF not only stimulates treadmilling of F-actin, but also severs or twists actin filaments *in vitro* [22,23]. *In vivo*, the function of cofilin has been mainly linked to cell motility, migration, and cytokinesis [24–26]. In the present work, we have reported the first evidence that cofilin can also modulate the intracellular Ca^{2+} signalling.

It has been known that the increase of Ca^{2+} is mainly due to the release from the intracellular stores through $InsP_3$- and cADPr/ryanodine-sensitive channels (reviewed in [27]), but we have recently demonstrated that the novel second messenger NAADP mediates Ca^{2+} influx through plasma membrane calcium channels [20].

The results of the present study indicate that cofilin modulates the kinetics of cellular Ca^{2+} increase by all three major Ca^{2+}-releasing second messengers, i.e., $InsP_3$, cADPr, and NAADP. In addition, injected cofilin also altered the spatio-temporal pattern of physiologically occurring Ca^{2+} signals during oocyte maturation and fertilization. Based on these results, several possibilities can be considered on the role of cofilin in Ca^{2+} signalling. Cofilin might directly modulate the activity of Ca^{2+}-releasing channels. Or, as it seems more likely, cofilin could fine-tune their activity indirectly by remodelling the cytoskeleton of the microenvironment. In line with this possibility, recent studies have demonstrated that the Ca^{2+} influx across the plasma membrane is regulated by cofilin [28,29]. Alternatively, cofilin might control Ca^{2+} signalling by still unknown mechanism directly involving the cytoskeleton. There have been reports suggesting that F-actin can store and release Ca^{2+} *in vitro*, as an actin-binding protein, profilin, could release Ca^{2+} by promoting treadmilling of actin filaments *in vitro* [30–32]. We have observed that the microinjection of gelsolin, another actin-binding protein sharing similar structural and functional properties to cofilin, also enhances Ca^{2+} release from the $InsP_3$-sensitive stores. In contrast, injection of other proteins did not produce such result (data not shown).

Although cofilin/ADF is yet to be cloned from starfish, a protein homologous to mammalian cofilin was purified from starfish oocytes (*Asterias amurensis*) [33,34]. Using the antibody against this protein, we have detected the expected 17 kDa band in the oocytes of Mediterranean starfish *A. auranciacus* (Fig. 7). Hence, the regulation of Ca^{2+} signalling by cofilin featured in this study is likely to be physiologically relevant to starfish oocytes. Future studies will be necessary to understand the general physiological significance and the molecular basis of our observations.

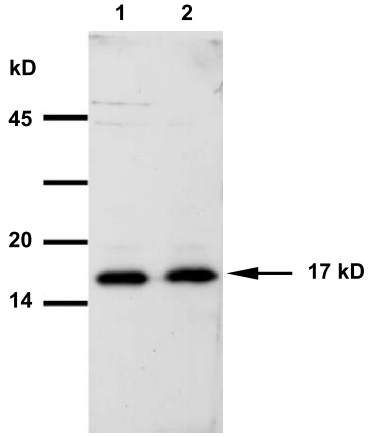

Fig. 7. A cofilin/ADF protein is expressed in starfish oocytes. Total proteins (50 μg) extracted from immature (lane 1) and 1-MA-matured (lane 2) oocytes were resolved on 15% SDS–PAGE and subjected to Western blot analysis as described in the Materials and methods section. Cofilin is present in both immature and mature starfish oocytes used in this study.

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