RESEARCH COMMUNICATION

Retraction of the *Drosophila* germ band requires cell–matrix interaction

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Integrins and laminins are important mediators of cell–matrix interactions in both vertebrates and invertebrates. Here, we show that germ-band retraction in the *Drosophila* embryo, during which the tail end of the embryo retracts to its final posterior position, allows the investigation of cell spreading and lamellipodia formation in real time in vivo. We demonstrate that $\alpha 1$, 2 laminin and α PS3 β PS integrin are required for the spreading of a small group of cells of the amnioserosa epithelium over the tail end of the germ band. We further implicate a role for this spreading in the process of germ-band retraction.

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Integrins and laminins have been shown to function in signaling, in stable adhesion of differentiated epithelia to the basement membrane, and in transient adhesion during cell spreading and migration (Brown et al. 2000; De Arcangelis and Georges-Labouesse 2000; Schöck and Perrimon 2002b). Laminins are extracellular matrix molecules consisting of a long α chain and shorter β and γ chains arranged in a cross-like structure (Martin et al. 1999). One of their most prominent interaction partners are the integrins, which form transmembrane heterodimers of α and β subunits. In *Drosophila* there are two α , one β , and one γ laminin genes, and five α and two β integrin genes (Brown et al. 2000; Hynes and Zhao 2000; Fig. 1A). Laminins and integrins have partially overlapping, but not identical phenotypes, because, even though they bind to each other, they also have various nonshared interaction partners (Brown et al. 2000; De Arcangelis and Georges-Labouesse 2000). In *Drosophila*, several morphogenetic processes require the presence of integrins, for example the formation of muscle attachments and wing-blade adhesion (Roote and Zusman 1995; Brown et al. 2000). Similar to integrin mutants, mutations in *Drosophila* laminin are associated with wing-blade adhesion and muscle-development defects (Henchcliffe et al. 1993; Yarnitzky and Volk 1995; Martin et al. 1999). Further, both $\alpha 1$, 2 laminin and β PS integrin mutants show a transient twisting of the germ band (Roote and Zusman 1995; Martin et al. 1999).

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Another process that is affected by the absence of integrins, but which has not been studied up to now, is germ-band retraction (Leptin et al. 1989; Walsh and Brown 1998). Germ-band retraction occurs in mid-embryogenesis after germ-band extension and prior to dorsal closure. It takes ~2 h and involves large-scale epithelial movements, by which the tail end of the germ band, or embryo proper, moves to its final posterior position (Martinez Arias 1993). At the end of this process, the amnioserosa, a squamous epithelium, has spread out and covers the yolk sac on the dorsal side of the embryo. We have shown previously that the amnioserosa and the germ band move as one coherent sheet during retraction. In addition, amnioserosa cells undergo a dramatic shortening along their dorsoventral axis during retraction (Schöck and Perrimon 2002a). Most interestingly, retraction is associated with lamellipodia formation and cell spreading of the posterior cell row of the amnioserosa, which causes the amnioserosa to slightly overlap the tail end of the germ band (Schöck and Perrimon 2002a; Fig. 4E, below). The lamellipodia of the amnioserosa spread on the apical extracellular matrix of the germ band, which is deposited by the end of embryonic stage 10 (Tepass and Hartenstein 1994).

To explore the mechanisms underlying the observed spreading of the amnioserosa, we analyzed mutants exhibiting germ-band retraction defects. Here, we show that $\alpha 1$, 2 laminin and α PS3 β PS integrin are required to generate the overlap of the amnioserosa over the tail end of the germ band, and that they interact genetically during retraction. Live imaging of embryos completely null for β PS integrin revealed that lamellipodia formation is disrupted and that there is no cell–matrix adhesion between the amnioserosa and the tail end of the germ band.

Results and Discussion

Analysis of maternal-effect U-shaped mutations

To determine whether germ-band retraction is a suitable system to study cell–matrix interactions and lamellipodia formation, we searched for genes involved in the cellular functions required for retraction. We screened a collection of zygotic lethal mutations for mutants associated with maternal-effect U-shaped embryonic phenotypes (Perrimon et al. 1996; N. Perrimon, unpubl.). U-shaped cuticle phenotypes are characterized by the dorsal location of abdominal denticle belts 6–8 and are indicative of a failure of retraction (Frank and Rushlow 1996). One of the mutants we uncovered, *4Y18*, shows a U-shaped phenotype when both the zygotic and the maternal contributions are removed using the germ-line clone method (Chou and Perrimon 1992; Fig. 1B,C). Mapping experiments revealed that *4Y18* fails to complement mutations at the *wing blister* (*wb*) locus, which encodes $\alpha 1$, 2 laminin, a polypeptide of the trimeric laminins (Martin et al. 1999). Sequencing of PCR-amplified *4Y18* genomic DNA revealed a mutation causing a truncation after 1427 amino acids, which deletes the trimerization domain of Wb (Fig. 1D). The mutant Wb protein appears to be unstable, because it was not detected with an N-terminal anti-Wb antibody in homozygous mutant embryos (data not shown), suggesting that *wb*^{*4Y18*} is a null allele.

Figure 1. Mutation in $\alpha 1, 2$ laminin disrupts germ-band retraction. (A) Mutations in a number of *Drosophila* integrin and laminin subunits are available as follows: *if*, *inflated*; *lanA*, *lamininA*; *mew*, *multiple edematous wings*; *mys*, *myospheroid*; *scb*, *scab*; *wb*, *wing blister*. *Wb* contains an arginine-glycine-aspartic acid (RGD) motif. The nomenclature of the *Drosophila* α laminin subunits is based on their similarities to the vertebrate $\alpha 1$ and $\alpha 2$ or $\alpha 3$ and $\alpha 5$ subunits, respectively (Martin et al. 1999). (B) Dark-field micrograph of the cuticle of a wild-type embryo with its distinctive ventral denticle belts. The position of abdominal segment eight (A8) in this panel, as well as in C and H, is indicated by an asterisk. (C) A *wb*^{4Y18} embryo that lacks both maternal and zygotic (m/z) $\alpha 1, 2$ laminin activity does not undergo retraction. (D) The *wb*^{4Y18} mutation truncates the $\alpha 1, 2$ laminin protein after amino acid position 1427. (E) Wild-type embryo at late stage 12 stained with anti- α Spectrin antibody. The amnioserosa slightly overlaps the tail end of the germ band (arrow; see also Fig. 4A). (F,G) Anti- α Spectrin antibody staining of a late stage 12 *wb*^{4Y18} m/z mutant embryo. A confocal surface section (F) shows the lack of overlap of the amnioserosa over the tail end of the germ band (arrow). A confocal z-section 20- μ m deeper (G) reveals multilayering of parts of the amnioserosa (arrowheads) and a few amnioserosa cells that still remain on top of the germ band (arrow). (H) *lanA*⁹⁻³² m/z embryos have variable embryonic defects that range from poor cuticle differentiation to milder phenotypes, such as segment fusions/deletions and twisting (shown here).

$\alpha 1, 2$ laminin mutant shows germ-band retraction defects

Consistent with our finding that the *wb*^{4Y18} maternal and zygotic (m/z) mutants exhibit U-shaped cuticle phenotypes, m/z mutant embryos in the β PS integrin *myospheroid* (*mys*) also show a U-shaped phenotype (Leptin et al. 1989; Fig. 5A, below). In addition, time-lapse recordings show that the U-shaped cuticle defect of *wb*^{4Y18} and *mys*^{XG43} m/z mutant embryos results from a failure of germ-band retraction (data not shown; Fig. 3B, below).

At the cellular level, *wb*^{4Y18} m/z mutant embryos exhibit pleiotropic defects most evident in the amnioserosa. Anti- α Spectrin antibody stainings showed that, similar to *mys* m/z mutants (see below), the overlap of the amnioserosa over the tail end of the germ band is defective, whereas cell-shape changes in the amnioserosa occur normally (Fig. 1, cf. F and wild type, E). In addition, the amnioserosa epithelium frequently exhibits multilayering, suggesting polarity defects (Fig. 1G, arrowheads). Laminin functions in epithelial polarity in other systems, for example during the development of the mammalian kidney epithelium, in which laminin is required to provide polarity cues (O'Brien et al. 2001). We cannot address where exactly $\alpha 1, 2$ laminin is required to mediate germ-band retraction, because it is a secreted protein. However, the *wb*^{4Y18} amnioserosa defects indicate that cell-matrix interactions are required between the amnioserosa and the underlying yolk sac and/or between the overlapping part of the amnioserosa and the apical extracellular matrix of the germ band.

We also analyzed the only other *Drosophila* α laminin, $\alpha 3, 5$ laminin, encoded by *lamininA* (*lanA*; Kutsche-Gullberg et al. 1992; Henchcliffe et al. 1993; Martin et al. 1999). We generated m/z mutant embryos of the null mutant *lanA*⁹⁻³² to remove a weak maternal contribution that had not been analyzed previously (Kutsche-Gullberg et al. 1992), and observed a range of defects. In more severe cases, embryos disintegrate before the onset of retraction, making it impossible to assess the contribution of *lanA* to germ-band retraction. However, in milder cases, *lanA* m/z embryos exhibit fusion or deletion of segments and twisting, but no retraction defects (Fig. 1H).

α PS3 integrin mutant exhibits germ-band retraction defects and interacts with $\alpha 1, 2$ laminin

Another mutant (5/38) identified in our screen for maternal-effect U-shaped phenotypes, was mapped to the *scab* (*scb*) locus, which encodes the α PS3 integrin subunit (Stark et al. 1997; Fig. 2A). α PS3 integrin mutants have dorsal closure defects, and, in addition, α PS3 is expressed in morphogenetically active tissues, such as the salivary glands and the tracheal pits during their invaginations, as well as in the amnioserosa (Stark et al. 1997). To assess whether α PS3 zygotic expression, particularly in the amnioserosa, is required for retraction, we analyzed zygotic *scb* mutant embryos and found that they have U-shaped phenotypes as well. The penetrance of these phenotypes is low, but is enhanced (about three-fold) in embryos transheterozygous for *scb* and a deficiency that deletes both α PS3 and the closely related α PS4 integrin (Fig. 2C), suggesting functional redundancy of these two closely related subunits. We have not yet assessed the contribution of the remaining two unrelated α PS integrin subunits, α PS1 and α PS2.

To determine whether $\alpha 1, 2$ laminin interacts with integrins *in vivo*, we tested for genetic interactions with a hypomorphic viable β PS integrin allele (*mys*^{nj42}) that shows a wing blister phenotype (Walsh and Brown 1998). Wing blisters arise due to a failure of cell-matrix interactions required for the apposition of two epithelia that form the wing blade (Walsh and Brown 1998). Consistent with the similarity of the *mys* and *wb* embryonic phenotypes, removal of one copy of *wb* in a hemizygous β PS integrin mutant background results in a significant in-

Figure 2. Mutation in α PS3 integrin disrupts germ-band retraction and interacts with α 1, 2 laminin. (A) Dark-field micrograph of the cuticle of a *scb^{5J38} m/z* embryo with defective germ-band retraction. A8 is indicated by an asterisk. (B) Homozygous *mys^{nj42}* females were crossed to *wb^{4Y18}/CyO* or *lanA⁹⁻³²/TM3* males. The number of hemizygous *mys^{nj42}* progeny with wing blisters is indicated by percent. (C) Frequency of germ-band retraction defects in various zygotic mutant backgrounds. Note the synergistic increase of retraction defects in *wb scb* double mutants compared with the respective single mutants, and the increase in the *scb/scb wb/+* mutant. (B,C) “n” refers to the number of flies or embryos scored. (D) Quantification of spreading assay: α PS1, α PS2m8, or α PS3 integrin genes were cotransfected with actin5CEGFP into nonadherent S2 cells and spread on indicated surfaces. The frequency of spread cells as a percentage of actin5CEGFP-transfected cells is shown. Bars indicate standard deviations from three independent experiments (>150 cells counted in each experiment). (E–G) α PS integrin-transfected S2 cells plated on α 1, 2 laminin. Merger of green (cotransfection marker actin5CEGFP) and red (filamentous actin stained with AlexaFluor 568 phalloidin) channels. (E) S2 cells transfected with α PS1 integrin do not spread. S2 cells spread after transfection of α PS2m8 (F) or α PS3 (G) integrin.

crease in wing blisters (Fig. 2B), whereas removal of one copy of *lanA* does not cause an increase (Henchcliffe et al. 1993). We next used the low penetrance of germ-band retraction defects in α PS3 integrin mutants to test for genetic interactions with α 1, 2 laminin mutants during retraction. We analyzed zygotic *wb scb* double mutants and zygotic *scb* mutants with only one copy of *wb*. In both cases, we observed a significant increase in the frequency of U-shaped cuticle defects (Fig. 2C). These results show that α PS3 integrin and α 1, 2 laminin interact in vivo during germ-band retraction.

α PS3 β PS integrin-containing S2 cells spread on α 1, 2 laminin

We next asked whether α PS3 β PS integrin is able to mediate cell–matrix interactions with α 1, 2 laminin, using a cell-spreading assay in tissue culture. Schneider’s line 2

(S2) *Drosophila* cells are particularly suitable for such assays because, even though they express β PS integrin, they do not spread due to the lack of expression of α PS integrins (Gotwals et al. 1994). The β PS integrin subunit heterodimerizes with α PS1, α PS2, and α PS3 integrin (Gotwals et al. 1994; Stark et al. 1997), and it was shown previously that α PS2 β PS integrin interacts with α 1, 2 laminin in a cell-spreading assay (Graner et al. 1998). We therefore transfected S2 cells with α PS1, the splice variant α PS2m8, or α PS3 and plated them on plates coated with a N-terminal α 1, 2 laminin fragment containing the RGD motif required for interaction with α PS2 β PS to compare their adhesion behavior (Fig. 2D–G). Similar to α PS2 β PS, α PS3 β PS mediates spreading on the N-terminal α 1, 2 laminin fragment, whereas α PS1 β PS does not (Fig. 2D). To assess the contribution of the RGD motif in the observed spreading behavior, we tested spreading on a short fibronectin analog peptide containing the RGD motif (GRGDSPK). Only α PS2 β PS exhibits spreading on this peptide, indicating that the contribution of the RGD motif to spreading of α PS3 β PS is smaller than for α PS2 β PS or is absent (Fig. 2D). Finally, all three integrin heterodimers may also bind to and spread on laminin domains not included in the α 1, 2 laminin fragment used for this spreading assay, as α PS1 β PS integrin-containing cells had been shown previously to spread on full-length α 3, 5 laminin (Gotwals et al. 1994). Altogether, our results demonstrate that α PS3 β PS integrin mediates spreading on α 1, 2 laminin, that these integrin and laminin subunits are required for germ-band retraction, and that they interact genetically.

β PS integrin mutant retracts the germ band only partially

To address more precisely the role of integrins during germ-band retraction, we used live imaging of β PS integrin (*mys*) mutant embryos. We focused our analyses on *mys* mutants, because α integrins must heterodimerize with β integrins in order to function, and *mys* m/z mutants show the highest penetrance of U-shaped cuticle phenotypes. *mys^{XG43} m/z* embryos are completely null for β PS integrin (Leptin et al. 1989), and 65% of the mutants display a severe U-shaped cuticle phenotype (Fig. 5E, below). To outline all cells in time-lapse recordings, we marked embryos with *ubiDE-cadherinGFP*. In paternally rescued maternal *mys* mutant embryos, which were genotyped by the additional GFP expression in the amnioserosa, retraction proceeds normally as in wild-type embryos (Fig. 3A). In contrast, in *mys* m/z mutant embryos, retraction progresses only for a short time, then stops prematurely, which results in an average of two to three abdominal segments remaining on the dorsal side (Fig. 3B). Most cell-shape changes are unaffected; in particular, amnioserosa cells still shorten along their dorsoventral axis (Fig. 3B; data not shown).

β PS integrin mutant does not adhere to the tail end of the germ band and does not form lamellipodia

We then characterized the effects of β PS integrin mutants on cell–matrix adhesion between the posterior part of the amnioserosa and the tail end of the germ band. In *mys* m/z mutants, the amnioserosa no longer overlaps the germ band, but instead, crowds in front of the tail end of the germ band (Fig. 4, cf. B and A). At a slightly

Figure 5. Expression of β PS integrin in the amnioserosa rescues retraction defects. (A) *mys^{XG43} m/z; UASmys*. (B) *mys^{XG43} m/z; Kr-Gal4 UASmys*. (C) *mys^{XG43} m/z; LP1-Gal4 UASmys*. (D) *mys^{XG43} m/z; c381-Gal4 UASTorso^D β PS_{cyt}*. The top row illustrates the expression of the Gal4 lines driving *UASsrcEGFP*. The bottom row depicts typical cuticles of embryos expressing the respective constructs. (E) Rescue efficiency: “n” refers to the number of embryos of the indicated genotype that were scored (see Materials and Methods). Bar, 20 μ m.

In contrast, neither the *UASmys* construct alone, nor the amnioserosal expression of an adhesion-deficient β PS integrin capable only of signaling (Martin-Bermudo and Brown 1999; Martin-Bermudo 2000) rescued the U-shaped phenotype (Fig. 5D,E). These data indicate that β PS integrin expression is required in the amnioserosa, and that the adhesive properties of β PS integrin are most likely required for retraction.

Conclusions

Altogether, we propose that in wild-type embryos, dorsoventral contraction of amnioserosa cells contributes to the extension of germ-band epithelial cells along the dorsoventral axis. This dorsoventral extension of the germ-band epithelium may then promote the retraction of the remaining segments that are still folded back. In the absence of proper laminin/integrin-mediated adhesion, the overlap of the amnioserosa over the tail end of the germ band is defective. We suggest that dorsoventral contraction of the amnioserosa in this mutant situation results in the collapse of the amnioserosa underneath the germ band, leading to an incorrect deployment of forces on the germ band and eventual complete or partial failure of retraction. We further note that the amnioserosa may also not adhere properly to the underlying yolk sac in the integrin mutants, which could also contribute to retraction defects. Our study demonstrates the involvement of α PS3 β PS integrin and α 1, 2 laminin in germ-band retraction and provides a hypothesis for how retraction proceeds.

To date, studies of integrin function during lamellipodia formation and cell spreading have been mostly limited to tissue culture. A wealth of information has been

obtained on the role of these molecules in the information flow from the extracellular matrix to the cytoskeleton during migration (Geiger et al. 2001). The process of germ-band retraction in the *Drosophila* embryo now provides an in vivo model system in which the function of the molecules identified in tissue culture experiments can be systematically tested. Uniquely, this system allows the study of lamellipodia formation and cell spreading in embryos mutant for candidate genes in real time and in vivo. Finally, the characterization of additional mutations associated with germ-band retraction defects will allow the identification of novel players involved in cell-matrix adhesion.

Materials and methods

Fly strains

The following fly strains were used: *Kr-Gal4 40°*, *c381-Gal4*, *LP1-Gal4*, *UASmys*, *UASTorso^D β PS_{cyt}*, *UASsrcEGFP*, *ubiDE-cadherinGFP*, *scb^{5/38}*, *FRTG13*, *scb²*, *mys^{XG43}*, *FRT101*, *mysⁿ¹⁴²*, *lanA⁹⁻³²*, *FRT79DF*, and *wb^{4Y18}*, *FRT40A* (Leptin et al. 1989; Martin-Bermudo and Brown 1996, 1999; Oda and Tsukita 1999, 2000; Deng and Ruohola-Baker 2000; Heranz and Morata 2001). We made the following recombinants using standard genetic techniques: *UASsrcEGFP Kr-Gal4 40°*, *UASTorso^D β PS_{cyt} UASmCD8GFP*, *UASmys UASsrcEGFP*, and *wb^{4Y18} scb²*.

Time-lapse recording

Time-lapse recordings were done as described (Schöck and Perrimon 2002a). To analyze embryos, we used *ubiDE-cadherinGFP*, which is ubiquitously expressed and localizes to adherens junctions, thereby outlining cells (Oda and Tsukita 2001), and *UASsrcEGFP*, which localizes to both cytoplasm and plasma membrane due to the Src myristilation anchor attached to EGFP. *mys* germ-line clone (GLC) embryos were analyzed for lamellipodia by crossing *FM7c*, *Kr-Gal4 UASGFP*; *UASsrcEGFP Kr-Gal4 40°* or *FM7c*, *Kr-Gal4 UASGFP*; *ubiDE-cadherinGFP* males to *mys* GLC females. This allowed us to distinguish paternally rescued embryos expressing nuclear GFP from *m/z* embryos.

Genetic studies

From a GLC screen of more than 6000 zygotic lethal mutations (Perrimon et al. 1996; N. Perrimon, unpubl.), a number of mutants were isolated that exhibit U-shaped embryonic phenotypes. GLCs were produced in females of the genotype *y w hsFLP*; *mutant FRT/ovo^{D1} FRT* using the *ovo^{D1}* system and mated to mutant or wild-type males for determination of paternal rescue as described (Chou and Perrimon 1992).

wb^{4Y18} and *scb^{5/38}* were mapped using deficiencies and alleles of the respective mutants. *4Y18* was mapped to a small region (35A) containing two loci that mutate to lethality; one of them, *wb*, did not complement *4Y18*. As expected, the smallest deficiency *Df(2L)el80f1* did not paternally rescue the *4Y18* GLC mutant. The *wb^{4Y18}* maternal effect U-shaped phenotype is partially penetrant and fully paternally rescueable. Twenty-two percent of the embryos from *wb^{4Y18}* GLC females crossed to *wb^{4Y18/+}* males show a U-shaped phenotype (A7 and A8 on dorsal side), whereas only 2% show this phenotype when *wb^{4Y18}* GLC females were crossed to wild-type males; *5/38* was mapped similarly to 51D-52A, and failed to complement mutants at the *scb* locus.

For the rescue experiments, we crossed *mys* GLC females to *Kr-Gal4 UASsrcEGFP/CyO*; *UASmys/TM3*, *actGFP*, *Ser* males or to *UASmys UASsrcEGFP/+* *LP1-Gal4/+* and *UASTorso^D β PS_{cyt} UASmCD8GFP/+*; *c381-Gal4/+* males, respectively. We sorted aged embryos for the presence of *Kr-Gal4 UASsrcEGFP* and the absence of *TM3*, *actGFP* or for the presence of *UASmys UASsrcEGFP* and *UASTorso^D β PS_{cyt} UASmCD8GFP*, respectively. We then aged these embryos further to allow paternally rescued *mys* GLC embryos to hatch.

Histochemistry and sequencing

Primary antibody stainings with polyclonal rabbit anti-Wb 25632 (1:100) and monoclonal mouse anti- α Spectrin (3A9 from DSHB, 1:10) were performed as described (Pesacreta et al. 1989; Martin et al. 1999). Fluorescein-conjugated goat anti-rabbit IgG (Vector, 1:400) and AlexaFluor 488-conjugated donkey anti-mouse IgG (Molecular Probes, 1:500) were used

as secondary antibody. Genomic DNA of wild-type and *wb^{4Y18}* homozygous mutant embryos was PCR-amplified with 16 primer pairs and sequenced by standard thermal cycle dideoxy sequencing.

Cell-spreading assay

The cell-spreading assay was performed as described (Zavortink et al. 1993). Briefly, a 340-amino-acid His-tagged RGD-containing fragment of $\alpha 1$, 2 laminin was purified under denaturing conditions (Graner et al. 1998). A 3.6-kb *XhoI* *SpeI* full-length cDNA fragment of α PS3 was cloned into pMK33 (Gotwals et al. 1994; Stark et al. 1997). S2 cells were transiently transfected and expression of α PS integrins was induced with 500 μ M CuSO₄ for 24 h. Cells were allowed to spread for 6 h on coated 96 well tissue culture plates and then fixed for 30 min in 4% formaldehyde, and at the same time stained for filamentous actin with AlexaFluor 568 phalloidin (Molecular Probes, 1:50). Experiments were done in triplicate with at least 150 cells counted in each experiment.

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