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The multiple hats of Vasa function and its regulation of cell cycle progression

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Summary

Vasa, an ATP-dependent RNA helicase, is broadly conserved among various organisms from cnidarians to mammals. It has a rich history of utility as a germline marker, and is believed to function as a positive translational regulator in the determination and maintenance of germline cells. Studies in non-model organisms, however, revealed that Vasa is also present in somatic cells of many tissues. In many cases these cells are multipotent, are non-germline associated, and give rise to a variety of different tissue types. Recent work now also demonstrates that Vasa functions in the regulation of the cell cycle. Here we discuss this newly described function of Vasa in mitotic and meiotic cell cycles, and we address the conundrum created within these observations, that is, that most cells are mitotically independent of Vasa, yet when Vasa is present in a cell, it appears to be essential for cell cycle progression.

Keywords

cell cycle; vasa; embryonic cells; germ cell; translational regulation

Introduction

Vasa is widely acknowledged as an indispensible germline marker. It was originally identified in Drosophila as an essential gene for germline development (Lasko and Ashburner, 1988; Hay et al., 1988a, Hay et al., 1988b), and since then it has been found in the germline of every organism examined (Raz, 2000). Based on its sequence similarity to the initiation factor eIF4A (Lasko and Ashburner, 1988; Hay et al., 1988b), analysis of its atomic structure (Sengoku et al., 2006), and gene knockout studies in flies (Johnstone and Lasko, 2004), Vasa is believed to function as a positive translational regulator in the determination and maintenance of germline cells. Importantly, Vasa is typically found within granules located near the nucleus of the germline cell, the so-called nuage (Hay et al., 1988a & b; Johnstone et al., 2005). Vasa's role in nuage — and the function of nuage in general — is not clear, but the proximity of nuage to nuclear pores and the presence of many RNA-binding proteins in nuage suggests a role for nuage in the processing or screening of mRNAs as they exit from the nuclear pore. The role of many proteins of the germline appears to be in quality control: e.g. piwi in reducing transposon movement in the Drosophila genome, and P-graules, the nuage-like structure associated with the germline cells in *Caenorhabditis elegans*, appear to play a major role in reducing the impact of biochemical stress on the germline (Gallo et al., 2010). The function of Vasa in nuage as a

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Quote: *"Vasa is not present in all cells, but where Vasa is present, it appears essential for normal cell cycle activities."*

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translational regulator may contribute to mRNA screening, perhaps even in the pioneering round of translation as a quality control device (Maquat et al., 2010).

Vasa is a founding member of the family of DEAD-box proteins, and its consensus sequence L-**D**-**E**-**A**-**D**-X-(M/L)-L-X-X-G-F shared with other DEAD-box members (e.g. eIF4A, p68, and PL10) reflects a unique version of the B-motif of ATP-binding proteins (Linder et al., 1989). Along with its RNA helicase domain and its highly conserved carboxy-terminal regions, Vasa appears to be a part of a larger translational complex (Johnstone and Lasko, 2004). Functional studies in Drosophila document that it interacts with eIF5B, and the observation that several proteins do not accumulate in Vasa-mutant flies, serves as the basis for the conclusion that Vasa functions as a positive translational regulator (Linder, 2003; Johnstone and Lasko, 2001; Carrera et al., 2000). Knowledge of its function and its mechanism of action, however, has been limited to research mostly in flies, until lately.

In addition to its essential role in the germline of the fly, Vasa recently has been reported to function outside of the germline in humans, planaria, polychaetes, sea urchins, cnidaria and other animals (e.g. Rebscher et al., 2007; Juliano and Wessel, 2010). In many of these cases, Vasa appears to function as a stem cell factor or a potency regulator more than in fate determination (e.g. Linder and Lasko, 2006; Rosner et al., 2009; Pfister et al., 2008; Shibata et al., 1999; Oyama and Shimizu, 2007; Rebscher et al., 2007; Juliano and Wessel, 2010). Clearly this classic germline marker functions in a variety of cellular developmental processes, yet its function outside of the germline has not been resolved.

The function of Vasa now also intersects the piRNA biogenesis pathway, at least in germ cells of male mice (Kuramochi-Miyagawa et al., 2010). Many proteins are involved in piRNA biosynthesis, and a “feed-forward loop”, or “ping-pong”, mechanism was originally postulated for the generation of piRNAs in Drosophila (Brennecke et al. 2007; Gunawardane et al. 2007). This ping-pong amplification process is mediated by two Drosophila PIWI family proteins, Aubergine (AUB) and Argonaut 3 (AGO3) (and by the murine orthologs of PIWI, MILI and MIWI2), which bind primarily to antisense primary piRNA and secondary sense piRNAs, respectively. Analysis of piRNAs in mouse Vasa homolog (MVH)-deficient germ cells of the fetal male mouse showed that MVH plays an essential role in the early phase of the ping-pong amplification cycle. Kuramochi-Miyagawa et al. (2010) also suggest that Vasa may play a role in the construction and/or function of intermitochondrial cement, and that Vasa is essential for transfer of piRNA from the intermitochondrial cement into the processing bodies, the so called P-bodies.

Vasa is also known to be closely linked to the formation and maintenance of tumors. Many human tumors are associated with Vasa expression, and the level of Vasa accumulation correlates strongly with tumor aggression and poor patient prognosis (e.g. Caballero and Chen, 2009; Simpson et al., 2005). Recent studies even demonstrate the essential function of Vasa in tumor formation and maintenance in Drosophila: In several brain tumors, e.g. *lethal (3) malignant brain tumor* [l(3)mbt] mutants, Vasa is up-regulated during tumorogenesis, and experimental removal of Vasa from these cells leads to tumor regression (Janic et al., 2010). Thus, the functional contribution of Vasa extends to phenotypes of cellular potential, to rapidly dividing cells, and presumably to translational regulation beyond those limited to the germline.

By combining these multiple functions of Vasa in somatic stem cells and tumor cells, one might speculate that Vasa is involved in cell cycle regulation in these highly proliferative cells. Indeed, two independent reports recently provide direct evidence of Vasa as a cell cycle regulator (Pek and Kai, 2011; Yajima and Wessel, 2011b). In both Drosophila germline stem cells and in sea urchin early blastomeres, Vasa presence was shown to be

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essential for mitotic progression. This phenotype seems too obvious to have overlooked in the past, but most studies utilized Vasa more as a germ cell marker. In cases of *vasa* gene disruptions, cell cycle perturbations were usually not a metric of the study largely due to the difficulty of following these cells through their prolonged development. Yet, a postulated role of Vasa in the regulation of the cell cycle now fits with some of the published observations made both in somatic and germline cells. For example, mouse spermatogenesis is severely hampered in *vasa* gene knockouts due to a severe lack of proliferation of the stem cell precursors (Tanaka et al., 2000).

Vasa function in mitotic cell cycle progression

The germline stem cells of Drosophila are abundant with Vasa, and it now appears to be essential for mitotic activity through an interaction with chromatin (Pek and Kai, 2011). The perinuclear nuage in germ cells is the normal location for Vasa in this organism, whereas the mitotic spindle, and especially the chromatin, is not normally ascribed to Vasa germline function. Pek and Kai (2011), however, demonstrated that Vasa interacts with chromosomes, not directly by binding to DNA, but through an interaction with Barr, a conserved component of the condensin 1 complex. Barr is required for proper chromosome condensation and segregation (Figure 1). In turn, proper Barr localization on mitotic chromosomes was also impaired in the Vasa-null mutant. Pek and Kai (2011) found that Vasa was present within a complex that also contained Aubergine (Aub), a germline piRNA component, and Spindle-E (Spn-E), an RNA helicase of the DE-H family that organizes microtubule dynamics, and that these two components are necessary for proper Vasa localization on mitotic chromosomes. Aub and Spn-E might be necessary for recruitment of Vasa onto the mitotic chromosomes, and perhaps Vasa promotes mitotic chromosome condensation by facilitating robust chromosomal localization of Barr (Fig. 1).

Vasa was also found to be essential for cell cycle progression in early embryos of the sea urchin (Yajima and Wessel, 2011b). In this animal, Vasa is recruited to the spindles during M-phase, is excluded from the newly formed nucleus at telophase, and is then repackaged with perinuclear granules — and this cycle repeats at the next prophase (summarized in Fig. 2). Interestingly, Vasa protein levels oscillate during the cell cycle, and depletion of Vasa synthesis in this embryo resulted in the prolonged M-phase and cell cycle delay. As one explanation for this phenomenon, Vasa was found to be necessary for the efficient translation of cyclinB. Sequence-specific Vasa interaction with mRNAs was reported previously to favor polyU sequences (Liu et al., 2009), and indeed, cyclin B of the sea urchin has several polyU tracts within its 3′UTR. Thus, Vasa may be recruited to spindles to locally regulate the translation of mitotic cyclins for rapid cell divisions in large embryonic cells, where diffusion of Vasa within the spindle region may be limiting. Previous results in examining this embryo for Vasa dynamics indeed shows that the area of the spindle is enriched for cyclin B, whereas more peripheral regions of the cell are cyclin B-reduced (Voronina et al., 2003). Unlike the results from Drosophila germline stem cells, however, Vasa was not enriched on chromatin in the sea urchin embryo. Rather, it appeared largely associated with the spindle microtubules, and only poorly with the aster microtubules. Although no altered phenotype was seen in the sea urchin for chromosome condensation upon Vasa knockdown, the overall function of Vasa in regulation of the cell cycle appears to be consistent between these two animals, albeit in differing cell poulations (e.g. the Drosophila germline stem cells and in sea urchin blastomeres).

Surprisingly, the translational activity of Vasa was not a requirement for its function in the cell cycle in Drosophila germline stem cells (Kai and Pek, 2011). The authors arrived at that conclusion with a point mutation of Vasa – deletion of proline 617 – previously reported to be important for interaction with eIF5B (Johnstone and Lasko, 2004). In the absence of this proline, Kai and Pek report that cell cycle progression and DNA condensation proceed as

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normal, and therefore is independent of the translational function of Vasa. Thus, Vasa may have multiple functions even within the mitotic apparatus – one involved in chromosome condensation that is independent of its translational activity, and one on the spindle that is translationally dependent and may be involved in localized translation of factors essential for cell cycle progression. Alternatively, since eIF5B is likely not the only translation initiation factor that interacts with Vasa, perhaps the version of the Vasa protein with the 617 proline deletion still interacts with other translation factors and mRNA that are important for cell cycle activities, and thus may still function as a translational regulator to control cell cycle progression, although not by direct interaction with eIF5B.

Vasa function in germ cells and somatic multipotent cells

Unresolved yet is the conundrum that Vasa is not present in all cells, but where Vasa is present, it appears essential for normal cell cycle activities. Most somatic cells lack Vasa, yet they still cycle, demonstrating that Vasa is not ubiquitous and not the rate limiting factor in the cell cycle, but rather it may function as a general cell cycle regulator only in certain cells. The cell cycle function of Vasa reported so far is only in Drosophila germline stem cells and in sea urchin (and sea star) embryos, yet Vasa is also present in a variety of somatic and germ cells whose cell cycle activity in the absence of Vasa has not been reported (Yoshida-Noro and Tochinai, 2010; Rebscher et al., 2007; Shibata et al., 1999; Noda and Kanai, 1977). In germ cells, Vasa may even be reversibly regulated: Vasa appears to be inactivated by phosphorylation in response to activation of a meiotic checkpoint during Drosophila oogenesis (Ghabrial and Schüpbach, 1999), implying that Vasa is involved in meiotic cell cycle progression, and furthermore, that structural modifications to the protein will change its involvement in translational activity.

Since quality control is an essential aspect for germ cell development, perhaps Vasa has a higher fidelity/quality product output to regulate germ cell proliferation. In multipotent somatic cells, Vasa may impart higher efficiency or a better quality translational product while going through rapid cell cycling. This explanation is only a hypothesis, but it is further supported by the cell-cycle activity of yeast DED1, as a general cell cycle regulator (Grallert et al., 2000). Yeast does not have Vasa/PL10, and DED1 is most similar to Vasa/PL10 in sequence within the same DDX4 clade (Hay et al., 1988a and b). Therefore, the original function of the ancestral Vasa-like molecule could be in cell cycle control, and its activity may have been retained for roles in facilitating translation of cell cycle regulators, particularly when the cell is multipotent, large, and/or rapidly dividing. Since many embryos, including mammals, have a maternal load of Vasa, this non-germline function of Vasa may reflect a broader and more conserved role than previously anticipated. It is still unclear, though, if Vasa is superseding the role of a different regulator within the cell in which it accumulates. If so, that alternative factor would likely be another DEAD-box helicase involved in broad translational mechanisms, and somehow down-regulated in the presence of Vasa. Alternatively, Vasa may function as an additional factor to enhance cell cycling by participating in an existing complex. In this case, an altered complex may result from Vasa knockdown that is somehow detrimental to cell cycle progression. Many cells that enrich for Vasa are also believed to be transcriptionally and metabolically less-active than neighboring cells, e.g. the small micromeres of the sea urchin embryo, and Vasa may enhance the translational efficiency within a limiting population of mRNAs.

Hypothesis: mechanisms of Vasa function in cell cycle progression

One explanation for Vasa function in the cell cycle is as a local translational activator. In the sea urchin, Vasa interacts with mitotic spindles during M-phase, and other independent evidence shows that many of the mitotic *cyclins*, including *cyclinB* mRNAs, accumulate on microtubules for local translation during M-phase in many organisms, especially in early

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embryos that lack G-phases (Blower et al., 2007). Therefore, we hypothesize that Vasa functions to regulate the translation of cell cycle-associated *cyclins* during M-phase on spindles to maintain the rapid cell cycling of early embryos (Fig. 3). This model is consistent with the enriched cyclin B seen in the region of the spindle during the cell cycle (Voronina et al., 2003). Our results, however, do not exclude the model that Vasa also functions during interphase in the cytoplasm, which may be with a different population of mRNAs. Cap-dependent mRNA translation is generally repressed during M-phase, and a different translational complex, such as a cap-independent complex, is formed to enhance translation during M-phase (Wilker et al., 2007). Therefore, we postulate that Vasa might be interacting with a different translational or cell-cycling complex, and it will be important to study in what complex(es) Vasa is involved during both M-phase and interphase. It is also conceivable that the mechanism of Vasa recruitment to the spindle is not through a series of protein interactions at the spindles, but to the mRNA that is already recruited to the spindle by yet unknown mechanisms (Blower et al., 2007). It has been reported that Vasa may prefer certain sequences such as polyU-tracts (Liu et al., 2009). Were those tracts present on mRNA bound to the spindle, perhaps Vasa may be preferentially localized there by virtue of its target mRNA sequence.

Importantly, Vasa accumulation in cells is not sufficient for a rapid cell cycle (Gustafson et al., 2011). We have seen Vasa levels as much as 10-fold higher in certain cell lineages without it altering mitosis or other phenotypes of the cell. This argues against a simple competition between Vasa and other DEAD-box members for translational control within the cell to regulate the cell cycle. In the sea urchin embryo, Vasa even accumulates to its highest levels in the small micromeres, the very cells with the slowest of cell cycles in the embryo (Yajima and Wessel, 2011a). The small micromeres, however, also accumulate Nanos, which is known to bind to the 3′UTR of *cyclin B* in a pumilio-dependent fashion and to repress *cyclin B* translation (Barker et al., 1992). Thus, Nanos activity trumps the Vasa function in the small micromeres, and Nanos-null-small micromeres display more rapid cell cycling and eventually apoptose, very similar to the phenotype seen in the pole cells of Drosophila (Juliano et al, 2009; Juliano et al., 2006; Fujii et al., 2009; Sato et al., 2007; Tsuda et al., 2003; Kobayashi et al., 1996; Hayashi et al., 2004).

A close interaction of Vasa and microtubules

A separate series of studies in several organisms such as ascidian, zebrafish, and Drosophila, report a close interaction of Vasa and microtubules during germ cell formation (Strasser et al., 2008; Lerit and Gavis, 2011; Prodon et al., 2009). The recent work in Drosophila demonstrated clearly that Vasa tracks on microtubules in a dynein-dependent mechanism during the formation of pole cells that are undergoing asymmetric cell divisions (Lerit and Gavis, 2011). Disrupting the transportation of Vasa in these embryos prevents incorporation of germ plasm into pole cell and impairs germ cell development. In this case, however, microtubules seem to be taking a more active role to deliver Vasa-positive germline components specifically to the future PGCs. Sea urchins also display Vasa asymmetrically transported to the small micromeres, the vegetal most blastomeres during their asymmetric cell division (Yajima and Wessel, 2011b; Fig.4). These observations further support a conserved role of microtubules for asymmetric distribution of Vasa.

Echinoderms, including sea urchins, exhibit several rapid cell divisions following fertilization, going from M-to-S phases without intervening G-phases (Horstadius, 1950). In the early sea urchin embryo, Vasa shows two different localization patterns within a single embryo. It is localized on the spindle in every dividing blastomere, whereas in small micromeres, which are involved in germ cell formation (Yajima and Wessel, 2011a), Vasa remains in a peri-nuclear region. We do not know if Vasa in somatic blastomeres and in small micromeres have different functions, nor what prevents Vasa from degradation in

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small micromeres after the completion of each cell cycle. We hypothesize, however, that Vasa in somatic blastomeres might function as a multipotent cell regulator that provides high quality translation of mitotic components in a rapid cell cycling environment. In the small micromeres, however, we suspect Vasa functions as a germline factor that might be involved in germ cell development by translating germline specific components, establishing a ping-pong pathway of piRNA biosynthesis, and/or regulating the cell cycle in association with other germline factors. Not many animals demonstrate these two possibly independent functions of Vasa within a single embryo, and thus the sea urchin may be a useful experimental tool to unveil the fundamental mechanisms of Vasa function that might be directly linked to the general mechanisms of the germ cell and the somatic cell functions.

Conclusions and Open Questions

A newly observed function of Vasa in the regulation of the cell cycle in two different animals suggests that this non-germline function of Vasa may reflect a broader and evolutionary more conserved role for this gene. Perhaps the population of proteins and mRNAs that Vasa associates with differ depending on the cell cycle, cell type (e.g. germ cells vs. somatic cells), and organism it is in. We anticipate, however, that the basic mechanisms of Vasa function likely overlap in these different cells. The newly defined, essential role of Vasa in tumor cells and its roles in multipotent cells together suggests that this classic molecule involves diverse roles and functions, well beyond the selective translational mechanism in germ cells that was observed over 20 years ago (Lasko and Ashburner, 1988).

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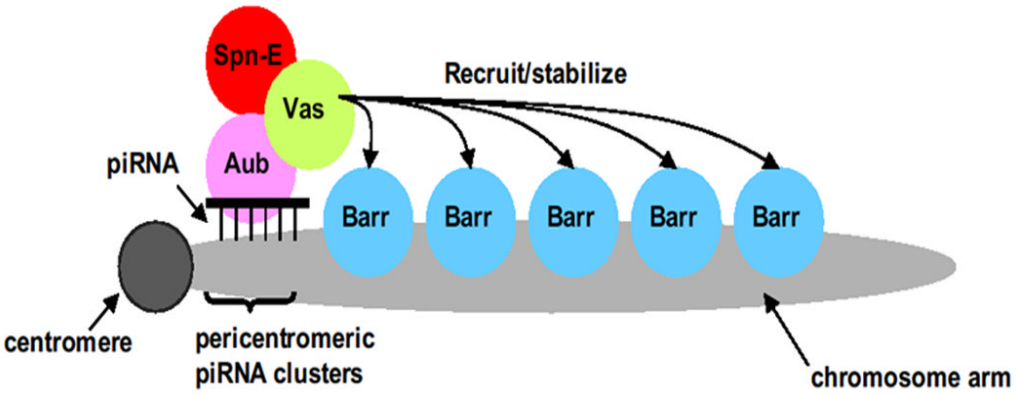

Fig. 1.

Adapted diagram from Fig.4G of Pek and Kai (2011). Hypothetical model of how Vas, Aubergine, (Aub) and Spindle-E (Spn-E) function during mitosis to facilitate robust Barr chromosomal localization. Vasa may promote local recruitment of Barr near pericentromeric regions. Alternatively, Vas could also promote long-range association of Barr with chromosomes.

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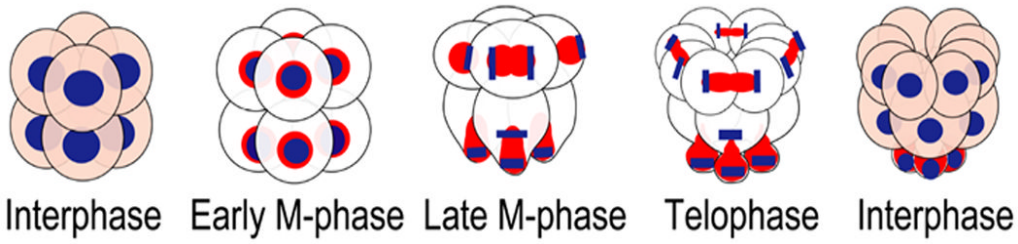

Fig. 2.
Adapted diagram from Yajima and Wessel (2011). A summary diagram of the dynamic localization of Vasa (red) during cell cycle progression.

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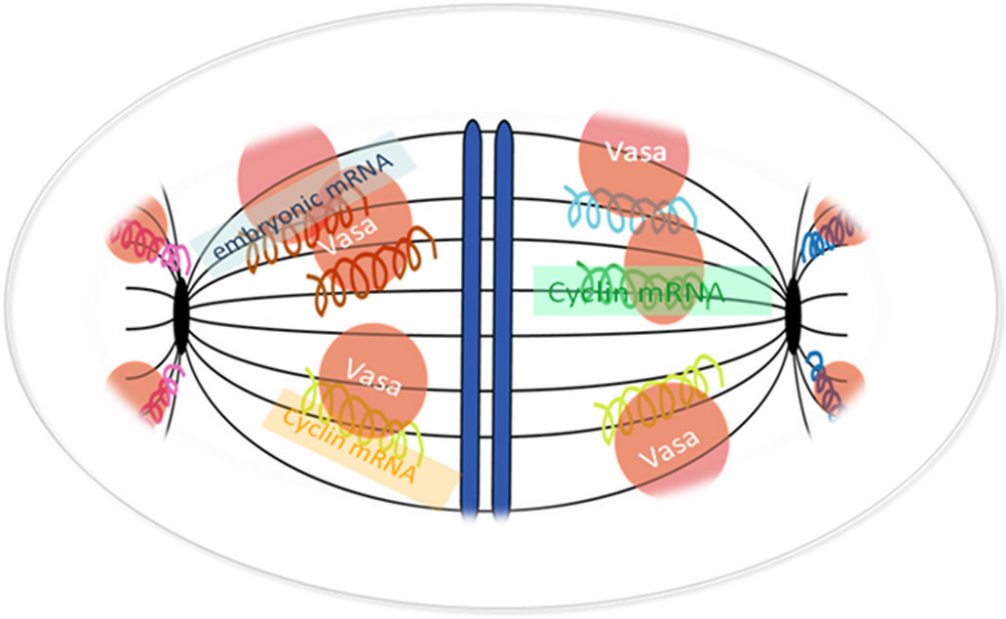

Fig. 3.

Hypothetical function of Vasa on spindles. Vasa is recruited on spindles during M-phase to locally regulate the mitotic cyclins and other mRNAs for rapid cell cycling in sea urchin embryonic cells.

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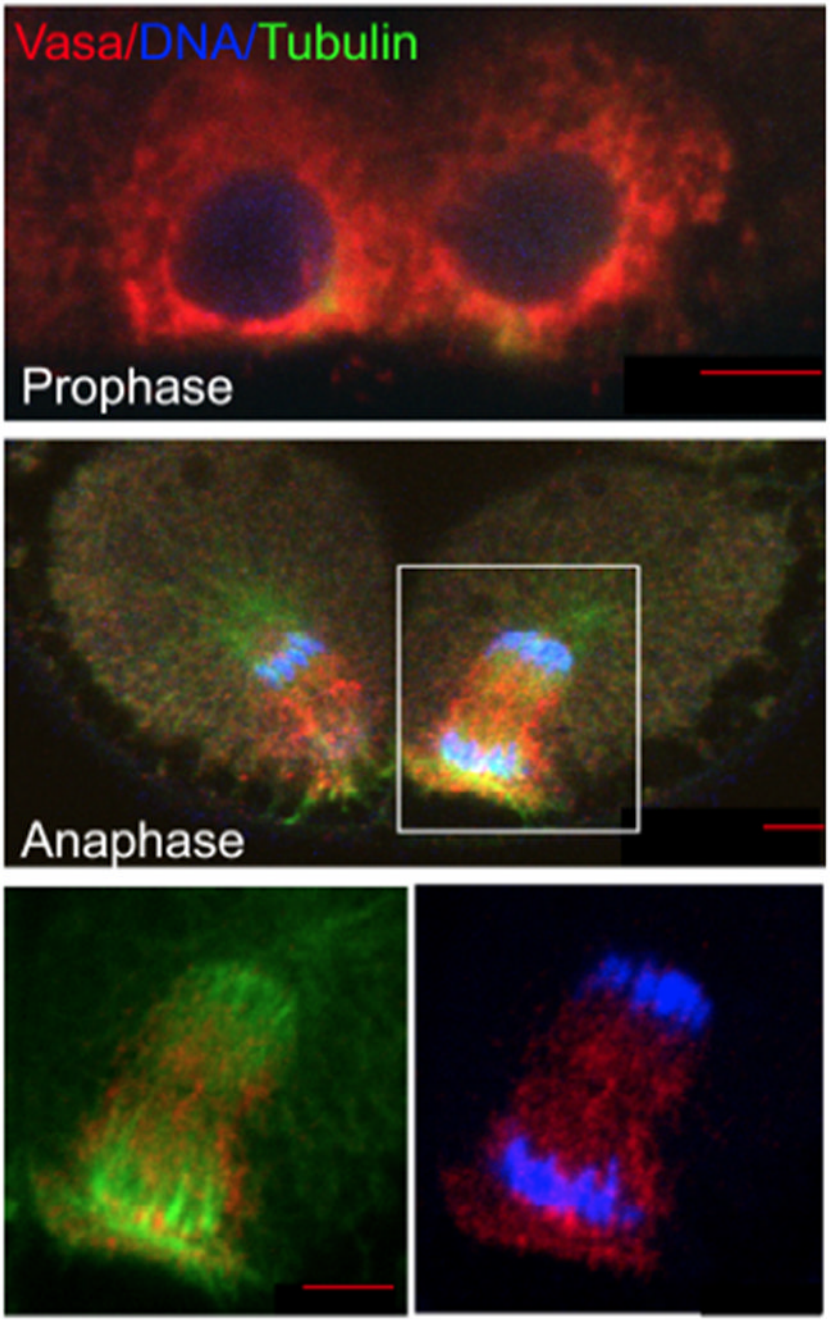

Fig. 4.

Adapted diagram from Yajima and Wessel (2011b). Vasa distribution during the unequal division during the 8- to 16-cell transition. At prophase, Vasa localizes to microtubules that are located at the vegetal pole just prior to an asymmetric division. At anaphase, Vasa on the vegetal-side is maintained, whereas on the opposite pole it disappears. Two bottom panels are magnified views of the white squared field. Scale bar, 5 μm.

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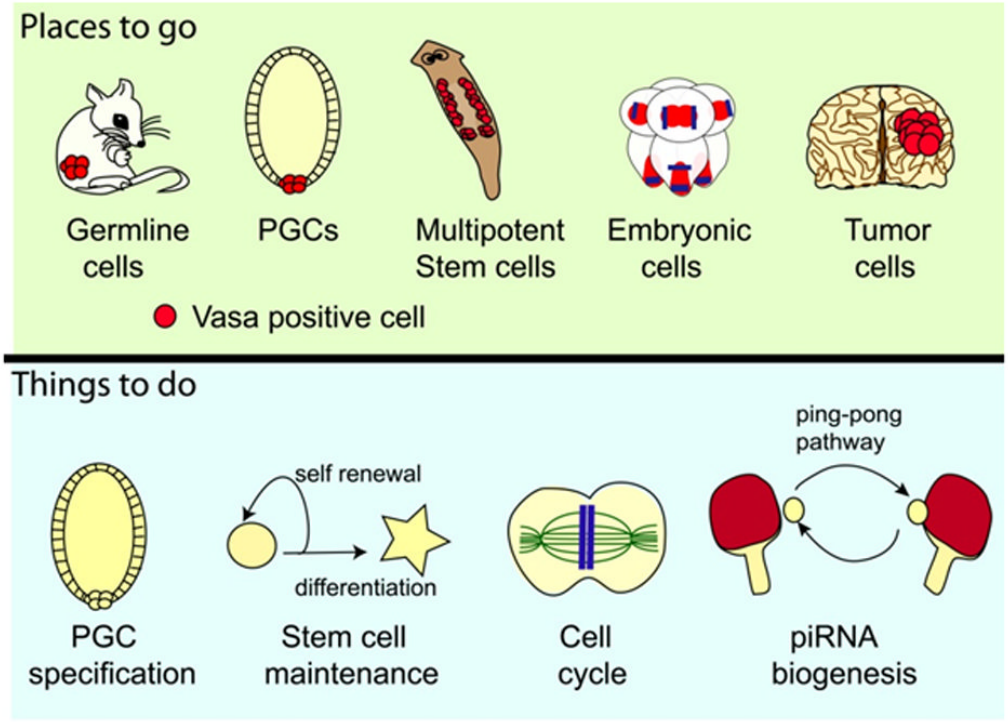

Fig. 5.
Places to go, things to do. Summary of Vasa expressing cells and known diversity of Vasa functions.