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COMMENTARY

Another morphogenetic movement on the map: Charting dorsal intercalation in *C. elegans*

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ABSTRACT

Dorsal intercalation is a coordinated cell migration event that rearranges hypodermal cells during *C. elegans* embryogenesis, and that resembles cell intercalation in many systems from flies to mice. Despite its conservation, the molecular mechanisms that govern dorsal intercalation in worms have remained elusive. Here, we comment on our recent publication, Walck-Shannon *et al.*,[1] which begins to spatially map the molecular requirements for intercalation. First, we provide a historical perspective on the factors that have previously hampered the study of dorsal intercalation. Next, we provide a summary of the molecular pathways identified in Walck-Shannon *et al.*,[1] pointing out surprises along the way. Finally, we consider the potential conservation of the molecular pathway we described and discuss future questions surrounding dorsal intercalation. Despite the challenges, dorsal intercalation is a process poised to advance our understanding of cell intercalation during morphogenesis throughout the animal kingdom.

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The uncharted territory: How protrusions function during dorsal intercalation

Dorsal intercalation is a visually striking, coordinated cell movement that rearranges right and left hand dorsal hypodermal cells shortly after their specification in the developing embryo.[2,3] Specifically, 2 rows of cells extend across the dorsal array, as their nuclei migrate contralaterally.[4,5] Shortly after intercalation is complete, the intercalating cells fuse to form a syncytium (hyp7). Drug studies performed nearly 20 y ago indicated that actin is required for dorsal intercalation; electron microscopy further indicated that the tips of cells extend basolaterally during intercalation.[2] However, the molecular pathways that link actin and medial tip extension remained unexplored.

Dorsal intercalation involves polarization along multiple axes

As a coordinated movement within a sheet of cells, dorsal intercalation involves cell polarity along multiple axes. Although whether the dorsal hypodermis is a fully organized epithelium that constitutes a permeability barrier remains an open question, it is clear that it expresses many classical markers of a *bona fide* epithelium.[6] First, as nascent epithelial cells, dorsal hypodermal cells display apicobasal polarity. Apical junctions, which include both the cadherin-catenin-complex and the more basal DLG/AJM complex, are assembled as intercalation ensues. Second, orthogonal to the apicobasal axis, dorsal cells display a striking mediolateral polarity, as their medial edges point toward the dorsal midline and their rounded, lateral edges maintain contact with non-intercalating seam cells. While others have tackled how hypodermal cells acquire apicobasal polarity,[6] how dorsal cells acquire mediolateral polarity was completely uncharted.

What has made intercalation hard to study?

Several features of dorsal intercalation have made it a challenging process to study. First, dorsal intercalation mutants have other phenotypes. Mutations in genes previously published or reasonably hypothesized to be involved in intercalation are pleiotropic; earlier defects in events such as gastrulation or cell specification may indirectly lead to intercalation problems. For example, in an attempt to study the role of the Dishevelled,

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DSH-2, during dorsal intercalation, King *et al.* observed cell specification defects due to DSH-2's role as an effector in the Wnt/β-catenin asymmetry pathway that precluded further analysis.[7] A genetic screen identified the zinc-finger transcription factor, DIE-1, as a key modulator of dorsal intercalation[8]; however, early ubiquitous expression of DIE-1 during gastrulation[8,9] makes the specificity of this transcription factor suspect. Similarly, 2 T-box transcription factors, TBX-8 and TBX-9, were discovered to function redundantly to promote dorsal intercalation, but body wall muscle formation was also disrupted in these mutants.[10] Calcium signaling also appears to play a role in dorsal intercalation, as embryos homozygous for weak alleles of the inositol 1,4,5 triphosphate receptor, *itr-1*, have generalized epidermal migration defects, but here, too, there seem to be widespread defects that may be somewhat non-specific.[11]

A second, rather surprising, difficulty in studying dorsal intercalation was that the loss of function of genes sensibly predicted to have a role during dorsal intercalation either had no obvious effect or led to uninterpretable phenotypes. For example, components of the planar cell (PCP) pathway, which polarizes sheets of intercalating cells in frogs and fish (reviewed in[12–16]), seem to have minimal roles in *C. elegans*; knockdown of PCP homologues led to no observable defects during intercalation.[7] Despite the observation that extending tips require actin,[2] the involvement of crucial regulators of protrusive activity was also unclear. For example, knockdown of Arp2/3 complex components[17] and *ced*-10/Rac1[18] was reported to have no effect on intercalation, while mutations in genes encoding WAVE complex components lead to a complete failure of epidermal morphogenesis.[18,19] We therefore sought to develop an approach that would allow temporal and spatially-specific loss of function in dorsal hypodermal cells that would allow us to systematically assess molecular requirements for dorsal intercalation.

Charting new territory: Insights into protrusion formation and function

What made this work possible?

In order to study dorsal intercalation more incisively, we needed to generate a genetic tool that could both spatially and temporally abrogate gene function in hypodermal cells at the time of dorsal intercalation. Interested particularly in protrusive activity, we were keen to begin with the Rho family GTPase, *ced-10/Rac1*. To do so, we manipulated the mRNA stability of dominant transgenes expressed tissue-specifically. We generated hypodermal-specific *ced-10* transgenes harboring either activating (CA) or dominant-negative (DN) mutations and encoding a 3′- untranslated region (UTR) sensitive to nonsense-mediated mRNA decay (NMD). A temperature-sensitive mutation in a member of the NMD machinery, *smg-1(cc546*ts), allowed us to temporally control expression of these *ced-10(CA)* and *ced-10(DN)* constructs. Using this system, *ced-10(DN)* expression was able to phenocopy previously unappreciated intercalation phenotypes seen in a *ced-10* null background. This Smg-mediated tissue-specific, inducible system can be applied broadly to modify the function of other genes using characterized dominant mutations.

Additional incorporation of a valuable F-actin reporter transgene[20] allowed us to observe and quantify basolateral protrusions in dorsal cells. This combination of genetic abrogation and protrusion quantification, in addition to careful measurements of intercalation time via DIC microscopy, gave us the tools that we needed to reinvestigate dorsal intercalation.

Unexpected terrain

Armed with these technological advances, we were able to answer longstanding questions about dorsal intercalation. We initiated our analysis by assessing whether dorsal intercalation works like other epithelial intercalation events, in which Rho-dependent polarized junctional rearrangement drives intercalation (reviewed in[21]). Our initial unpublished results showed that neither RNAi-knockdown of junctional components nor dominant-negative *rho-1/RhoA* expression grossly interrupted intercalation. Therefore, we chose to focus on the mediolaterally polarized basolateral protrusions that are so prominent during intercalation (Fig. 1A).

Mapping the protrusive territory: Rac marks the spot

F-actin imaging showed that dynamic protrusions were clearly polarized to the extending, medial edge during intercalation, but previous reports did not describe intercalation phenotypes in strong *ced-10* loss

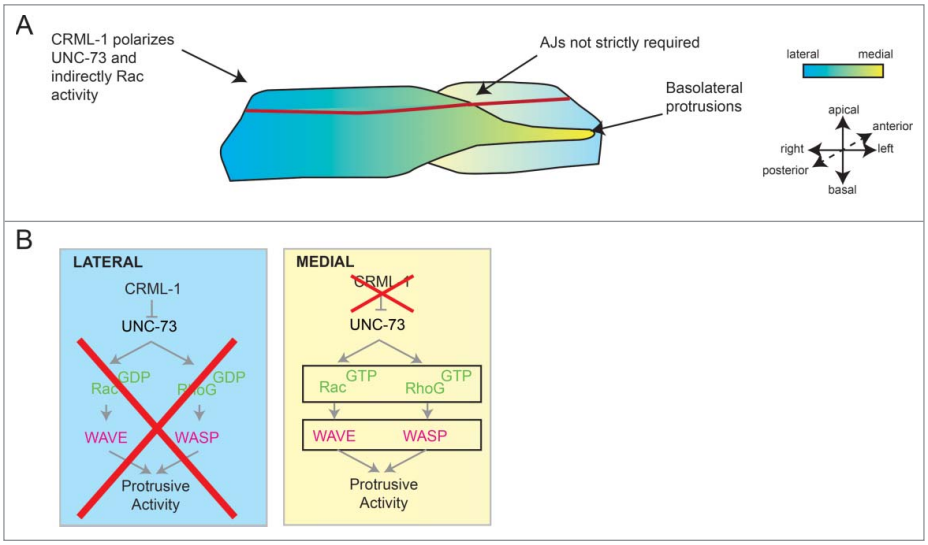

Figure 1. A molecular map of dorsal intercalation. A) Three surprises from the work published in Walck-Shannon *et al.*[1] organized according to their apicobasal and mediolateral location. Apically, apical junction (AJs, red band) are not strictly required, Basolaterally and medially, protrusions are polarized and contribute toward cell migration. Laterally, CRML-1/CARMIL is a polarizing cue that inhibits UNC-73/Trio activity. B) Molecular pathway that governs dorsal intercalation organized medially (blue) and laterally (yellow). Rho family GTPases in green, actin nucleation promoting factors in pink. Molecules boxed together are functionally redundant. At lateral edges, the presence of CRML-1 represses UNC-73 activity, whereas the absence of CRML-1 medially allows UNC-73 activation of Rac and RhoG, which in turn promote protrusion formation.

of function mutants.[18,22] However, using the tissue-specific, inducible approach described above to express *ced-10(DN)*, we found clear evidence that *ced-10/Rac1* is required for protrusion formation: by DIC microscopy both embryos expressing *ced-10/Rac1* dominant-negative constructs and embryos homozygous for strong loss-of-function alleles took longer to intercalate than wildtype. This clear evidence finally gave us an entry point to construct a map of the molecular players that control protrusive activity during dorsal intercalation.

A key insight that arose from our experiments was that functional redundancy is prevalent during dorsal intercalation; often loss of the function of single genes only resulted in subtle phenotypes (boxes in Fig. 1B). For example, even *ced-10/Rac1* loss does not completely prevent intercalation, which is likely why its role was overlooked previously. When *ced-10/Rac1* loss is combined with the loss of another RhoGTPase, *mig-2/RhoG*, however, intercalation fails completely. In a similar fashion, we were able to implicate functionally redundant downstream effectors of these GTPases, *wve-1/WAVE* and *wsp-1/WASP*. Identifying these redundancies was important for assessing potential upstream activators as well. Along with expression analysis, the finding that both Rac and RhoG were required allowed us to narrow down our list of guanine nucleotide exchange factors (GEFs), to one compelling candidate, which has specificity for both Rac and RhoG, *unc-73/Trio*.[23,24]

A new player: CRML-1/CARMIL

With the identification of UNC-73/Trio as a key regulator of CED-10 and MIG-2 (Fig. 1A), we next asked how UNC-73 might be regulated. UNC-73B::GFP was expressed uniformly along cell membranes, even though downstream protrusive activity was clearly polarized to the medial tips. Initially puzzled by this, we soon discovered Gian Garriga's group had identified a novel, conserved protein that can form a complex with UNC-73, capping Arp2/3 myosin I linker, CRML-1/CARMIL.[25,26] In growth cones, *crml-1* loss can suppress *unc-73* mutants, placing CRML-1 and UNC-73 in both a physical and functional pathway. In the dorsal epidermis *crml-1* loss resulted in excessive protrusions, particularly at non-medial edges, where protrusions are normally absent. Further, an epidermally-expressed rescuing construct was enriched at these non-medial edges, where we expected UNC-73/Trio to be inhibited. Genetic suppression of excessive protrusions in the *crml-1* mutant by *unc-73* loss provided further evidence that spatially restricted CRML-1 may mediate polarized inhibition

of protrusive activity by downregulation of UNC-73 laterally. In the end, a complicated pathway of redundancy and asymmetric inhibition during dorsal intercalation was finally coming into view (Fig. 1B).

Odd or familiar territory? Do these results reflect anomalies in *C. elegans*?

As mentioned previously, this story was developed after earlier results that were incongruent with the existing epithelial intercalation literature, raising some question about its conservation. Instead of being powered by myosin II-dependent junctional contraction, dorsal intercalation seems to be mediated by directional protrusions, which is the predominant mechanism used by intercalating mesenchymal cells. Significantly, as we were preparing our work, Williams and colleagues[27] found that both apical junctional rearrangement and basolateral protrusive activity drive intercalation in the mouse neuroepithelium. Together with previous reports of protrusive activity in the sea urchin archenteron[28] and ascidian notochord,[29,30] we suspect that basolateral protrusive activity represents a second, but not mutually exclusive, mechanism that can be deployed during epithelial intercalation. While it is unclear why dorsal intercalation so prominently features basolateral protrusions, one possibility relates to the relative immaturity of the intercalating hypodermis. Hypodermal cells are born immediately before intercalation begins, when junctional complexes are first coalescing,[31,32] making it possible that junctions are insufficiently mature to be major drivers of intercalation. This intriguing hypothesis deserves future study.

Whether CARMIL-mediated polarization is a widely conserved feature of intercalating epithelia also awaits future study. While worms have only one CARMIL homolog, at least 3 paralogs exist in vertebrates (reviewed by Edwards *et al.*[33]). Like worm CRML-1, vertebrate CARMIL1 retains the ability to co-immunoprecipitate with Trio,[26] but seems to promote—rather than inhibit—protrusive activity. On the other hand, CARMIL2 seems to have roles in cell polarity similar to worm CRML-1.[26] Given this subfunctionalization of vertebrate CARMILs, it is possible that any conserved CARMIL-dependent polarization mechanisms that act during intercalation might include additional molecular players or that the relevant pathways may have undergone some alterations of molecular detail.

Future territory: Open questions about dorsal intercalation

Despite the advances made by Walck-Shannon *et al.*,[1] many questions still remain. We sketch a few of these questions here. At the apical surface of dorsal epidermal cells, how are junctions rearranged during intercalation? Although classical planar polarization is not obvious at the apical junctions of dorsal epidermal cells, during intercalation junctions nevertheless must be disassembled as one cell squeezes its way between contralateral cells. One recent publication[34] suggests that SUMOylation of HMR-1/Cadherin is important for normal junctional localization during dorsal intercalation. It is possible that this and additional post-translational modifications of junctional components, rather than an overall overt accumulation of junctional material at preferred junctional boundaries, will be an important aspect of junctional dynamics during intercalation.

Orthogonal to the apicobasal axis, along the mediolateral axis (Fig. 2A), another question arises: how does CRML-1/CARMIL become polarized laterally? One testable hypothesis is that cortical flow is responsible for rearward movement of CRML-1. In early *C. elegans* embryos, actomyosin-based flows of molecules associated with the inner side of the plasma membrane (the cortex) are responsible for localizing a subset of polarity proteins.[35] If a similar mechanism functions in the intercalating epidermis to polarize CRML-1, there are at least 2 expectations: 1) CRML-1 should initially have a uniform distribution, which becomes more polarized over time; and 2) perturbation of the actomyosin machinery should disrupt cortical flow and prevent CRML-1 polarization. Careful, early imaging of an existing $P_{lbp\text{-}1}$*::crml-1::gfp* transgene combined with the use of temperature-sensitive *nmy-2*/non-muscle myosin II mutants[36] could answer this question. Alternatively, if CRML-1 remains polarized in *nmy-2*(ts) mutants, then it may be actively targeted to the lateral edge through a yet-to-be-determined binding partner.

Our study addressed the apicobasal and mediolateral axes but other pre-existing axes in the embryo may also affect intercalation. A third axis, the right-left axis (Fig. 2B), also deserves further analysis.

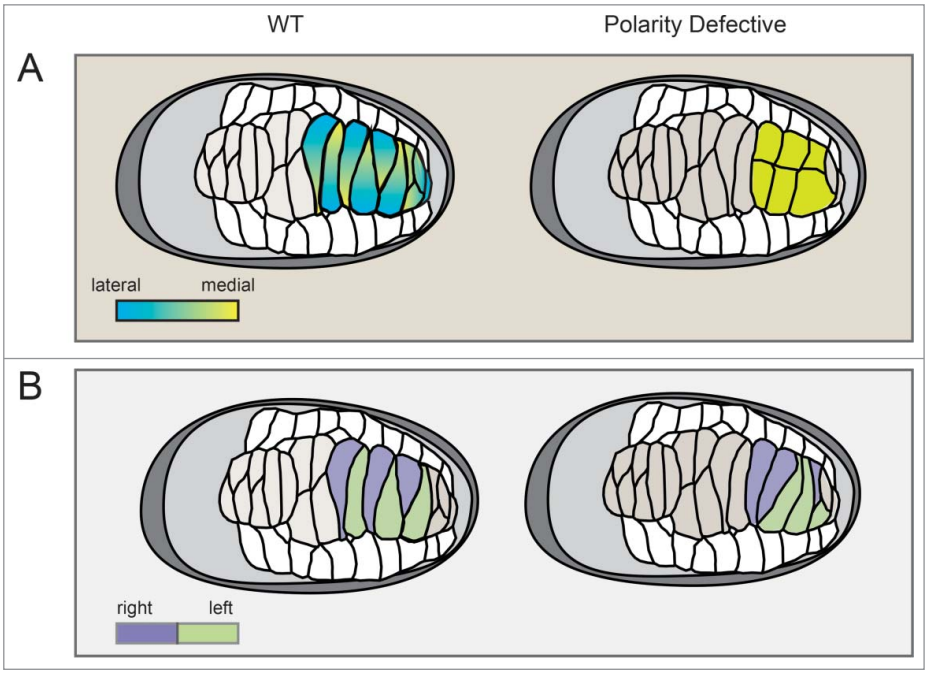

Figure 2. Polarity along a subset of relevant axes for dorsal intercalation. Left cartoon represents wildtype, right cartoon represents an embryo where polarity is lost. A) Walck-Shannon *et al.*[1] focused on the mediolateral axis (yellow to blue), characterizing a lateral polarization cue and medial protrusive activity. When the polarizing cue (CRML-1/CARMIL) is lost, the rest of the cell behaves more like the medial edge (ectopic protrusive activity). B) The right-left axis deserves further characterization. Using transgenes, others have observed differences in gene expression among right and left cells (see main text). If right-right polarity is perturbed (cells still colored right and left for emphasis of phenotype), one predicted phenotype is that adjacent cells might migrate together across the dorsal array.

Others have reported intriguing right-left asymmetry of *vab-1/Eph*[37] and *lat-1/latrophilin*[38] expression. While the functional significance of these asymmetries is currently unknown, defects in right/left polarity might result in the comigration of adjacent right- or left-hand cells across the dorsal array (Fig. 2C). How *vab-1* and *lat-1* might fit into our existing understanding of dorsal intercalation remains an interesting mystery.

Much remains to be charted regarding the mechanisms of dorsal intercalation, but the system is poised for new discoveries and promises to hold many surprises as its mysteries continue to yield to experimental analysis.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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