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A clean start: degradation of maternal proteins at the oocyte-to-embryo transition

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In many organisms, the transition from oocyte to embryo occurs in the absence of mRNA transcription. Therefore, early developmental programs rely on maternal mRNAs and proteins that are synthesized during oogenesis. The regulated translation of maternal RNAs is essential for the proper deployment of regulatory factors during early embryogenesis. Recent studies suggest that the degradation of maternal proteins by the ubiquitin–proteasome pathway is also crucial for the oocyte-to-embryo transition. In this article, we explore the hypothesis that the coordinated degradation of germline proteins is essential for remodeling the oocyte into a totipotent zygote that is capable of somatic development.

Multicellular organisms begin their development with a remarkable transition. At fertilization, the quiescent egg is transformed into a dynamic embryo that is ready to differentiate into many cell types. This transition begins with oocyte maturation when a hormonal or sperm-dependent cue signals to the egg to resume meiosis and prepare for fertilization. In turn, fertilization triggers, probably through Ca^{2+} oscillations, several cellular and developmental changes that eventually remodel the egg into a totipotent zygote [1]. These changes include the switch from meiosis to mitosis and the switch from a germ cell to a zygote that can generate both somatic and germ cells. In many organisms, these changes occur before the onset of mRNA transcription and, therefore, depend on modulation of the maternal dowry of RNAs and proteins that are present in the oocyte. The recruitment of maternal RNAs for translation has long been recognized as being a widespread mechanism to generate new proteins in maturing oocytes and fertilized eggs (for review, see Ref. [2]). Conversely, RNAs that are no longer needed are actively degraded in the early embryo (for review, see Ref. [3]). In this article, we explore the hypothesis that protein degradation functions as a complementary mechanism to erase the oogenic program and drive eggs into embryogenesis. We describe recent published examples of oocyte-protein degradation in *Caenorhabditis elegans* and consider the possibility that similar mechanisms operate in other organisms (Table 1).

Transitioning from meiosis to mitosis: degradation of MEI-1 and MEI-2

Before fertilization, oocytes arrest during meiosis, typically in prophase of meiosis I or after maturation in

Table 1. Oocyte proteins targeted for degradation in different organisms[a]

Organism	Target	Degron	E3 ligase	Regulator promotes (P) or inhibits (I) degradation	Refs
Caenorhabditis elegans	MEI-1	PEST	MEL-26–CUL-3	MBK-2 kinase (P)	[5,8,11,13–15,17,21,51,52]
	OMA-1	PEST		MBK-2 kinase (P)	[18–21]
	PIE-1 POS-1 MEX-1 MEX-5 MEX-6	CCCH finger	ZIF-1–CUL-2	MEX-5 and MEX-6 (P) PAR-1 kinase (I) MBK-2 kinase(P)	[21,32,33]
Xenopus	CPEB	PEST		CDC2 kinase (P)	[23–27]
Drosophila	Oskar			Par-1 kinase (I)	[42]
	Vasa			Fat facets DUB (I) Gustavus	[45,46]
Zebrafish	Vasa				[50]

[a]Abbreviations: DUB, deubiquitinating enzyme; ZIF-1, zinc-finger-interacting factor 1.

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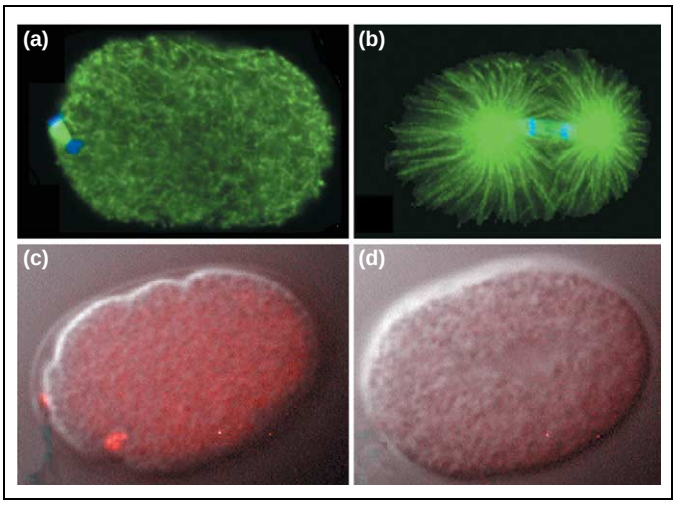

Figure 1. MEI-1 degradation at the meiosis-to-mitosis transition. **(a–b)** *Caenorhabditis elegans* zygotes stained for microtubules (green) and DNA (blue). The meiotic spindle is small and located close to the cortex (a). By contrast, the mitotic spindle (b) is much larger and is located more centrally. **(c–d)** MEI-1 (red) accumulates on the meiotic spindle and throughout the cytoplasm during meiosis (c), and has been mostly degraded by the onset of mitosis (d). Images courtesy of Thimo Kurz and Bruce Bowerman.

meiosis II. Fertilization triggers the completion of meiosis and the transition to mitosis. The meiotic and mitotic spindles differ in their behavior and morphology (Figure 1) but, remarkably, these structures form in the same cytoplasm, often within minutes of each another [4]. In *C. elegans*, the transition from the small meiotic spindle to the large mitotic spindle requires down-regulation of the microtubule-severing complex katanin [4,5]. The katanin complex is a p60–p80 heterodimeric complex that is capable of disassembling microtubules [6]. In *C. elegans*, the katanin subunits are encoded by the *mei-1* and *mei-2* genes and are required specifically for meiosis: loss-of-function mutations in either *mei-1* or *mei-2* disrupt meiosis without affecting mitosis [7]. MEI-1 and MEI-2 proteins accumulate on the meiotic spindle and are rapidly turned over after meiosis [4,8]. Mutations that block the turnover of MEI-1 and MEI-2 cause the proteins to accumulate on the mitotic spindle and interfere with spindle elongation and rotation [4,5]. Two classes of mutation were initially found to block MEI-1 and MEI-2 turnover: a mutation in *mei-1* itself [9] and mutations in a second locus, *mel-26* [5]. The *mei-1* mutation disrupts a PEST motif [9], which is an amino acid sequence that is known to promote the rapid turnover of proteins [10]. These observations suggested that MEI-1 might be actively targeted for degradation after meiosis.

The first clue that the ubiquitination pathway (Box 1) might be involved in the degradation of MEI-1 and MEI-2 came with the discovery of *rfl-1*, another locus required for MEI-1 degradation [11]. RFL-1 is the homolog of yeast Uba3, a member of the neddylation pathway that activates cullins by modifying them with the ubiquitin-like protein Nedd8 (for review, see Ref. [12]). RNA interference (RNAi) screening of the five *C. elegans* cullins identified CUL-3 as the one that is crucial for MEI-1 degradation [11]. These data suggested that MEI-1 and MEI-2 might be targeted by an E3-ubiquitin-ligase-containing CUL-3 for ubiquitination and degradation. Recent work focusing on MEL-26 has confirmed this hypothesis.

MEL-26 is a Broad-Complex, Tramtrack and Bric-a-brac (BTB)-domain protein that binds to CUL-3 *in vitro* and *in vivo* [13–15]. Remarkably, MEL-26 also binds to MEI-1 [13,14]. Mutations in the PEST sequence of MEI-1 that stabilize MEI-1 during mitosis block the MEI-1–MEL-26 interaction. A CUL-3–MEL-26 complex that is immunoprecipitated from 293T cells promotes MEI-1 ubiquitination *in vitro* [15]. Together, these data suggest that MEL-26 links MEI-1 to CUL-3, thus stimulating the ubiquitination of MEI-1. In other E3 ligases that have been described to date, substrates that are to be ubiquitinated are linked to a cullin by two intermediate proteins: a substrate-recruitment factor that binds to the substrate and a BTB-domain protein (e.g. SKP-1 and Elongin C) that binds to the substrate-recruitment factor and the cullin (Box 1). MEL-26 is the first BTB protein that has been shown to merge the properties of the cullin-binding protein and the substrate-recruitment factor into a single polypeptide but it is likely that others will follow. CUL-3 binds to several BTB proteins in *C. elegans* and *Schizosaccharomyces pombe* [14,16]. In *C. elegans*, *cul-3*-mutant zygotes have more-complex phenotypes than *mel-26* zygotes have [5,11,17], which is consistent with CUL-3 functioning with other BTB partners to degrade substrates other than MEI-1.

Degradation of other PEST proteins

The other CUL-3 substrates are not yet known but another example of a PEST protein that is degraded in *C. elegans* zygotes is OMA-1. OMA-1 is a putative RNA-binding protein that functions in oocyte maturation [18,19]. The levels of OMA-1 protein are highest in maturing oocytes and they decrease rapidly after fertilization. Like MEI-1, OMA-1 contains a PEST motif, mutations in which stabilize OMA-1 in embryos [20]. The PEST mutation does not interfere with the function of OMA-1 during oocyte maturation but it disrupts cell-fate specification in embryos, which leads to embryonic lethality. How stabilized OMA-1 interferes with cell fates is not yet known but it seems to be linked to the ability of OMA-1 to stabilize other maternal proteins. The E3 that is required for OMA-1 degradation has not yet been reported but it seems to be distinct from the E3 that targets MEI-1 [21].

An example in another organism of a PEST-domain protein that is degraded at the egg-to-embryo transition is cytoplasmic polyadenylation-element-binding protein (CPEB). CPEB is an RNA-binding protein, best characterized in *Xenopus*, that regulates the translation of oocyte RNAs during maturation (for review, see Ref. [22]). CPEB levels remain high midway through oocyte maturation and drop suddenly before the first meiotic division [23–25]. Inappropriate stabilization of CPEB interferes with meiosis, which indicates that CPEB degradation is required for the completion of egg maturation [26]. Several lines of evidence implicate

Box 1. Ubiquitin and protein degradation

The prevalent mode of regulated protein degradation in eukaryotic cells is ubiquitination (the covalent attachment of a polyubiquitin chain to a protein), followed by degradation of the protein by the proteasome (for review, see Ref. [60]). Ubiquitination is initiated by a ubiquitin-activating enzyme (E1) that activates ubiquitin for nucleophilic attack. Activated ubiquitin is passed on to a ubiquitin-conjugating enzyme (E2) that, in conjunction with a ubiquitin-ligating protein (E3), transfers the ubiquitin to the substrate that is to be degraded. Most organisms have only a small number of highly conserved E1 and E2 enzymes that participate in all ubiquitination reactions. By contrast, E3 ligases are numerous and often multimeric, which reflects their unique role in target recognition. Typically, multimeric E3 ligases are composed of a cullin-containing core (e.g. CUL-1, 2 or 3) and a variable substrate-recognition factor. The latter provides substrate specificity to the ubiquitination reaction by binding to one or a small number of targets. For example, some targets are recruited by a family of substrate-recognition factors known as F-box proteins (Figure Ia). F-box proteins link the target to the CUL-1–RBX-1 core of an E3 ligase through the SKP-1 bridging protein. Similarly, a second group of substrate-recognition factors, suppressor of cytokine signaling (SOCS)-box proteins, links targets to a CUL-2–RBX-1 core of an E3 ligase through an Elongin-B–Elongin-C bridging complex (Figure Ib). A third type of complex has been described recently [13–16], in which the substrate-recruitment factor and the bridging protein are merged into one protein (Figure Ic). In this complex, targets are recruited to CUL-3 directly by a Broad-Complex, Tramtrack and Bric-a-brac (BTB)-domain protein such as MEL-26.

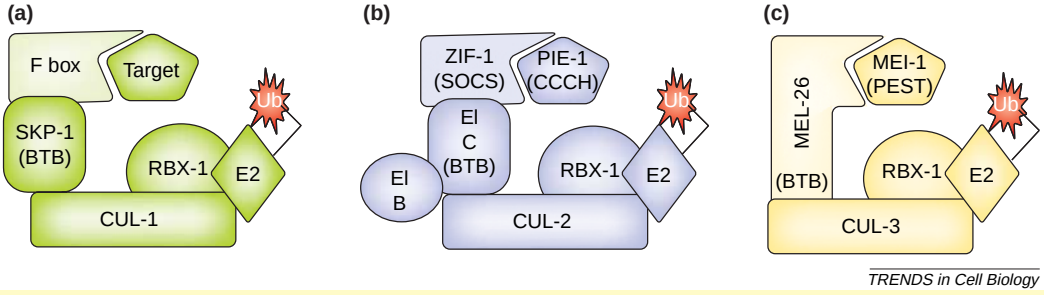

Figure I. Examples of multisubunit E3 ubiquitin ligases. Abbreviations: BTB, Broad-Complex, Tramtrack and Bric-a-brac; SOCS, suppressor of cytokine signaling; Ub, ubiquitin; ZIF-1, zinc-finger-interacting factor 1.

the ubiquitin–proteasome system in this process. CPEB is ubiquitinated when it is incubated in egg extracts [26] and CPEB degradation can be inhibited either by deleting the PEST domain or by exposing oocytes to proteasome inhibitors [25]. CPEB degradation is activated upon phosphorylation by CDC2 kinase [26,27] but the E3 involved has not yet been reported.

Transition from the 'germline-only' egg to the 'soma-and-germline' embryo: localized degradation of germ-plasm proteins

The destruction of CPEB occurs primarily in the vegetal pole of the *Xenopus* egg. In embryos, CPEB persists in the animal pole, in which it is required for cell division [28]. There is another class of maternal protein that continues to function in embryos, albeit only in certain cells. These are the proteins that reside in the germ plasm, a specialized cytoplasm essential for the formation of the embryonic germline. Germ-plasm proteins are not required in somatic cells but they must be maintained in the embryonic germline. Recent evidence from *C. elegans*, *Drosophila* and zebrafish suggests that germ-plasm proteins are actively degraded outside of the germline and are protected from degradation in germ cells.

C. elegans germ-plasm proteins

Among the germ-plasm proteins in *C. elegans*, the behavior of three CCCH-finger proteins – PIE-1, POS-1 and MEX-1 – is understood best. These putative RNA-binding proteins are restricted to the germline by at least two mechanisms (Figures 2,3). First, at each asymmetric division that gives rise to a somatic blastomere and a germline blastomere, PIE-1, POS-1 and MEX-1 are segregated preferentially to the germline daughter [29–31]. Second, they are actively degraded in somatic blastomeres [32,33]. This degradation depends on zinc-finger-interacting factor (ZIF)-1, which is a protein that binds to CCCH fingers [33]. Two lines of evidence suggest that ZIF-1 is a substrate-recruitment factor for a multisubunit E3 ubiquitin ligase. First, ZIF-1 contains a suppressor of cytokine signaling (SOCS) box, which is a motif that is typical of substrate-recruitment factors that complex with Elongin C (the BTB partner for CUL-2) [34]. ZIF-1 binds to Elongin C in yeast two-hybrid assays and this interaction requires the SOCS box [33]. Second, RNAi knockdowns of ZIF-1, Elongin C, CUL-2 or the E2 ubiquitin-conjugating enzyme UBC5 (also known as LET-70) stabilize CCCH proteins in somatic cells. These observations are consistent with ZIF-1 functioning in the context of an E3 ubiquitin ligase that targets CCCH proteins for degradation in somatic cells (Box 1). RNAi knockdowns of Elongin C, CUL-2 and UBC5 cause cell-cycle defects [33,35], in addition to blocking CCCH-finger degradation, which suggests that these core E3 components also regulate the degradation of other proteins. By contrast, *zif-1(RNAi)* embryos seem to have normal early divisions, which is consistent with the specificity of ZIF-1 for CCCH proteins [33]. *zif-1(RNAi)* embryos die during late embryogenesis, possibly because the perdurance of CCCH proteins interferes with somatic development.

Whereas the CCCH proteins are unstable in somatic cells, they are stable in germline blastomeres. How is degradation restricted to somatic cells? This question is particularly perplexing because CUL-2 is present in all

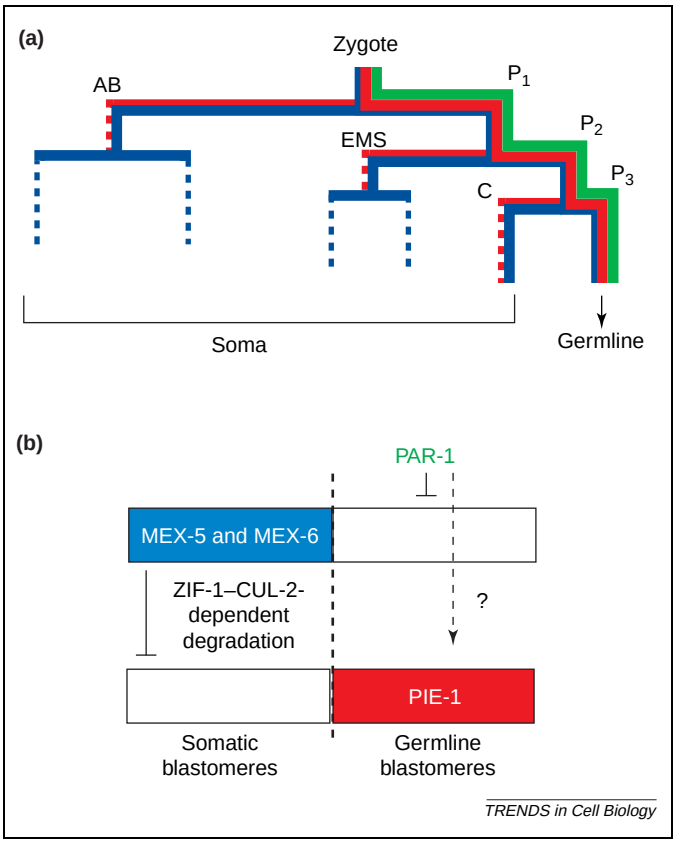

Figure 2. Soma-specific degradation of CCCH-finger proteins in *Caenorhabditis elegans* embryos. **(a)** Early *C. elegans* lineage. A series of asymmetric divisions gives rise to somatic (AB, EMS, C, D) and germline (P_1–P_4) blastomeres. At each asymmetric division, MEX-5 and MEX-6 (blue) are segregated preferentially to the somatic daughter, whereas PIE-1, MEX-1, and POS-1 (red) are segregated preferentially to the germline daughter. After division, all CCCH-finger proteins persist in the germline blastomeres but are degraded (broken lines) in somatic blastomeres. The kinase PAR-1 (green) segregates specifically with the germline blastomeres. **(b)** High levels of MEX-5 and MEX-6 activate zinc-finger-interacting factor (ZIF)-1-dependent degradation in somatic blastomeres. PAR-1 prevents this degradation in germline blastomeres by restricting MEX-5 and MEX-6 to the anterior. Experiments in *Drosophila* suggest that PAR-1 might also have a direct protective function in the germline.

blastomeres and the same is probably true for the other core E3-ligase components, all of which seem to have essential cell-cycle functions [33,35]. The localization of endogenous ZIF-1 has not yet been reported. Like other substrate-recruitment factors, ZIF-1 seems to be unstable: a green fluorescent protein (GFP)–ZIF-1 fusion is visible only in embryos with depleted levels of CUL-2 and, under these conditions, it is ubiquitous [33].

What restricts the activity of the ZIF-1–Elongin-C–CUL-2 ligase to somatic cells? The answer seems to be two CCCH-finger proteins: MEX-5 and MEX-6. Unlike the other CCCH proteins, MEX-5 and MEX-6 segregate preferentially to the somatic daughters at each asymmetric division [36] (Figures 2,3). Genetic experiments suggest that MEX-5 and MEX-6 function redundantly [36] and that, together, they are required to activate ZIF-1-dependent degradation in somatic cells [33]. In wild-type embryos, MEX-5 and MEX-6 levels are high in somatic blastomeres [36]. The levels are kept low in germline blastomeres by PAR-1, a serine/threonine kinase enriched in the germ lineage and required for overall anterior–posterior polarity [37]. In embryos that lack PAR-1, MEX-5 and MEX-6 levels are high in all cells [36] and ZIF-1-dependent degradation is activated in all cells [33] (Figure 2). By contrast, the RNAi knockdown of MEX-5 and MEX-6 stabilizes CCCH-finger proteins in all cells in both wild-type and *par-1*-mutant embryos. These results suggest that MEX-5 and MEX-6 activate ZIF-1-dependent degradation and that PAR-1 opposes this activity, perhaps by maintaining low levels of MEX-5 and MEX-6 in germline cells.

How do MEX-5, MEX-6 and PAR-1 function? These proteins regulate many anterior–posterior differences in the embryo [36,37], which raises the possibility that they affect ZIF-1-dependent degradation indirectly. Like other CCCH-finger proteins, however, MEX-5 and MEX-6 bind to ZIF-1 and are subject to ZIF-1-dependent degradation themselves [33]. It has been suggested that high levels of substrate proteins stabilize substrate-recruitment factors in other systems [38]. This raises the possibility that MEX-5 and MEX-6 activate ZIF-1-dependent degradation by stabilizing ZIF-1 specifically in somatic blastomeres. It will be important to determine whether the binding of MEX-5 and MEX-6 to ZIF-1 is essential for activating ZIF-1 and, furthermore, how PAR-1 interferes with this process.

Drosophila germ-plasm proteins

Studies using *Drosophila* support the view that germline proteins are unstable outside of the germline and are stabilized in germ cells by PAR-1. In *Drosophila*, RNAs that encode proteins that are important for germline development (e.g. *oskar*) are transported on a microtubule network to the posterior pole of the oocyte during oogenesis [39]. The PAR-1 kinase also localizes to the posterior pole and is required to polarize the oocyte microtubule network [40,41]. Using a combination of hypomorphic *par-1* alleles with sufficient activity to polarize the oocyte, Reichman *et al.* determined that PAR-1 is also required to stabilize the germ-plasm protein Oskar [42]. Oocytes with reduced PAR-1 activity localize *oskar* RNA as in wild-type oocytes but they accumulate lower levels of Oskar protein in the posterior. Conversely, the overexpression of PAR-1 kinase increases Oskar levels and Oskar phosphorylation, which suggests a direct interaction between these proteins. Consistent with this hypothesis, purified PAR-1 phosphorylates Oskar protein *in vitro* and this increases Oskar stability in oocyte extracts. The activity that is responsible for Oskar degradation is not yet known but it is likely to involve the ubiquitin pathway. When incubated in *Xenopus* extracts, Oskar is ubiquitinated and degraded in a proteasome-dependent manner, which suggests that Oskar might be targeted by an E3 ubiquitin ligase in the same way as described for CCCH proteins in *C. elegans*.

The analysis of Vasa in *Drosophila* further implicates the ubiquitin pathway in the localization of germ-plasm proteins. Vasa is another essential regulator of germ-cell fate that is recruited to the posterior pole of the oocyte by Oskar [43,44]. Vasa accumulation in the posterior requires not only Oskar but also the

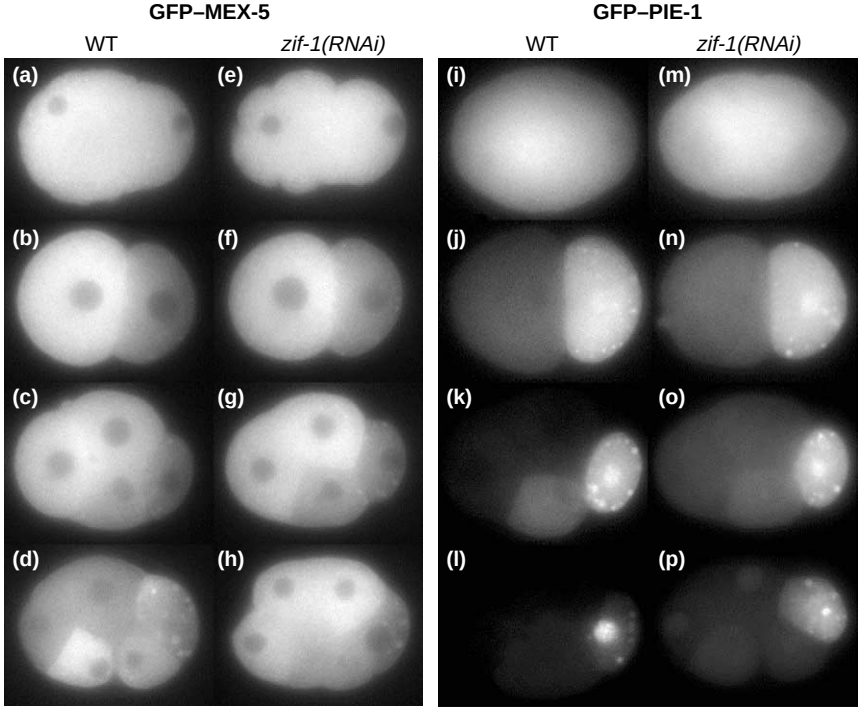

Figure 3. Zinc-finger-interacting factor (ZIF)-1-dependent degradation of PIE-1 and MEX-5 in somatic cells. Images from time-lapse recordings of live wild-type (WT) embryos **(a–d, i–l)** and embryos in which ZIF-1 has been depleted by RNA interference (RNAi) **(e–h, m–p)**. At each asymmetric division, green fluorescent protein (GFP)–MEX-5 (a–h) segregates with the somatic daughter (left-hand side of each image), whereas GFP–PIE-1 (i–p) segregates with the germline daughter (right-hand side of each image). This segregation is not absolute and small amounts of protein remain in the other daughter. GFP–PIE-1 and GFP–MEX-5 are both turned over in somatic cells but, possibly, at different rates [compare (k) with (c)]. Eventually, MEX-5 is eliminated completely from somatic cells (at time points beyond those shown). In *zif-1(RNAi)* embryos, asymmetric segregation occurs as in wild-type embryos [compare (b) with (f), and (j) with (n)] but degradation in somatic daughters fails [compare (d) with (h), and (l) with (p)].

deubiquitinating enzyme Fat facets [45] and the SOCS-box protein Gustavus [46]. Several lines of evidence support a direct role for Fat facets in promoting Vasa stability in the posterior pole. Vasa and Fat facets interact physically *in vivo*, as demonstrated by co-immunoprecipitation [45]. In *fat facets* mutants, Vasa is polyubiquitinated and accumulates at lower levels in the posterior compared with wild type, resulting in fewer germ cells during embryogenesis. Together, these observations suggest that Fat facets stabilizes Vasa in the posterior by reversing the ubiquitination of Vasa and that this activity is essential for accumulating enough Vasa for efficient germ-cell formation.

The role of the SOCS-box protein Gustavus is less clear. As described for ZIF-1, SOCS-box proteins typically function as substrate-recruitment factors for E3 ubiquitin ligases [34] – they bind to specific targets and stimulate their ubiquitination and degradation. However, like Fat facets, Gustavus is required for Vasa accumulation in the oocyte posterior pole [46], which is not easily reconciled with a potential role in stimulating Vasa turnover. Gustavus binds to a domain in Vasa that is essential for Vasa localization *in vivo*, which suggests that the Gustavus–Vasa interaction is, instead, essential for Vasa translocation to the posterior. It will be important to determine whether Gustavus functions in the context of an E3 ligase or in another capacity.

Zebrafish Vasa

Evidence from studies in zebrafish also supports the view that Vasa localization depends, at least in part, on localized protein degradation. *vasa* RNA localizes to four discrete regions on cleavage furrows in the early embryo [47–49]. The localization of *vasa* RNA depends on sequences in the 3′-untranslated region (UTR) [50]. When these sequences are removed, *vasa* RNA is found throughout the embryo but, surprisingly, Vasa protein is detected only in primordial germ cells. Conversely, when GFP-coding sequences are fused to the *vasa* 3′-UTR, GFP is found throughout the embryo, even though the RNA is maintained only in germ cells. These observations suggest that Vasa protein is actively targeted for degradation outside of the germline. Although the ubiquitin–proteasome pathway has not yet been implicated in this process, the parallels with *C. elegans* and *Drosophila* suggest that zebrafish Vasa is under similar regulation.

Coordinated protein degradation?

The translational recruitment of maternal RNAs is regulated in a coordinated manner. CPEB co-regulates the translation of many RNAs during oocyte maturation (for review, see Ref. [22]). Is maternal-protein degradation also under the coordinated control of a single gene? Recent evidence from *C. elegans* supports this possibility and points to the dual specificity and Yak1-regulated kinase (DYRK) kinase MBK-2 as being a candidate master

regulator. The loss of MBK-2 delays and/or blocks the degradation of MEI-1, OMA-1 and CCCH-finger proteins [21,51,52]. MBK-2 is also required for the posterior enrichment of the germ plasm in zygotes, which raises the possibility that this process also involves protein degradation, although this remains to be determined. Partial loss of MBK-2 can yield embryos with normal MEI-1 degradation but abnormal germline-protein turnover [21], which suggests that MBK-2 regulates these processes independently [51,52]. Strong loss-of-function *mbk-2* mutants resemble mutants that arrest in meiosis I, which also fail to degrade MEI-1 and OMA-1, and do not localize germline proteins. *mbk-2* mutants, however, complete meiosis and initiate mitosis as in wild type [21,51,52]. These observations suggest that *mbk-2*, although not required for meiosis to proceed, is necessary for zygotes to 'sense' passage through meiosis. Such sensing could be crucial for ensuring that oocyte proteins are turned over at the proper time [i.e. only after MEI-1 has completed its meiotic function and after the sperm asters have defined distinct anterior (somatic) and posterior (germline) regions in the zygote].

The possibility that MBK-2 functions as a meiosis sensor is supported by the observation that the localization of a GFP–MBK-2 fusion changes dramatically during meiosis [21]. GFP–MBK-2 accumulates uniformly throughout the cortex of oocytes and newly fertilized embryos, and abruptly coalesces into cortical speckles during the transition from meiosis I to meiosis II. The significance of this relocalization is not yet known but it is consistent with the idea that meiotic progression triggers developmental changes in the zygote.

How does MBK-2 activate oocyte-protein degradation? Generally, MBK-2 is not required for proteasome function because cyclin-B degradation during meiosis proceeds normally in *mbk-2(RNAi)* embryos [21]. MBK-2 is also unlikely to be required for cullin function because *cul-2* and *cul-3* mutants exhibit phenotypes that are not seen in *mbk-2* mutants [11,17,35,53,54]. Because some proteins require phosphorylation before ubiquitination [55], MBK-2 could function at the level of each target, perhaps by phosphorylating the target in a manner that stimulates recognition by the respective E3 ligases. Although the exact mode of action of MBK-2 remains to be determined, the range of *mbk-2* phenotypes strongly suggests that maternal-protein degradation is regulated in a coordinated manner and is linked to meiotic progression.

Concluding remarks

The proteins highlighted in this article probably represent only a small subset of all proteins that are degraded during the oocyte-to-embryo transition. The complex phenotypes observed in *C. elegans* zygotes that lack various components of the ubiquitination machinery suggest that protein degradation regulates many developmental events in early embryos [11,17,35,53,54]. Because the ubiquitination machinery also has a prominent role in cell-cycle progression (for review, see Ref. [56]), it has, at times, been difficult to distinguish direct developmental effects from indirect ones that are caused by cell-cycle arrest [57,58]. As more developmental targets and regulators are identified, it should become possible to separate the cell cycle and the developmental functions of protein degradation and to understand better how the two are connected.

We suggest that the degradation of oocyte proteins is an essential component of the egg-to-embryo transition, the purpose of which is to erase the oogenic (germline) program and make way for somatic development. Intriguingly, a requirement for protein degradation during developmental transitions has also been documented in yeast. Laney and Hochstrasser showed recently that the efficient switching from *MAT*α to *MAT*a mating type depends on the proteolysis of the α2 transcription factor [59]. Failure to degrade α2 impairs mating-type switching and causes cells to adopt a hybrid fate with deleterious consequences for mating. As noted by Laney and Hochstrasser [59], degradation can be constitutive (as in the case of α2) or can be triggered by the developmental transition that requires it (as described for MBK-2-dependent degradation). The careful regulation of proteolysis is likely to be particularly important in oocytes, which are predominantly transcriptionally inactive and must often wait long periods before fertilization. Newly available proteomic methods should help to determine how widespread protein turnover is in eggs and the extent to which this turnover contributes to one of the most crucial transitions in development: the remodeling of an oocyte into a totipotent zygote.

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