Gene Expression Patterns 9 (2009) 31–36

Contents lists available at ScienceDirect

Gene Expression Patterns

journal homepage: www.elsevier.com/locate/gep

Expression patterns of cadherin genes in *Drosophila* oogenesis

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ARTICLE INFO

Article history:
Received 7 August 2008
Received in revised form 28 August 2008
Accepted 3 September 2008
Available online 11 September 2008

Keywords:
Drosophila
Cadherin
Oogenesis
Gene expression
Morphogenesis
Adhesion
Pattern formation
Follicle cell
Epithelium

ABSTRACT

In *Drosophila* oogenesis, the follicular epithelium that envelops the oocyte is patterned by a small set of inductive signals and gives rise to an elaborate three-dimensional eggshell. Several eggshell structures provide sensitive readouts of the patterning signals, but the formation of these structures is still poorly understood. In other systems, epithelial morphogenesis is guided by the spatial patterning of cell adhesion and cytoskeleton genes. As a step towards developing a comprehensive description of patterning events leading to eggshell morphogenesis, we report the expression of *Drosophila* cadherins, calcium-dependent adhesion molecules that are repeatedly used throughout development. We found that 9/17 of *Drosophila* cadherins are expressed in the follicular epithelium in dynamic patterns during oogenesis. In late oogenesis, the expression patterns of cadherin genes in the main body follicle cells is summarized using a compact set of simple geometric shapes, reflecting the integration of the EGFR and DPP inductive signals. The multi-layered composite patterning of the cadherins is hypothesized to play a key role in the formation of the eggshell. Of particular note is the complex patterning of the region of the follicular epithelium that gives rise to the dorsal appendages, which are tubular structures that serve as respiratory organs for the developing embryo.

1. Results and discussion

Epithelial morphogenesis is characterized by the sequential execution of a core set of programmed stereotypical cell movements and shape changes, which result from the differential expression of cytoskeleton and adhesion genes (Pilot and Lecuit, 2005; Ray Keller, 2003; Schock and Perrimon, 2002; Tepass, 1999). In *Drosophila* oogenesis, the follicular epithelium, which surrounds the nurse cells and oocyte, serves as an established model for studying epithelial patterning and morphogenesis, amenable to live imaging and sophisticated genetic perturbations (Berg, 2005; Dorman et al., 2004; Duffy, 2002; Wu et al., 2008). Particularly striking morphogenetic events occur during the later stages of oogenesis, when the main body follicle cells (MBFCs), which encapsulate the oocyte, undergo a series of cell shape changes and movements to form and secrete an elaborate three-dimensional eggshell, including tubular structures called dorsal appendages (DAs) that project out from the main eggshell body and act as respiratory tubes for the developing embryo (Hinton, 1969; Ward and Berg, 2005; Waring, 2000).

Little is known about the expression, regulation, and function of effector genes required for proper eggshell morphogenesis. As one important class of effector molecules in epithelial morphogenesis, cadherins are glycoproteins that mediate Ca^{2+}-dependent cell–cell adhesion and contain multiple, conserved cadherin domains (Halbleib and Nelson, 2006; Tepass et al., 2000). The *Drosophila* genome encodes 17 cadherins (Hill et al., 2001; Hynes and Zhao, 2000) with representative members in each of the known subgroups of cadherins, excluding desmosomal cadherins (Hill et al., 2001; Tepass et al., 2000) (Table 1). *Drosophila* cadherins are subdivided into classical cadherins, defined by the presence of a conserved catenin-binding domain (Shotgun/DE-Cad, Cadherin-N/DN-Cad, and CadN2), and nonclassical cadherins, which lack any recognizable catenin-binding domain (Fung et al., 2008; Hill et al., 2001; Tepass et al., 2000). Nonclassical cadherins consist of Fat-like cadherins (Fat, Fat2, Dachsous), seven-pass transmembrane cadherins (Starry Night/Flamingo), Calsyntenin cadherins (Calsyntenin-1), protein kinase cadherins (Ret and Cad96Ca), and currently uncategorized cadherins (Cad74A, Cad86C, Cad87A, Cad88C, Cad89D, Cad96Cb, and Cad99C) (Fung et al., 2008; Hill et al., 2001).

As a first step to providing a comprehensive analysis of the differential expression of potential effector molecules in the follicular epithelium, we have constructed a gene expression atlas of *Drosophila* cadherin genes. Nine expression patterns were identified in the follicle cells throughout all stages of oogenesis, five of which are newly reported: *fat2*, *Cad86C*, *Cad87A*, *Cad88C*,

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doi:10.1016/j.gep.2008.09.001

Table 1
Cadherin classification and expression in the *Drosophila* genome

Gene	Subcategory	Expression		Selected references
		Early S<10	Late S>10	
Shotgun (shg)/DE-Cad	Classical	+	+	Godt and Tepass (1998), Niewiadomska et al. (1999), Oda et al. (1997), and Pacquelet and Rorth (2005)
Cadherin-N (CadN)/DN-Cad	Classical	+	–	Tanentzapf et al. (2000))
CadN2	Classical	–	–	Yonekura et al. (2007)
Starry Night/Flamingo (stan/fmi)	Seven-pass transmembrane	–	–	Oda et al. (1997)
fat2	Fat-like	+	+	Castillejo-Lopez et al. (2004)
fat	Fat-like	–	–	Castillejo-Lopez et al. (2004), Demontis et al. (2006), and Saburi et al. (2008)
dachsous (ds)	Fat-like	–	–	Tanoue and Takeichi (2005)
Calsyntenin-1 (cals)	Calsyntenin	+	+	Vogt et al. (2001)
Ret oncogene (Ret)	Protein kinase	–	–	Abrescia et al. (2005), Fung et al. (2008), and Sugaya et al. (1994)
Cad74A	Nonclassical	+	+	Zartman et al. (2008)
Cad86C	Nonclassical	–	+	Schlichting and Dahmann (2008)
Cad87A	Nonclassical	+	+	Fung et al. (2008), Hill et al. (2001), and Tepass et al. (2000)
Cad88C	Nonclassical	–	+	Demontis et al. (2006), Fung et al. (2008), and Lovegrove et al. (2006)
Cad89D	Nonclassical	–	–	Hill et al. (2001) and Tepass et al. (2000)
Cad96Ca	Protein kinase	–	–	Demontis et al. (2006)
Cad96Cb	Nonclassical	–	–	Lovegrove et al. (2006)
Cad99C	Nonclassical	+	+	D'Alterio et al. (2005), Schlichting et al. (2005). and Schlichting et al. (2006)

and *cals*. Expression patterns for two genes, *Cad74A* and *Cad99C* were reported in the literature previously (D'Alterio et al., 2005; Schlichting et al., 2006; Zartman et al., 2008). Finally, expression of *DE-Cad* and *DN-Cad* were examined earlier, but later stages of mRNA expression were not previously shown explicitly (Becam et al., 2005; Godt and Tepass, 1998; Niewiadomska et al., 1999; Schnorr and Berg, 1996). Below we describe the expression patterns and group them into spatial and temporal categories.

1.1. Spatial and temporal expression of cadherin genes

Gene expression patterns of the nine detected cadherin genes can be subdivided into two temporal stages: early oogenesis, before stage 10, as defined by (Spradling, 1993), and later stages, stages 10–14, when the diversity of patterns is greater (Fig. 1 and Table 1). During early oogenesis, seven cadherins were detected: *DE-Cad* (Fig. 1A1 and inset), *DN-Cad* (Fig. 1B1), *fat2* (Fig. 1C1), *cals* (Fig. 1D1 and inset), *Cad74A* (Fig. 1E1, arrows), *Cad87A* (Fig. 1G1) and *Cad99C* (D'Alterio et al., 2005; Schlichting et al., 2006) (Fig. 1I1).

Late FC morphogenesis begins in stage 10B when the main body follicle cells (MBFCs) undergo a series of cell shape changes and movements to form the dorsal anterior eggshell structures (Fig. 2A): the operculum, which is formed by midline cells (M), the micropyle, which is shaped by the centripetal migrating follicle cells consisting of a row of anterior follicle cells (A) and border cells (Montell et al., 1992), and dorsal appendages, which are formed by the roof (R) and floor (F) primordia, two cell populations that form the dorsal and ventral sides of each of the DAs (Dorman et al., 2004; Ward and Berg, 2005). While the patterning by EGFR and DPP signaling and the morphogenesis of the follicle cells has been studied extensively, less is known about the effectors of FC morphogenesis (Berg, 2005; Dorman et al., 2004; Horne-Badovinac and Bilder, 2005; Ward and Berg, 2005; Wu et al., 2008). Two-dimensional expression patterns are most easily categorized in stages 10–12, when the midline, floor, and roof cells have already been specified, but before significant three-dimensional shaping of the dorsal appendages occurs (Yakoby et al., in press). The dynamics of the nine expressed cadherin genes during oogenesis are discussed below.

1.1.1. Shotgun/DE-Cad

Strong *shotgun* (*DE-Cad)* expression consistently precedes major morphogenetic movements of the FCs. *DE-Cad* is expressed in both the germline and the somatic follicle cells and is required for anchoring the somatic stem cell in the germarium niche (Song and Xie, 2002) and positioning the oocyte in the posterior of the egg chamber (Godt and Tepass, 1998; Gonzalez-Reyes and St. Johnston, 1998). *DE-Cad* is also expressed in the border cells during stage 9 before border cell migration (Niewiadomska et al., 1999; Oda et al., 1997) (Fig. 1A1, arrowhead).

DE-Cad shifts from being expressed in an anterior band, corresponding to the centripetal migrating follicle cells (CMFCs) at stage 10A, to strong expression in the midline cells and weak expression in the floor and roof cells during stage 10B, when these cells apically constrict and intercalate (Fig. 1A2–A5; James et al., 2002). The pattern continues to show differential *DE-Cad* expression in the cells forming the dorsal anterior eggshell structures during stages 11 and 12. *DE-Cad* is also expressed in the posterior FCs, which form the aeropyle (Fig. 1A5, inset).

1.1.2. Cadherin-N/DN-Cad

DN-Cad is expressed during early oogenesis in the FCs (Fig. 1B1). The adherens junctions contain both DN-cadherin and DE-cadherin until stage 10 (Tanentzapf et al., 2000), which is unusual because *DE-Cad* and *DN-Cad* are not usually co-expressed (Horne-Badovinac and Bilder, 2005). *DN-Cad* expression is not detected in the FCs after stage 9 (Fig. 1B2–B6).

1.1.3. fat2

fat2 is expressed during the early stages of oogenesis, but the resolution of the assay is not sufficient to determine if it is the germline or the FCs (Fig. 1C1). Later at stage 10A, *fat2* shifts from being expressed uniformly in all MBFCs and nurse cells to being expressed very strongly in the floor cells and weakly in the roof cells (Fig. 1C2–C6) with loss of expression in the other MBFCs during stages 10B–14. The transcript is found in the apical region of FCs. Fat2 shares similarity to *Drosophila* Fat in the extracellular domain, but lacks the PCP signaling domain found in the intracellular domain of Fat (Castillejo-Lopez et al., 2004; Saburi et al., 2008). *fat2* has been implicated in tube formation throughout embryogenesis, including the trachea, salivary glands, proventriculus, and hindgut (Castillejo-Lopez et al., 2004). Based on cultured cell studies and

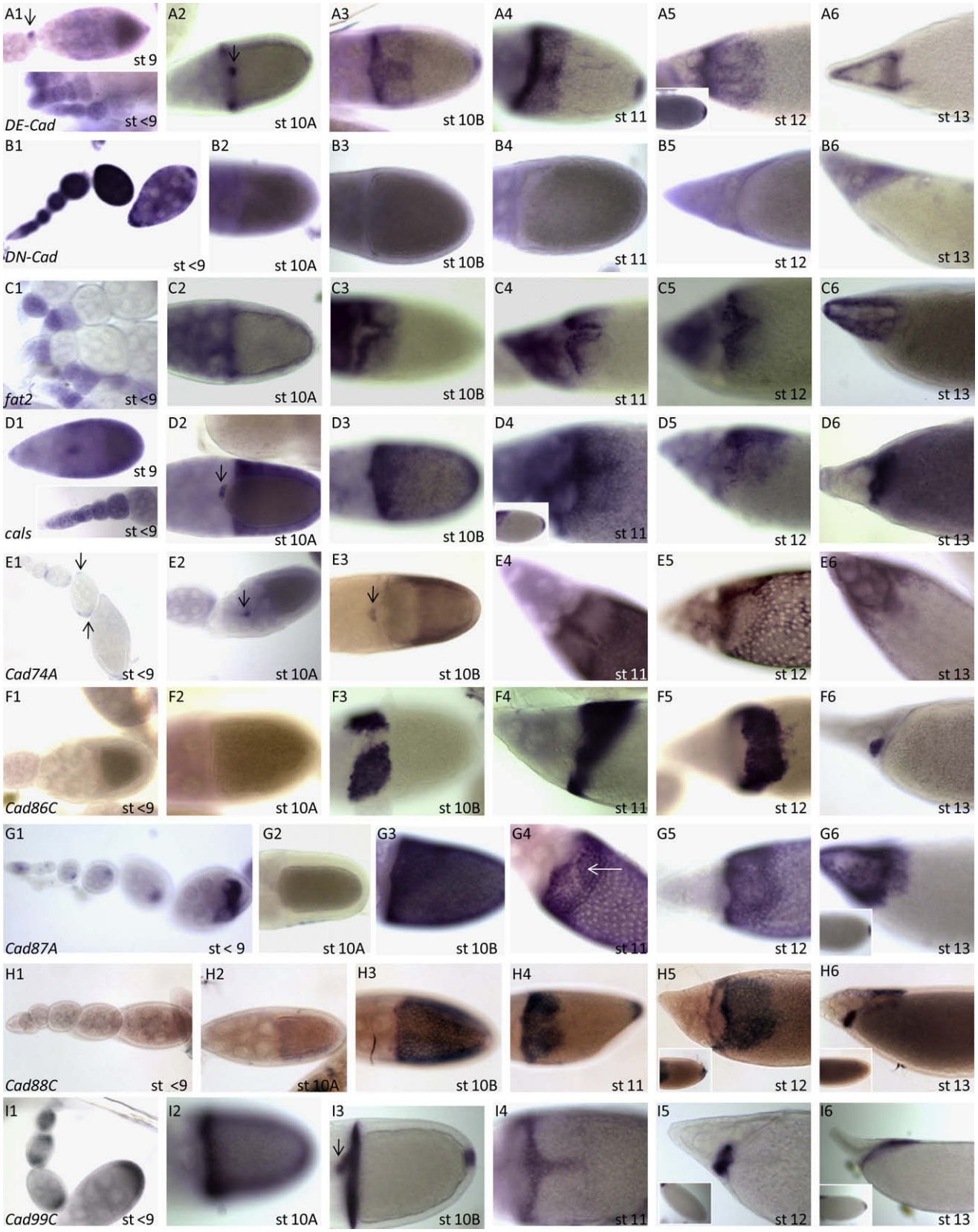

Fig. 1. Expression patterns of cadherin genes in *Drosophila* oogenesis. Expression of cadherin genes at stages <10 (1), stage 10A (2), stage 10B (3), stage 11 (4), stage 12 (5), and stage 13 (6) for (A) *DE-Cad*, (B) *DN-Cad*, (C) *fat2*, (D) *Calsyntenin-1 (cals)*, (E) *Cad74A*, (F) *Cad86C*, (G) *Cad87A*, (H) *Cad88C*, and (I) *Cad99C*. Inserts show expression in the earliest stages or the posterior in late stages. Dark arrows point to visible staining in the border cells. (G4) Arrow points to repression in the floor cells.

in vivo loss-of-function analysis, Castillejo-Lopez et al. propose that *fat2* does not play a role in adhesion but, perhaps due to its size, acts as a spacer for the tube lumen (Castillejo-Lopez et al., 2004).

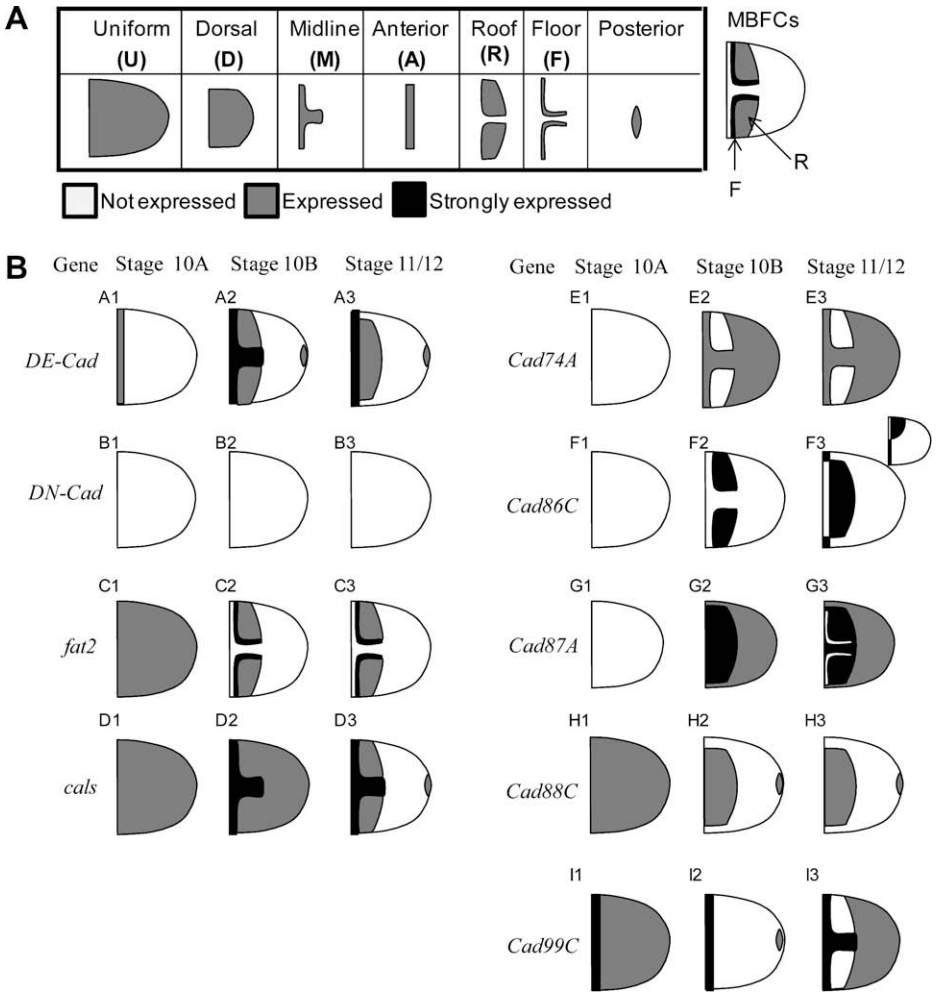

Fig. 2. Pattern classification and abstracted expression. (A) Pattern annotation scheme for the main body follicle cells (MBFCs), as proposed in (Yakoby et al., in press). Patterns have been described using three differential levels of expression: Expression not detected (no shading), basal expression (grey) and strong expression (black). (B) Abstracted expression patterns are shown as cartoons for the nine cadherin genes. Roof versus floor plus roof expression was determined by counting the number of cells between the patches (2 cells for floor plus roof, 4 for roof patterns).

1.1.4. Calsyntenin-1 (cals)

Calsyntenin-1 shows expression during stages 7–9 in the MBFCs and in the border cells during migration (Fig. 1D1 and inset). *Calsyntenin-1* (*cals*) expression is uniform during stage 10A (Fig. 1D2), but is restricted to the dorsal region at stage 10B (Fig. 1D3) with stronger expression in midline in stage 11/12 (Fig 1D4–D5). Expression is also detected in the posterior FCs during the late stages (Fig. 1D4, inset).

1.1.5. Cad74A

The expression patterns for *Cad74A* (Fig. 1E1–E6) was published previously (Zartman et al., 2008). *Cad74A* is expressed in the polar cells during early oogenesis (Fig. 1E1, arrows). During late oogenesis, *Cad74A* is expressed in all FCs contacting the oocyte in stage 10B, except for the roof cells where high levels of the zinc-finger transcription factor Broad (Deng and Bownes, 1997; Dorman et al., 2004; Tzolovsky et al., 1999; Ward and Berg, 2005) are sufficient to repress *Cad74A* expression. Overexpression of *Cad74A* in the roof cells results in short, flattened DAs due to the hindered migration of roof cells, suggesting a possible role in the remodeling of the adherens junctions or modulation of the apical membrane. The *Cad74A* null allele shows reproducible but incompletely penetrant DA defects (Zartman et al., 2008).

1.1.6. Cad86C

Cad86C is not expressed (Fig. 1F1 and F2) until stage 10B, when it is strongly detected in the roof cells and in a ventral band, corresponding to high Broad levels (Fig. 1F3–F6) (Dorman et al., 2004). During stages 11 and 12, a strong hybridization signal is detected in the roof cells and the midline cells separating the roof primordia. Overexpression of *Cad86C* in the imaginal discs is sufficient to cause apical constriction (Schlichting and Dahmann, 2008), suggesting that it may be involved in apical constriction of the roof cells during dorsal appendage formation.

1.1.7. Cad87A

Identified as a possible vertebrate *Cadherin23* homolog (Fung et al., 2008), *Cad87A* is expressed in the oocyte during the early stages of oogenesis (Fig. 1G1). During stage 10B, *Cad87A* is expressed uniformly in the FCs, with stronger expression in the dorsal anterior (Fig. 1G3). During stage 11/12, expression is particularly strong in the dorsal region except for the floor cells (Fig 1G4, arrow).

1.1.8. Cad88C

Cad88C expression is not detectable in the follicle cells up to stage 10A (Fig. 1H1 and H2). In stage 10B, all follicle cells contacting the oocyte express *Cad88C* (Fig. 1H3). In stages 11–12, expres-

sion is confined to dorsal anterior cells and posterior cells (Fig. 1H4–H5).

1.1.9. Cad99C

The expression and function of *Cad99C* was previously reported and is required for microvilli morphology and the proper secretion of the vitelline membrane (D'Alterio et al., 2005; Schlichting et al., 2006). *Cad99C*, a homolog of Protocadherin 15 and required for microvilli morphology, is expressed in stages 4–8 in the anterior and posterior follicle cells and in the follicle cells that migrate to contact the oocyte at stage 9 (D'Alterio et al., 2005; Schlichting et al., 2006) (Fig. 1I1). However, we also find that *Cad99C* is repressed in the roof cells at stage 11/12 (Fig. 1I4).

1.2. Towards a spatial atlas of morphogenesis

Implementation of the morphogenetic program in several contexts has been found to be robust to the single loss-of-function perturbations of many effector proteins (Kleve et al., 2006; Lovegrove et al., 2006; Schlichting and Dahmann, 2008; Zartman et al., 2008). In the case of our recent study on *Cad74A* (Zartman et al., 2008), the lack of a strongly penetrant phenotype led us to hypothesize that perhaps other cadherins are expressed in similar expression patterns. In an unbiased pilot screen for expression patterns of morphogenesis genes, we found that a significant fraction (9/17) of the *Drosophila* cadherin superfamily is differentially expressed during *Drosophila* oogenesis. Our analysis of mRNA expression addresses the variety of spatial patterns but does not account for gene or protein activity, which must be examined to understand the lack of visible phenotypes in loss-of-function perturbations.

Remarkably, cadherin expression patterns are especially diverse during the later stages of oogenesis (stages 10–14). To provide abstractions of patterns, we have recently proposed an annotation system which compactly describes gene expression patterns during stages 10–12 of oogenesis (Fig. 2A and B; Yakoby et al, in press). The geometric annotation terms are derived from the underlying signaling dynamics of the EGFR and BMP signaling pathways and summarize all known FC expression patterns during mid/late oogenesis (Goentoro et al., 2006; Lembong et al., 2008; Yakoby et al., in press). All expression patterns are summarized as Boolean combinations of seven primitive shapes: uniform (U), dorsal (D), midline (M), anterior (A), roof (R), floor (F), and posterior (P) (Fig. 2A). Three principle operations are performed to construct more complex patterns representing the integrate output of EGFR and DPP signaling: union (∪), difference (\) or intersection (∩) (Table 2; Yakoby et al., in press). In the case where the union operation leads to a loss of spatial structure, the analog operation of addition is used (+), to indicate a stronger nonzero level of expression.

Of particular interest, several cadherins show complex overlapping dynamic expression patterns in the dorsal anterior FCs: midline, floor, and roof cells, which are responsible for forming the operculum and DAs (Fig. 2B). Remarkably, no two cadherin genes share an identical expression profile, suggesting that the robustness of morphogenesis is not due to an absolute redundancy in cadherin expression.

Cad74A (stages 10B–12) and *Cad99C* (stage 11/12) show repression in the roof cells relative to expression in the MBFCs (Fig. 2B). *DE-Cad*, *fat2*, and *cals* show high expression in the floor cells and graded expression in the roof cells. *Cad86C* initially shows strong expression only in the roof cells, whereas *Cad87A* shows relative repression in the floor cells. *Cad88C* also shows specific expression to the dorsal anterior cells. Dissecting the regulatory network that leads to such spatial pattern diversity will provide insight into how roof, floor, and midline cell identities are maintained during late oogenesis. In particular, the relationship between previously mentioned cadherins and Broad, which is a zinc-finger transcription factor highly expressed in the roof cells (Deng and Bownes, 1997; Dorman et al., 2004; Ward and Berg, 2005; Yakoby et al., 2008), will need to be investigated further and compared to the regulation model of *Cad74A* as well as the expression of other classes of effector molecules (Kleve et al., 2006; Laplante and Nilson, 2006; James et al., 2002; Zartman et al., 2008).

The expression patterns found in this study adds further weight to the possibility that a "combinatorial code" of cadherin expression may play a role in segregating and maintaining different cell sub-populations in the FCs (Foty and Steinberg, 2005; Fung et al., 2008; Lovegrove et al., 2006; Schlichting and Dahmann, 2008). For example, similar overlapping patterns for the nonclassical cadherins are found in other developmental contexts (Lovegrove et al., 2006; Schlichting and Dahmann, 2008). Based on previous reports and the new patterns identified in this study, we hypothesize that the partially overlapping syn-expression of a subset of adhesion genes ensures robust morphogenesis of the dorsal appendages, providing built-in degeneracy to the epithelial folding code. Deciphering and parsing the spatial grammar of morphogenesis during DA formation will require manipulating the relative expression of sets of adhesion genes. Comparison of the relative overlaps between cadherin expression patterns in other models of morphogenesis will provide a necessary test for the universality of an epithelial folding code that converts spatial patterns of gene expression into mechanical properties and a final morphology.

2. Experimental procedures

2.1. Whole-mount in situ hybridization

cDNA clones for *fat*, *fat2*, *Ret*, *Cad74A*, *Cad87A*, *Cad96Ca*, and *Cad99C* were gifts of M. Halfon. cDNA for *dachsous* came from the *Drosophila* Genomics Resource Center (Bloomington, IN). Primers used to amplify the remaining cadherin genes from cDNA obtained from the ovary are listed in Table 3. Products from PCR amplification were cloned using a StrataClone PCR Cloning Kit (Stratagene). For *Cad88C*, the underlined restriction sites (Table 3) for BamHI and

Table 2
Geometric annotations of cadherin patterns in the MBFCs

Gene	Stage 10A	Stage 10B	Stage 11/12
DE-Cad	A	(M+D) ∪ P	A ∪ D ∪ P
DN-Cad	–	–	–
fat2	U	R ∪ F	R ∪ F
cals	U	U + M	(M+D) ∪ P
Cad74A	–	U\R	U\R
Cad86C	–	R	(A ∪ D)\(A ∩ D)
Cad87A	–	U + D	(U + D)\F
Cad88C	U	D + P	D ∪ P
Cad99C	U+A	A ∪ P	U\R

Table 3
Primers used for mRNA probe generation

Gene	Forward primer	Reverse primer
DE-Cad	GCCCAATGGTCACAAGAACT	CTCGTTTTGGAGCACAGTGA
DN-Cad	GTCAATCGTCCGGTTCAGTT	CACCGATTTTCCCTCAGTGT
CadN2	TGCCAATCTCAGCGTTACAG	CCATCATCCAGCGTTTTCTT
Starry Night/Flamingo	CTTTTCGTCTCCGTCAAAGC	GATCGAGGGAGGCATATTGA
Calsyntenin-1	TGGCAACACCGATAATGAAA	CTCCTATGCATTGCGACAGA
Cad88C	CGGGATCCCTTTAGCATTCG AGAGATCG	GGGGTACCTTTAGCCACTGATG CTGCTC
Cad89D	CAAGCCCAATACACCGAACT	ACTTTGCTAGGTCCCGGTTT
Cad86C	CACTGAATCTGGACGCTGAA	GCCAGAAGAGCACCTTGTTC
Cad96Cb	AATCTCGAGCGGATTCCTTT	GAGGGCCATGCTACTACTGG

Asp718 were used for cloning the PCR product into pBluescript and the clone was sequenced. Clones were designed to be between 900 and 1200 bases. Clones were then sequenced (GeneWiz) and BLASTed against the *D. melanogaster* genome (FlyBase) to confirm clone identity and orientation. Digoxigenin-labeled RNA probes were made from the cDNA clones. During the in situ experiments, a previously tested control probe was used to ensure the quality of in situ hybridization assay. The in situ hybridization protocol is optimized for assaying gene expression in the follicle cells and was the same as previously described (Wang et al., 2006; Yakoby et al., 2008) without an RNase treatment step. *Ore R* and *y w* were used for the in situ hybridization experiments.

Acknowledgements

We thank M. Halfon for providing cDNA clones for several cadherin genes and the DGRC (Bloomington, IN) for cDNA clones for *ds* and C. Bristow for helpful comments on the manuscript. J.J.Z. is supported by the Fannie and John Hertz Foundation and the Princeton Wu fellowship. This work has been supported by the following NIH Grants: P50 GM071508 and R01 GM078079 to S.Y.S.

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