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LETTER

Caenorhabditis elegans Aurora A kinase AIR-1 Is Required for Postembryonic Cell Divisions and Germline Development

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Summary: Many kinases are required for progression through the eukaryotic cell cycle. The Aurora kinases comprise a highly conserved family of serine/threonine kinases that have been implicated in chromosome segregation and cytokinesis in several organisms. We have isolated a sterile *Caenorhabditis elegans* mutant in which the majority of the locus encoding the Aurora A kinase *air-1* has been deleted. Complementation tests with previously isolated sterile mutations in the *air-1* genetic interval demonstrate that the *air-1* and *let-412* loci are identical. Previous analysis of AIR-1 function by RNA-mediated interference (RNAi) has shown that AIR-1 is required for embryonic survival. The characterization of the three sterile *air-1* mutant alleles described here extends these studies by revealing an allelic series that differentially affects postembryonic cell divisions and germline development. genesis 34:244–250, 2002.

Key words: AIR-1; Stu; Aurora kinase; cell division; meiotic chromosomes; *let-412*

INTRODUCTION

Mitosis is regulated at many steps by a number of different protein kinases. The founding members of the Aurora kinase family, *Drosophila* Aurora and budding yeast Ipl1p, were both identified in screens for mitotic defective mutants (Chan and Botstein, 1993; Glover *et al.*, 1995). Aurora homologs have since been found in a variety of species (Giet and Prigent, 1999). The yeasts each harbor a single Aurora kinase (Chan and Botstein, 1993; Petersen *et al.*, 2001), whereas most metazoan species express two (commonly referred to as Aurora A and B) (Giet and Prigent, 1999; Nigg, 2001). The Aurora A kinases are associated with mitotic centrosomes and are required for mitotic spindle formation (Schumacher *et al.*, 1998a; Giet and Prigent, 1999; Hannak *et al.*, 2001). In contrast, the Aurora B kinases are recruited to chromosomes in prophase and translocate to the central spindle microtubules at anaphase (Adams *et al.*, 2001). Interference with Aurora B expression or function leads to defects in chromosome segregation and cytokinesis (Schumacher *et al.*, 1998b; Terada *et al.*, 1998; Giet and Glover, 2001).

Caenorhabditis elegans AIR-1 Is Encoded by the *let-412* Locus

Our previous studies used RNA-mediated interference (RNAi) to examine the function of the *C. elegans* Aurora A kinase AIR-1 during embryogenesis. *air-1(RNAi)* embryos display severe defects in chromosome segregation that ultimately result in lethal aneuploidy (Schumacher *et al.*, 1998a). The primary defect appears to be a failure in centrosome maturation (Schumacher *et al.*, 1998a; Hannak *et al.*, 2001). To further address the role of AIR-1 during development, we employed a PCR-based screen (Liu *et al.*, 1999) to isolate an *air-1* mutant allele, *vw5,* that deletes the majority of the *air-1* coding region. DNA sequencing of this allele revealed that the deletion removed the first six of seven *air-1* exons (K07C11.2) and the first two exons of the neighboring gene, K07C11.9. RNAi of K07C11.9 (performed as described in Methods) revealed no visible phenotype for this locus. Given these results as well as the similarity between the *vw5* and *s1598* alleles (see below), the removal of the two exons of K07C11.9 does not appear to contribute to the phenotype observed in *vw5* animals.

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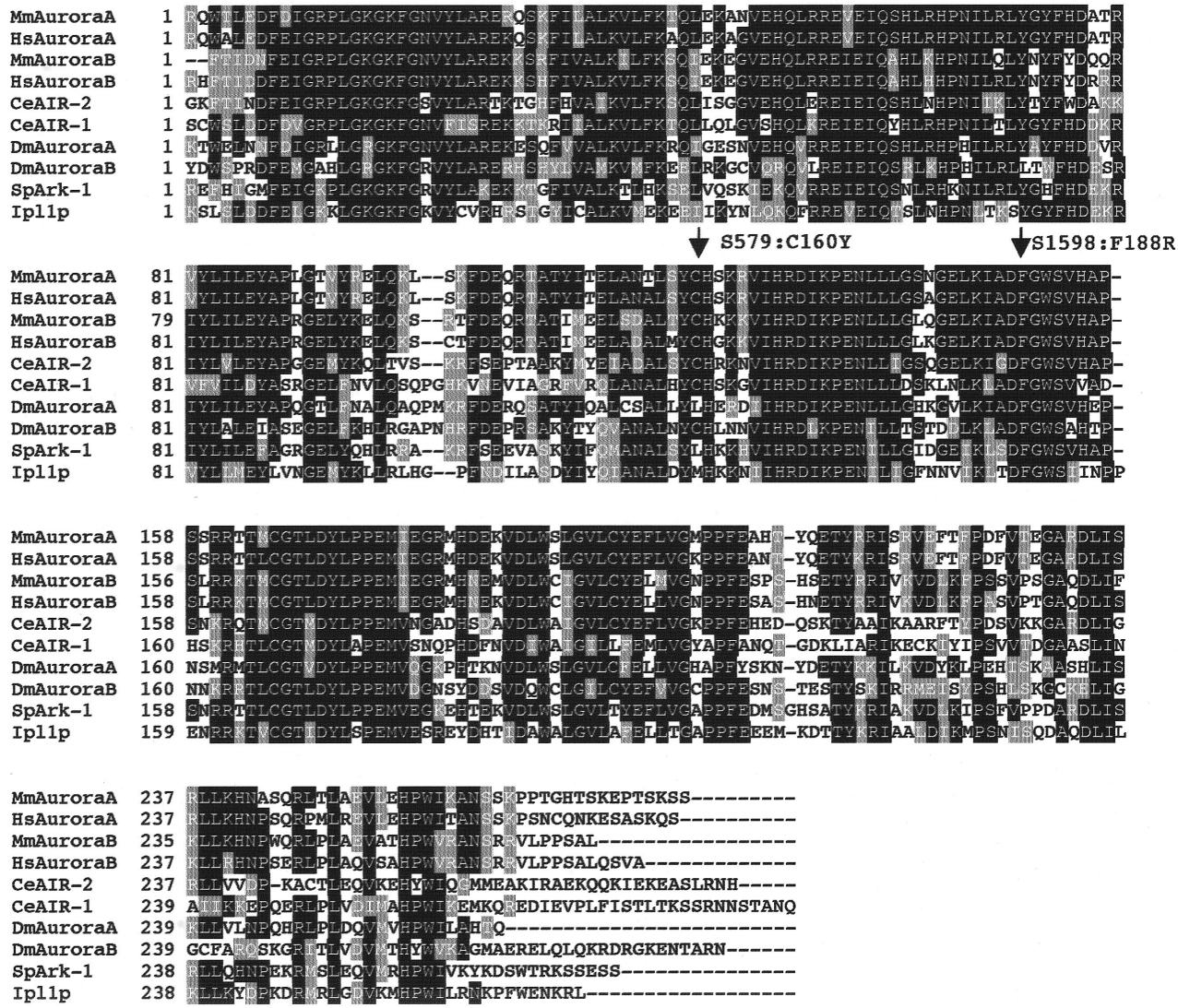

FIG. 1. *let-412* and *air-1* mutations are allelic. An amino acid alignment of the kinase domain of the Aurora kinases from humans (Hs), *M. musculus* (Mm), *D. melanogaster* (Dm), *S. pombe* (Sp), *S. cerevisiae,* and *C. elegans* (Ce) is shown. Identical residues are shaded in black and similar residues shaded in gray. The missense mutations corresponding to *s579* and *s1598* are indicated by arrows above the mutated residues.

While maternal stores of AIR-1 are sufficient for *vw5* homozygotes to complete embryogenesis, adult *vw5* animals display a vulvaless (Vul), sterile and uncoordinated (Stu) phenotype that is typical of many genes that are required for postembryonic cell cycles (O'Connell *et al.*, 1998; Boxem *et al.*, 1999). Complementation tests with other sterile mutants in the *air-1* interval revealed that *vw5* failed to complement alleles of the *let-412* locus *(s1598* and *s579)* (Johnsen and Baillie, 1991).

To confirm that *let-412* and *air-1* are the same locus, we determined the DNA sequence of the *air-1* coding region in the *s1598* and *s579* mutant backgrounds. This analysis revealed that *s1598* and *s579* both harbor missense mutations at highly conserved amino acids within the AIR-1 kinase domain (Fig. 1). *s579* is mutated at a residue that is conserved in all the known Aurora kinases with the exception of *Drosophila* Aurora A, *S. pombe* Ark-1, and budding yeast Ipl1p. *s1598* results in a change at an amino acid which is completely conserved in all family members. The degree of sequence conservation between the affected amino acids correlates very well with the severity of the *s579* and *s1598* alleles, as *s579* displayed a weaker phenotype than *s1598* or *vw5* animals (see below). Given these results, the *let-412* locus has been renamed *air-1*.

AIR-1 Is Differentially Required for Germ Cell Proliferation and Development

To determine the cause of sterility in *vw5, s1598*, and *s579* animals, homozygous *dpy-11 air-1* mutant her-

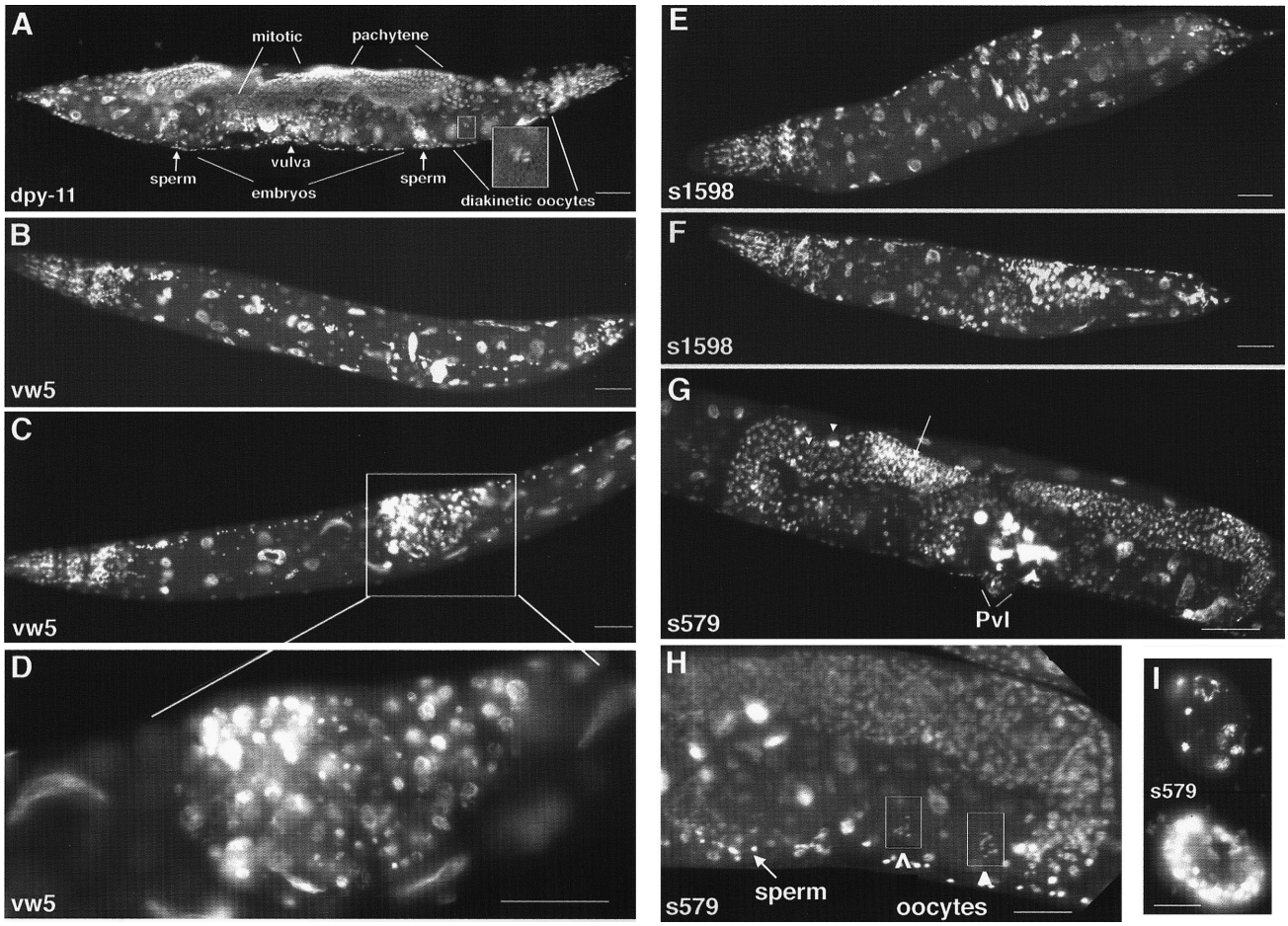

FIG. 2. *air-1* mutants are defective in germline proliferation and development. *dpy-11, dpy-11 air-1(vw5), dpy-11 air-1(s1598),* and *dpy-11 air-1(s579)* hermaphrodites were fixed with ethanol and stained with DAPI. **A:** *dpy-11* animals wild-type at the *air-1* locus have hundreds of germ cells at various stages of differentiation. Mitotic and pachytene germ cell nuclei, diakinetic oocytes, sperm, embryos, and vulva are noted. The inset is a diakinetic oocyte at high magnification; five of the six bivalent chromosomes are visible in this focal plane. Scale bar = 20 μm. **B–D:** *vw5* animals have no vulva or germ cells (**B**), or few germ cells (**C,D**) Scale bar = 20 μm. **E,F:** *s1598* animals are identical to *vw5*. Scale bar = 20 μm. **G:** *s579* animals have near normal levels of germ cells; however, germ cell development is abnormal (arrow, polyploid mitotic germ cell; arrowheads, abnormal pachytene cells, protruding vulva is noted (Pvl)). Scale bar = 20 μm. **H:** *s579* proximal gonads contain sperm (arrow) and diakinetic oocytes (open arrowhead). Some oocytes have 12 univalent chromosomes (closed arrowhead). Scale bar = 10 μm. I) arrested embryos from *s579* mothers. Scale bar = 10 μm.

maphrodites were fixed and stained with DAPI to visualize the germline. *dpy-11* is present in the genetic background because the *dpy-11* locus is linked to *air-1* on Chr I and was used as a marker for outcrossing and complementation tests.

The hermaphrodite gonad is comprised of two mirror-image arms that enclose a common syncytial cytoplasm that is populated by hundreds of germ cell nuclei (Fig. 2A). The nuclei undergo mitotic proliferation at the distal end of the gonad and pass through the various stages of meiotic prophase (pachytene, diplotene, diakinesis) as they progress proximally toward the vulva. The proximal gonad contains cellularized oocytes that each have six highly condensed bivalent chromosomes arrested in diakinesis of meiotic prophase I (Fig. 2A, Inset: five of the six bivalents can be distinguished in a single focal plane of this oocyte). Individual oocytes then undergo meiotic maturation and are ovulated into the spermatheca where they are fertilized. The fertilized oocytes then pass into the uterus where they continue to develop before being released into the environment through the vulva.

DAPI staining of *vw5* and *s1598* homozygotes revealed a nearly complete failure in germ cell proliferation and no vulval cells (Figs. 2B–F, 3). Some *vw5* and *s1598* mutant animals had no apparent germ cells (Fig. 2B,E), whereas others had only a small number (Fig. 2C,D,F). In contrast, gonads of *s579* homozygotes were filled with normal numbers of germ cells and either had a normal vulva (52%, n = 26), no vulva (11%, n = 26), or had a protruding vulva (Pvl) (37%, n = 26) (Figs. 2G, 3). Although *s579* gonads displayed near normal levels of

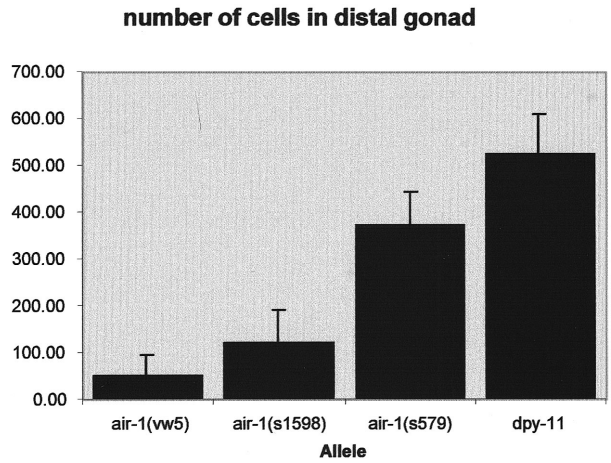

FIG. 3. Quantitative comparison of germ cell proliferation in *air-1* mutants. The number of germ cells in the distal gonads of DAPI stained *dpy-11, dpy-11 air-1(vw5), dpy-11 air-1(s1598)* and *dpy-11 air-1(s579)* adult hermaphrodites (24 h post L4) were scored and averaged with respect to n = the number of animals counted for each genotype. *dpy-11* (n = 7), *dpy-11 air-1(vw5)* (n = 17), *dpy-11 air-1(s1598)* (n = 32), and *dpy-11 air-1(s579)* (n = 16). Germ cells were counted from the distal tip to the bend of the gonad where nuclei become cellularized, approx. 120 μm. Error bars represent standard deviation.

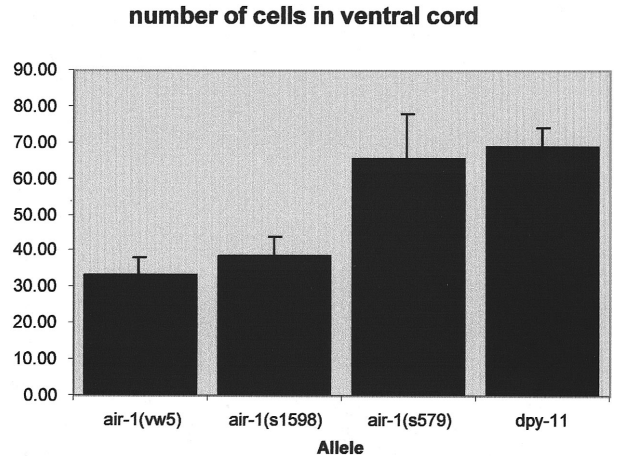

FIG. 4. Quantitative comparison of ventral cord nuclei in *air-1* mutants. The number of ventral cord nuclei in DAPI stained *dpy-11, dpy-11 air-1(vw5), dpy-11 air-1(s1598),* and *dpy-11 air-1(s579)* adult hermaphrodites (24 h post L4) were scored and averaged with respect to n = the number of animals counted for each genotype. *dpy-11* (n = 17), *dpy-11 air-1(vw5)* (n = 17), *dpy-11 air-1(s1598)* (n = 32), and *dpy-11 air-1(s579)* (n = 16). Error bars represent standard deviation.

germ cell proliferation, the cells did not undergo a wild-type pattern of development (Fig. 2G,H). The mitotic region contained many polyploid nuclei (Fig. 2G, arrow) and the pachytene nuclei had an abnormal appearance (Fig. 2G, arrowheads). Although 85% of *s579* proximal gonads contained diakinetic oocytes and 93% had sperm (n = 26), many of these oocytes clearly had more than six chromosomes (50%, n = 28 oocytes). Some of these oocytes appeared to have 12 or more univalent chromosomes (14%, n = 28 oocytes) (Fig. 2H, solid arrowhead). Similar abnormal oocytes have been observed in *air-1(RNAi)* animals that escape embryonic lethality (J. Schumacher, unpubl.). These observations suggest that chromosome segregation defects in the mitotic region of the gonad can result in aneuploid oocytes, or that the AIR-1 kinase may play a role in homolog pairing and sister chromatid cohesion. Interestingly, univalent chromosomes are found in oocytes with ectopic activity of the *C. elegans* Aurora B kinase AIR-2 and meiotic chromosomes are not properly separated in oocytes that lack AIR-2 (Rogers *et al.*, 2002). The meiotic cohesion protein REC-8 appears to be a specific substrate of AIR-2, supporting a direct role for the AIR-2 kinase in the cohesion of chromosomes during meiosis I and II (Rogers *et al.*, 2002). Our current results suggest that Aurora A kinase AIR-1 may also play a role in these events.

Although gametogenesis is clearly abnormal in *s579* animals, 67% went on to produce dead embryos (n = 26) (Fig. 2I). This suggests that a number of *s579* oocytes are competent for fertilization. However, the resultant fully penetrant embryonic lethality could be due to defects in the oocyte or a failure in the embryonic divisions reminiscent of *air-1(RNAi)* embryos (Schumacher *et al.*, 1998a).

AIR-1 Is Required for Division of the Ventral Cord Cells

In addition to being vul and sterile, *vw5* and *s1598* animals were also uncoordinated. This phenotype is often associated with an abnormal number of cells in the postembryonically derived ventral cord (O'Connell *et al.*, 1998; Boxem *et al.*, 1999). To determine whether *vw5*, *s1598*, and *s579* animals were defective in the ventral cord cell divisions, well-separated ventral cord nuclei were counted in DAPI stained *dpy-11* and *dpy-11* animals homozygous for mutations in the *air-1* locus. This analysis revealed that *vw5* and *s1598* mutants had far fewer ventral cord nuclei than found in *dpy-11* animals (*dpy-11 vw5*: avg. = 34 cells, n = 17; *dpy-11 s1598*: avg. = 39 cells, n = 32; *dpy-11*: avg. = 69 cells, n = 17). The number of ventral cord nuclei in *dpy-11 s579* animals (avg. = 66 cells, n = 16) was comparable to *dpy-11* animals (Figs. 4, 5). *vw5* and *s1598* ventral cord nuclei were often polyploid (Fig. 5, arrows) or appeared to be connected to one another by chromatin bridges (data not shown).

AIR-1 Mutants Are Defective in Vulva Development

The *C. elegans* vulva is derived from the mitotic progeny of the vulva precursor cells (VPCs) P5p-P7p (Greenwald, 1997). As stated above, *air-1, vw5,* and *s1598* mutant hermaphrodites are vul, whereas *s579* animals can be vul, pvl, or have a functional vulva. To more

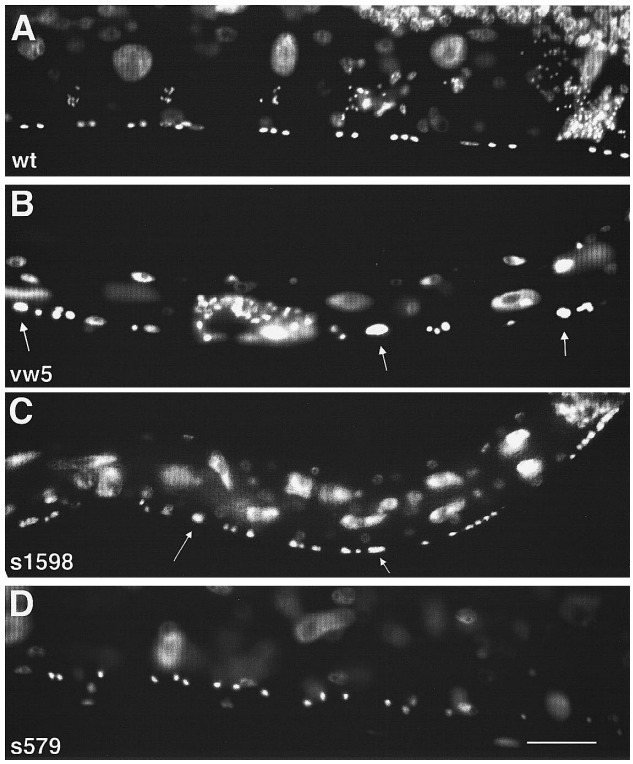

FIG. 5. Cell divisions of ventral cord cells are defective in *air-1* mutant animals. To count the number of cells in the ventral cord, wild-type (wt), *air-1(vw5), air-1(s1598),* and *air-1(s579)* hermaphrodites were fixed with ethanol and stained with DAPI. (**A**) wt and (**D**) *s579* animals have comparable numbers of ventral cord cells, whereas *vw5* and *s1598* animals have fewer (**B,C**). Polyploid nuclei (arrows) are found in *vw5* and *s1598* ventral cords (**B,C**). Scale bar = 10 μm.

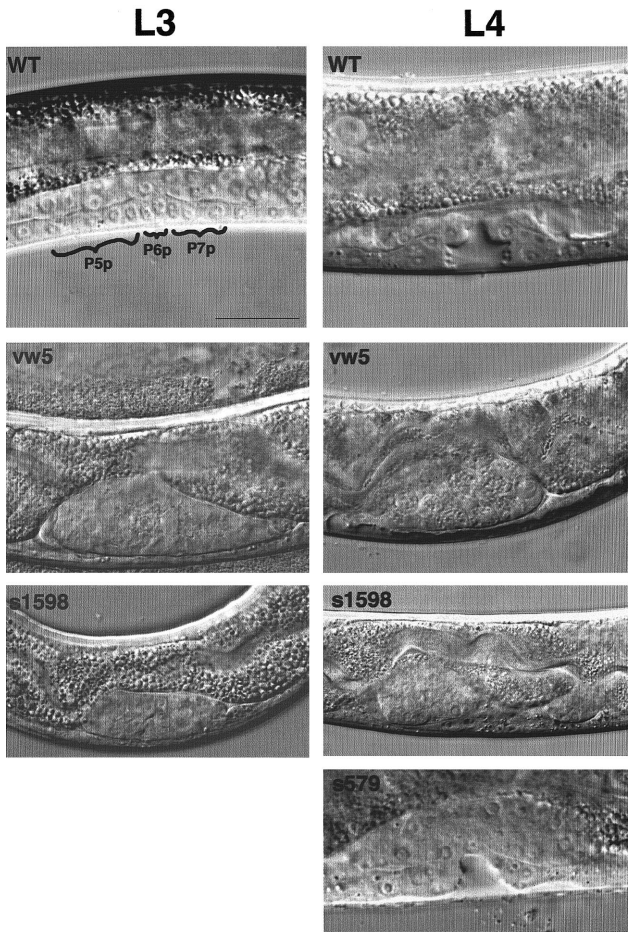

FIG. 6. *air-1* mutant animals are defective in the divisions of the VPCs. To examine vulva development, wild-type (wt), *air-1(vw5), air-1(s1598),* and *air-1(s579)* L3 and L4 larvae were mounted and examined by DIC optics. Left column, L3 larvae; right column, L4 larvae. In all panels the ventral side is down. WT panel: brackets indicate position of the descendent of P5p, P6p, and P7p. Scale bar = 10 μm.

closely inspect the cause of the vulva defects, we examined wild-type and *air-1* mutant animals with DIC optics. In wild-type L3 larvae, the descendents of the VPCs are easily distinguishable along the ventral side of the animal (Fig. 6). By the L4 stage, the developing vulva has invaginated and takes on a characteristic morphology (Fig. 6). In contrast, VPC progeny are not distinguishable along the ventral side of *vw5* (n = 3) or *s1598* (n = 4) L3 mutants and there is no structure resembling the developing vulva in *vw5* (n = 13) or *s1598* (n = 12) L4 mutant larvae (Fig. 6). In agreement with the presence of a functional or protruding vulva in the majority of the *s579* mutant animals (89%, n = 26), the developing vulva is readily apparent in *s579* L4 larvae (n = 6); however, in many cases it appears to have an abnormal morphology (4/6) (Fig. 6). The vulva defects revealed in this analysis correlates very well with the data presented above for the requirement of the AIR-1 kinase in the mitotic proliferation of the germline and the cells of the ventral cord. The complete absence of VPC progeny in the strongest *air-1* alleles implies that AIR-1 is also necessary for the mitotic divisions of the vulva lineage.

Altogether, our results suggest that the kinase encoded by the *C. elegans air-1* locus is required for the postembryonic divisions that give rise to the germline, ventral cord, and vulva. Although not all postembryonic cell lineages were examined in this study, we expect that the majority, if not all, of postembryonic divisions are likely to be defective. While *vw5* and *s1598* are likely to be null or near-null alleles, *s579* appears to be only partially defective. Although the *s579* mutant kinase is functional enough to mediate proliferation of the germline, ventral cord, and some vulva development, proper germ cell differentiation and meiotic chromosome integrity appears to be very sensitive to AIR-1 activity. In conclusion, the examination of this *air-1* allelic series has revealed that the AIR-1 kinase is required for postembryonic mitotic divisions and may have a previously unrecognized role in germline development and meiotic chromosome dynamics.

MATERIALS AND METHODS

Caenorhabditis elegans Strains

The Bristol strain N2 was used as the standard wild-type strain. Culturing, handling, and genetic manipulations of *C. elegans* were performed using standard procedures (Brenner, 1974). The following strains were used in this analysis (full descriptions can be found at http://elegans.swmed.edu/CGC/): **LGIII:** *dpy-18(e364)*; **LGV:** *dpy-11(e224), unc-46(e177), mom-2(or42), let-474(ss1577), let-411(s223), let-423(s818), let-449-(s1343), mig-6(e1931), let-405(s116), let-335(s1439), let-414(s114), let-408(s827), emb-22(g32ts), rol-3-(e754), let-412/air-1(s579), let-412/air-1(s1598), air-1(vw5), let-456(s1479), let-413(ss1451), let-436-(s1403), let-464(s1504), let-424(s384), let-414(s114), let-470(s1581), let-445(s1419), let-408(s827), srf-9(dv4).* Chromosomal rearrangements, deletions, and extrachromosomal arrays were as follows: eT1(III;V), nT1(IV;V), sDf20(V), sDf35(V), sDf29(V), vwEx1[rol-6(su1006d) air-1(+)].

PCR-Based Deletion Screen

The *air-1(vw5)* deletion mutation was isolated using a PCR-based screen of DNA from a frozen library of *C. elegans* mutagenized with 4,5′8-trimethylpsoralen (TMP). The library was screened by two rounds of PCR using nested primers flanking the *air-1* coding region. The first-round PCR primers were: 5′–GTCGACAGCAGTTGCTC-TACCC–3′ and 5′–GCTCCGTCAGTCACAACACTTGG–3′. Second-round primers were: 5′–CAGGCATTCATCAAGAAC-GATCG–3′ and 5′–GCAAACCGGCACACGCATCTCG–3′. A single *air-1* deletion mutant was identified and isolated by sib selection (Liu *et al.*, 1999). The mutant was outcrossed at least six times and balanced over eT1(III;V) or nT1(IV;V). DNA sequencing of this allele revealed that the deletion removed the first six of seven *air-1* exons (K07C11.2) and the first two exons of the neighboring gene, K07C11.9. RNAi of K07C11.9 revealed no visible phenotype for this locus.

RNA-Mediated Interference

Sense and antisense RNA corresponding to the entire coding region or exons 1 and 2 of K07C11.9 were synthesized from the appropriate DNA templates using T7 and T3 In Vitro Transcription Kits (Ambion, Austin, TX) according to the manufacturer's instructions. Equal volumes of each single-stranded RNA were mixed, placed at 65°C to denature the RNAs, and slow cooled at room temperature to anneal the complementary strands. The K07C11.9 dsRNAs or a control dsRNA that resulted in embryonic lethality (*air-2*) were microinjected into the gonads of L4 and adult N2 hermaphrodites. The injected animals were incubated at 15°C, 20°C, or 25°C and examined 24–48 h postinjection for any visible phenotypes.

Genetic Analysis

In order to accurately place the *air-1* locus on the genetic map, the *air-1* deletion allele was placed in trans to the following deficiencies in the *air-1* genetic interval (LG V, 1.0): sDf20, sDf35, sDf29. This analysis revealed that the *air-1* locus is within the interval deleted by sDf35 and not by the other deficiencies. Various lethal mutations that had been mapped with respect to sDf35 were tested for complementation with the *air-1* deletion allele. These included: *mom-2(or42), let-474(ss1577), let-411(s223), let-423(s818), let-449(s1343), mig-6(e1931), let-405(s116), let-335(s1439), let-414(s114), let-408(s827), emb-22(g32ts), rol-3(e754), let-412/air-1(s579), let-412/air-1(s1598), air-1(vw5), let-456(s1479), let-413(ss1451), let-436(s1403), let-464(s1504), let-424(s384), let-414(s114), let-470(s1581), let-445(s1419), let-408(s827), srf-9(dv4)*. The *air-1* allele complemented the sterile phenotype of all tested mutations except alleles of *let-412 (s1598* and *s579). s1598* and *s579* were subsequently outcrossed at least six times and balanced over eT1 or nT1.

DNA Sequence Analysis

All DNA sequencing was performed by the UTMDACC DNA Sequencing and Analysis Facility (supported by the core NCI Grant CA-16672). The breakpoints of the *air-1* deletion were determined by sequencing the first-round PCR product. To determine the genetic lesions in *s1598* and *s579*, single worm PCR (Williams *et al.*, 1992) was performed using primers specific for the *air-1* coding region. All PCR products were cloned into the TOPO II cloning vector (Invitrogen, Carlsbad, CA) and sequenced using primers specific for the *air-1* locus.

Microscopy

To quantify the number of ventral cord and germ cells in *dpy-11* and *dpy-11air-1* mutant animals, adult hermaphrodites (24 h after L4 stage) were fixed with 100% ethanol and stained with DAPI to visualize DNA. For DIC microscopy, staged animals were mounted in M9 media supplemented with sodium azide (0.1%) on agarose pads. Images were captured using a Spot digital camera (Diagnostic Instruments, Sterling Heights, MI) attached to a Leica DMR compound microscope (Meyer Instruments, Houston, TX) equipped for DIC and fluorescence microscopy.

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