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Convergent extension: using collective cell migration and cell intercalation to shape embryos

Masazumi Tada[1,*] and Carl-Philipp Heisenberg[2,*]

Summary

Body axis elongation represents a common and fundamental morphogenetic process in development. A key mechanism triggering body axis elongation without additional growth is convergent extension (CE), whereby a tissue undergoes simultaneous narrowing and extension. Both collective cell migration and cell intercalation are thought to drive CE and are used to different degrees in various species as they elongate their body axis. Here, we provide an overview of CE as a general strategy for body axis elongation and discuss conserved and divergent mechanisms underlying CE among different species.

Key words: Convergent extension, Collective cell migration, Cell intercalation, Planar cell polarity

Introduction

Convergent extension (CE) is a key process by which tissues undergo narrowing along one axis and concomitant extension along another axis. The first identified and best-studied example of CE in development is body axis elongation during gastrulation (reviewed by Keller et al., 2000). Generally, CE in body axis elongation is characterized by the collective movement of germ layer progenitor cells towards the dorsal side of the gastrula, where the embryonic body axis will form, accompanied or followed by cell intercalations along their axis of movement. This combination of collective cell movement and cell intercalations triggers narrowing of the body axis along its medial-lateral (ML) axis (i.e. the convergence) and elongation along its anterior-posterior (AP) axis (i.e. the extension). CE thus includes two fundamentally different types of cell movement (Fig. 1): collective cell migration (see Glossary, Box 1), which commonly describes the coordinated movement of a highly cohesive sheet of cells; and cell intercalations (see Glossary, Box 1), whereby oriented exchanges of neighboring cells alter tissue geometry.

In this Primer (see Box, Development: the big picture), we review how cells intermittently use collective migration and cell intercalation in CE-driven body axis elongation during gastrulation in various species. We also discuss the cell-intrinsic and extrinsic factors that determine the contribution of these different movement types to CE. Finally, we highlight the key molecular and genetic pathways involved in CE, but refer the reader to recent reviews of this topic (Gray et al., 2011; Skoglund and Keller, 2010) for further details on these pathways.

CE during zebrafish gastrulation: a case for collective cell migration

At the onset of gastrulation in zebrafish, mesoderm and endoderm (mesendoderm) progenitor cells internalize at the germ ring margin (see Glossary, Box 1) and subsequently migrate away from the margin towards the animal pole (Fig. 2A). Progenitors that internalize in the region of the embryonic organizer (the shield) and give rise to the anterior axial mesendoderm (the prechordal plate) migrate as a highly cohesive cluster of cells, typical of collective migration (reviewed by Friedl and Gilmour, 2009). Once all of the prechordal plate progenitor cells have internalized, the prechordal plate moves as an oval-shaped cell sheet in a straight path away from the germ ring margin towards the animal pole of the gastrula. Within the forming prechordal plate, cells at the leading edge are highly polarized and form different types of cell protrusions (Fig. 1A), such as lamellipodia and blebs, that are oriented in the direction of their movement (Montero et al., 2003: Diz-Muñoz et al., 2010). Behind the leading edge, prechordal plate cells exhibit highly coordinated and aligned movements with very few neighbor exchanges. Interfering with protrusion formation in prechordal plate cells by inhibiting platelet-derived growth factor (PDGF)/phosphatidylinositol 3-kinase (PI3K) signaling leads to pronounced defects in the anterior migration of prechordal plate cells (Montero et al., 2003), suggesting that PDGF-dependent cell protrusion formation and active migration are required for prechordal plate movement. Furthermore, modifying cell polarization and cohesion of prechordal plate progenitors by blocking Wnt/planar cell polarity (PCP) signaling (see Glossary, Box 1) interferes with the coordination and directionality of prechordal plate cell movements (Ulrich et al., 2005), indicating that Wnt/PCP signaling is crucial for collective migration of prechordal plate cells. Taken together, these observations suggest that prechordal plate progenitor cells undergo collective cell migration from the germ ring margin towards the animal pole, thereby contributing to body axis elongation during gastrulation.

At the mid-gastrula stage, a second phase of collective migration is observed in lateral regions of the gastrula, where mesendoderm progenitors start converging dorsally towards the forming embryonic axis (convergence movements). At the onset of mesendoderm convergence, cells appear only loosely associated, are not clearly polarized, and show little coordinated or directed movement (Sepich et al., 2005). However, once these cells get closer to the forming embryonic axis and thus cell density increases, the cells polarize along their ML axis and exhibit increasingly coordinated and directed convergence movements (Fig. 2A), reminiscent of collective migration (Sepich et al., 2000). Eventually, mesendoderm cells arriving near the presumptive

Development: the big picture

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[1]Department of Cell and Developmental Biology, University College London, Gower Street, London, WC1E 6BT, UK. [2]Institute of Science and Technology Austria, Am Campus 1, A-3400 Klosterneuburg, Austria.

*Authors for correspondence (m.tada@ucl.ac.uk; heisenberg@ist.ac.at)

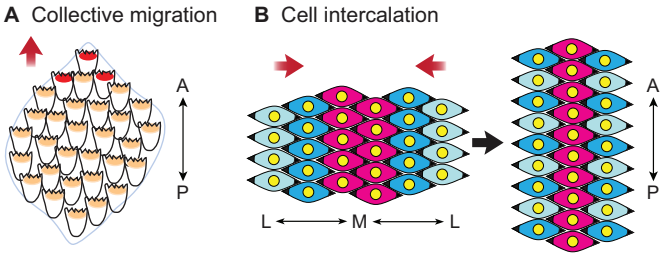

Fig. 1. CE includes two different types of cell movement. (**A**) In collective migration, cells migrate as a cohesive sheet and do not exchange neighbors. The cells at the leading edge are highly polarized and produce different types of protrusions, such as lamellipodia and blebs (red), than the cells located behind the leading edge (orange). Red arrow indicates the direction of collective cell movement. (**B**) In medial-lateral cell intercalation, cells orient with the lamellipodia on their medial and lateral ends, intercalate, and then redistribute their positions in the anterior-posterior axis of the tissue. The red arrows indicate directions of cell movement. A, anterior; P, posterior; M, medial; L, lateral.

notochord initiate ML cell intercalations (Fig. 1B; see Glossary, Box 1) and radial cell intercalations (see Glossary, Box 1), both of which contribute to the extension of the posterior body axis (Yin et al., 2008). These intercalation movements are crucial for body axis elongation, as defects in cell intercalation are usually accompanied by impaired body axis elongation (Sepich et al., 2000). This suggests that both collective mesendoderm cell migration and intercalation are key aspects of CE movement during the early stages of gastrulation in zebrafish. A ventral-to-dorsal gradient of BMP signaling has been proposed to direct the convergence movement of mesendoderm progenitors by regulating a dorsal-to-ventral gradient of N-cadherin activity (von der Hardt et al., 2007). Mesendoderm cells are thus thought to move from a region of low cohesion laterally to a region of high cohesion dorsally. This is consistent with the observation that these cells transit from a loosely associated to a highly coherent assembly during their convergence movements. BMP signaling is also thought to function in CE by inhibiting the expression of Wnt/PCP components in ventral regions of the gastrula (Myers et al., 2002), thereby restricting CE movements to dorsolateral regions. Wnt/PCP signaling has again been shown to be crucial for both lateral mesendoderm collective migration and cell intercalation by controlling cell movement persistency and ML cell polarization, respectively (Sepich et al., 2000; Topczewski et al., 2001; Jessen et al., 2002; Heisenberg et al., 2000; Sepich et al., 2000; Carreira-Barbosa et al., 2009).

The collective migration of prechordal plate progenitors and of lateral mesendoderm progenitors share similar features. In both cases, the direction of movement relies on proper cell polarization and protrusion formation. The correct ratio between lamellipodia and blebs, which is controlled by the degree of adhesion between the plasma membrane and the underlying cortical cytoskeleton, is key for prechordal plate progenitors to undergo directional migration (Diz-Muñoz et al., 2010). Likewise, ectopic blebs triggered by elevated actomyosin contractility are correlated with reduced directionality of lateral mesendoderm progenitor cell migration (Weiser et al., 2009). Furthermore, proper Cadherin-mediated cell cohesion of prechordal plate and lateral mesendoderm progenitors is crucial for their directed and collective migration (Ulrich et al., 2005; von der Hardt et al., 2007; Warga and Kane, 2007; Arboleda-Estudillo et al., 2010). Thus, the regulation of protrusion formation and cell cohesion represent key aspects in the collective migration of both prechordal plate and lateral mesendoderm progenitors.

In contrast to prechordal plate and lateral mesendoderm progenitors, notochord progenitors, which originate from cells that internalize at the shield after prechordal plate progenitors and give rise to the posterior axial mesoderm/notochord, exclusively undergo ML cell intercalation to extend the body axis (Glickman et al., 2003). It appears that notochord progenitors rarely intercalate with neighboring lateral mesendoderm/somite progenitors, even before a boundary between these tissues becomes morphologically apparent (Glickman et al., 2003). This is supported by observations that cells transplanted laterally to the shield at the early gastrula stage are not incorporated into the presumptive notochord (Heisenberg et al., 2000). Consistent with this, embryos with compromised convergence movements of lateral mesendoderm progenitors do not necessarily also exhibit notochord extension defects (Bakkers et al., 2004), suggesting that lateral mesendoderm convergence and notochord extension are controlled independently. Taken together, CE movements during zebrafish gastrulation are mediated by collective cell migration and, to a lesser extent, cell intercalation.

CE during *Xenopus* gastrulation: a case for cell intercalation

In developing *Xenopus* embryos, head mesendoderm cells are the only progenitor cell population that undergoes collective migration during CE. Cells at the leading edge of the head mesendoderm originate from a deep part of the dorsal endoderm of pregastrula stage embryos, whereas cells behind the leading edge are involuted prechordal mesoderm cells (Bouwmeester et al., 1996). Head mesendoderm cells orient towards the blastocoel roof (BCR; see Glossary, Box 1), polarize along their animal-vegetal axis and migrate as a cohesive sheet in a highly directed manner (Fig. 2B). Individual head mesendoderm cells typically form unipolar lamellipodia-like protrusions in the direction of their migration (Davidson et al., 2002; Weber et al., 2012). Directed movement of head mesendoderm cells is thought to be mediated by a gradient of putative chemoattractant(s), such as PDGF, which attract head mesendoderm cells towards the BCR and trigger their polarization and spreading on the BCR (Damm and Winklbauer, 2011; Nagel et al., 2004). Collectively migrating head mesendoderm cells use the extracellular matrix protein Fibronectin, which is deposited on the BCR, as a substrate for migration (Dzamba et al., 2009). Notably, isolated mesendoderm cells can undergo directed migration on Fibronectin substrates in the absence of PDGF (Davidson et al., 2002; Winklbauer, 1990). Moreover, E-cadherin-mediated pulling between co-migrating head mesendoderm cells has been shown to be required for the coordinated cell polarization and collective migration of these cells (Weber et al., 2012). Thus, head mesendoderm cell polarization and directed migration are controlled by a combination of biochemical and mechanical cues.

Mesoderm progenitor cells located in the dorsal marginal zone simultaneously undergo involution and convergence movements. Soon after involution, chordamesoderm cells, which give rise to notochord and somites, polarize along their ML axis, form stable lamellipodia on their medial and lateral ends, and undergo ML cell intercalations (Shih and Keller, 1992) (Fig. 2B). Thus, CE movements of chordamesoderm tissue are predominantly triggered by ML cell intercalations. Notably, chordamesoderm CE appears

to be a cell/tissue-autonomous morphogenetic process, as isolated chordamesoderm tissues can undergo CE movements in the absence of external substrates (Keller and Danilchik, 1988). Wnt/PCP signaling is required for elongation and polarization of chordamesoderm cells, and disrupted chordamesoderm cell elongation/polarization due to reduced or elevated Wnt/PCP signaling activity leads to impaired CE movements (Wallingford et al., 2000) (reviewed by Skoglund and Keller, 2010). Wnt/PCP-defective, non-polarized chordamesoderm cells are unable to intercalate with properly polarized cells (Kinoshita et al., 2003), suggesting that ML cell polarization is a prerequisite for undergoing cell intercalation. Although Wnt/PCP signaling is required for both polarization and elongation of chordamesoderm cells, elongation and polarization are independently regulated processes, as only cell elongation, but not polarization, is compromised if the downstream Wnt/PCP effector Fritz is abrogated (Kim et al., 2010). Wnt/PCP is also thought to function in chordamesoderm cell elongation by controlling actomyosin contraction (Kim and Davidson, 2011). Besides Actin and Myosin II, microtubule polarity has also been proposed to be crucial for chordamesoderm cell elongation independently of Wnt/PCP signaling (Shindo et al., 2008).

Cell-matrix adhesion between chordamesoderm cells and the BCR plays a crucial role in regulating mechanical features of chordamesoderm CE. Fibronectin deposition on the BCR surface is required for proper CE movements of chordamesoderm cells, and inhibition of Fibronectin assembly via disruption of Integrin binding to Fibronectin in chordamesoderm cells interferes with chordamesoderm CE movements (Davidson et al., 2006). Moreover, Cadherin-mediated adhesion between BCR cells generates tissue tension that organizes Fibronectin matrix deposition on the BCR (Dzamba et al., 2009). Conversely, Integrin-mediated binding of chordamesoderm cells to Fibronectin modulates Cadherin-mediated adhesion between chordamesoderm cells, which again is required for chordamesoderm intercalation during CE (Marsden and DeSimone, 2003). Wnt/PCP signaling also plays an important role in regulating Fibronectin fibril assembly (Dzamba et al., 2009; Goto et al., 2005), and Fibronectin-Integrin binding feeds back to modulate Wnt/PCP signaling (Davidson et al., 2006; Muñoz et al., 2006). Furthermore, signaling through Paraxial protocadherin (PAPC) has been implicated in regulating chordamesoderm CE. PAPC controls chordamesoderm cell polarization through Wnt/PCP-dependent and -independent mechanisms (Unterseher et al., 2004; Schambony and Wedlich, 2007; Wang et al., 2008) and modulates chordamesoderm cell-cell adhesion by regulating the activity of C-cadherin (Chen and Gumbiner, 2006). However, evidence for C-cadherin directly controlling chordamesoderm CE is still lacking.

Other than chordamesoderm, the neural plate (see Glossary, Box 1) also undergoes CE by narrowing along its ML axis and extending along its AP axis during gastrulation/neurulation. In *Xenopus*, the neural plate consists of two cell layers – a superficial layer of epithelial cells and a deep layer of mesenchymal cells. Neural plate CE has been shown to be independent of chordamesoderm CE and appears to be triggered by ML intercalations of cells within the mesenchymal cell layer of the neural plate (Elul et al., 1997). Moreover, cells within the mesenchymal layer of the neural plate exhibit monopolar protrusive activity directed towards the boundary between neural plate midline cells (notoplate) and cells in more lateral regions of the neural plate. This process, termed boundary capture, has been suggested as a force-generating mechanism for lateral mesenchymal neural plate cells to undergo CE (Elul and Keller, 2000). As in chordamesoderm, Wnt/PCP signaling is required for cell intercalation during neural plate CE (Wallingford and Harland, 2002). In addition, Myosin II has been shown to mediate cell protrusion formation in the notochord (Skoglund et al., 2008) and cell shape changes in neural plate mesenchymal cells independently of Wnt/PCP signaling (Rolo et al., 2009).

Box 1. Glossary

Blastocoel roof (BCR). The animal pole region of the ectodermal tissue that faces the blastocoel cavity of the early *Xenopus* embryo.

Cell intercalation. The exchange of neighbors, as observed in both mesenchymal and epithelial cells.

Collective cell migration. A mode of cell migration in which the cells move as a cohesive cluster and there are no neighbor exchanges involved.

Germ ring margin. The margin of the blastopore, where internalization occurs to produce mesoderm and endoderm progenitors.

Germband epithelium. A simple epithelium in the presumptive segmented trunk (the germband) of the *Drosophila* embryo during gastrulation.

Medial-lateral (ML) cell intercalation. Cells intercalate along the ML axis of the embryo in order to become distributed along the anterior-posterior (AP) axis of the embryo.

Neural plate. Part of the epiblast/ectoderm becomes fated to the future neural tube during gastrulation following neural induction.

Planar cell polarity (PCP). A genetic pathway originally identified in *Drosophila* epithelia. The core pathway components referred to here are Wnt11, Wnt5, Frizzled 7, Dishevelled, Vangl2, Prickle and Celsr (Flamingo). In this Primer, we have referred to PCP in terms of general pathway activities, rather than providing details of such as differences in individual pathway components.

Radial cell intercalation. Cells intercalate along the superficial-deep axis of the embryo in order to increase the surface area of the tissue.

CE as a general strategy for body axis elongation

The molecular and cellular basis of CE was originally addressed by studying the behavior of mesenchymal cells in body axis elongation during *Xenopus* and zebrafish gastrulation, as discussed above. However, there is mounting evidence to suggest that CE represents a common process that mediates body axis elongation in other vertebrate and invertebrate species.

Cell intercalations trigger germband extension during gastrulation in *Drosophila*

During gastrulation in *Drosophila*, the germband epithelium (see Glossary, Box 1) narrows along its dorsal-ventral (DV) axis and extends along its AP axis, reminiscent of the CE movements that occur during vertebrate gastrulation. However, the apicobasally polarized epithelial germband employs modes of cell intercalation to drive germband extension that are considerably different from the ML cell intercalation behavior described for mesenchymal cells undergoing CE during vertebrate gastrulation (Irvine and Wieschaus, 1994). Myosin II-mediated remodeling of apical junctions is thought to constitute a key process driving the cell intercalation required for germband extension (Bertet et al., 2004; Zallen and Wieschaus, 2004). There are two principal modes of cell intercalation triggered by remodeling of apical junctions: T1-T2-T3 transitions involving four cells; and rosette formation involving 5-12 cells (Bertet et al., 2004; Blankenship et al., 2006) (Fig. 3). In

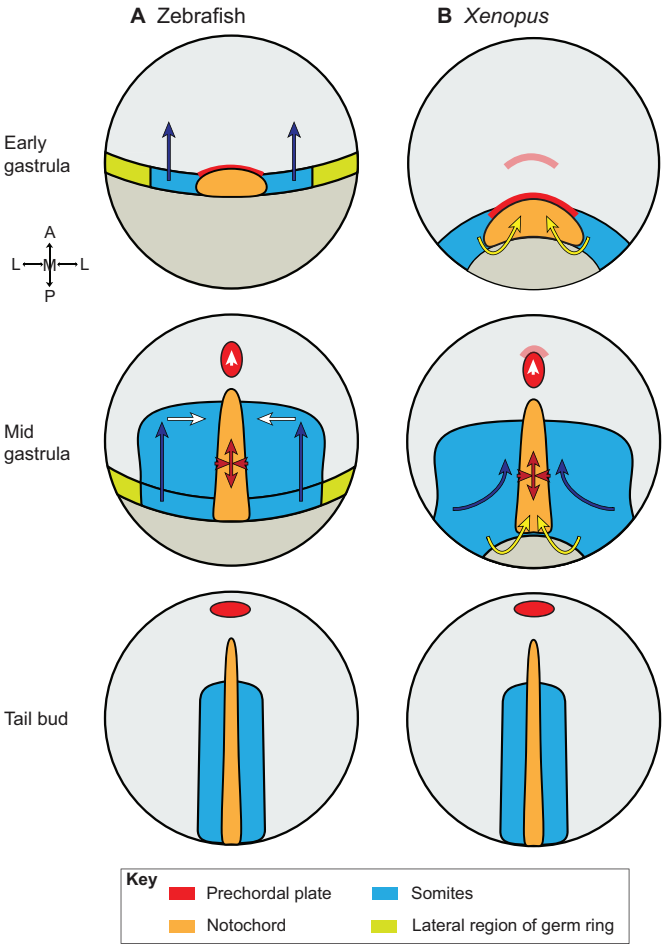

Fig. 2. Cell movement modes during CE in zebrafish and *Xenopus*. (**A**) Schematic dorsal views of zebrafish embryos at different stages of gastrulation. At the early gastrula stage [shield stage, 6 hours postfertilization (hpf)], the first cells internalizing at the region of the shield (organizer) are prechordal plate progenitors (red), followed by progenitor cells of the forming notochord (orange). Black arrows indicate the direction of internalization of mesendoderm cells. At the mid-gastrula stage (75% epiboly, 7-8 hpf), prechordal plate progenitors undergo collective migration (white arrowhead), whereas notochord progenitors exclusively undergo ML cell intercalation (red arrows and arrowheads). At the same time, lateral mesendoderm progenitors (the presumptive somites, blue) begin convergence movement (white arrows) and undergo collective migration towards the midline. Closer to the presumptive notochord, lateral mesendoderm progenitors also initiate ML cell intercalation. By the tail bud stage, prechordal plate cells reach the head region, and the notochord extends along the AP axis. (**B**) Schematic dorsal views of *Xenopus* embryos at different stages of gastrulation. At the early gastrula stage (stage 10), deep endoderm cells (pink), together with the first internalized axial cells (red), form the head mesendoderm. The following populations of axial and paraxial cells simultaneously involute and converge (yellow arrows). At the mid-gastrula stage, head mesendoderm cells exclusively undergo collective migration (white arrowhead), while notochord cells undergo ML cell intercalation (red arrows and arrowheads). By the tail bud stage, prechordal plate cells migrate into the head and notochord cells distribute along the entire body axis. Anterior is to the top.

both of these processes, Myosin II-mediated tension at junctions preferentially oriented along the DV axis between either a pair (in the case of the T1-T2-T3 transition) or a group of cells (in the case of rosette formation) leads to a shortening of these junctions (T1-T2 transition, rosette formation), followed by the formation of a new junction along the AP axis (T2-T3 transition, rosette resolving), thus triggering germband extension. Shortening of the junctions along the DV axis (DV junctions) is enhanced by a positive-feedback loop in which the force generated by actomyosin-mediated junctional contraction leads to recruitment of more Myosin II to this junction (Fernandez-Gonzalez et al., 2009). More recently, pulsatile contractions of an apical actomyosin web in epithelial germband cells has been proposed to trigger the shortening of the DV junctions, while Myosin II accumulation at the shortening DV junctions is predominantly required for stabilizing them (Rauzi et al., 2010). Moreover, endocytosis and recycling of E-cadherin at the DV junctions is required for their Myosin II-mediated shortening (Levayer et al., 2011). Thus, the coordinated activities of actomyosin contractility and cell-cell adhesion mediate the junctional remodeling underlying the cell intercalations that trigger *Drosophila* germband extension (Simões et al., 2010; Tamada et al., 2012).

Collective cell migration and intercalation drive streak formation in chick

Prior to gastrulation in chick, global cell flows within the epithelial epiblast cell layer have been associated with positioning of the forming primitive streak (Cui et al., 2005). Epiblast cells are thought to function in this process by undergoing cell intercalations, reminiscent of CE, that contribute to the elongation of the primitive streak (Lawson and Schoenwolf, 2001; Voiculescu et al., 2007). Once the streak is formed, body axis elongation is driven by regression of the embryonic organizer (Hensen's node) during gastrulation. Importantly, abrogation of core PCP genes leads to defects in epiblast cell intercalations and primitive streak formation (Voiculescu et al., 2007), suggesting that Wnt/PCP-dependent epiblast cell intercalations drive primitive streak formation. However, other studies showing that abrogation of core PCP genes does not inhibit primitive streak formation but instead causes shortening of the body axis during gastrulation (Chuai et al., 2006), have challenged this view. Primitive streak formation has also been suggested to be triggered by the collective migration of epiblast cells, which are directed by chemoattractants and/or repellents expressed within the streak (Vasiev et al., 2010). Prime candidates for such chemoattractants and repellents are the fibroblast growth factors (FGFs), which are expressed within the primitive streak and required for collective migration of epiblast cells (Chuai et al., 2006). Taken together, primitive streak formation during chick gastrulation appears to be driven by a combination of epiblast cell intercalation and collective migration, which depend on Wnt/PCP-mediated cell polarization and/or FGF-guided directional migration.

Cell intercalation mediates CE in the mouse notochord/neural plate

In contrast to zebrafish and *Xenopus*, there is little evidence that convergence movement of lateral/somitic mesoderm progenitor cells contributes to body axis elongation in mice. Consistent with this, there is no obvious lateral expansion of the somites in Wnt/PCP-deficient mice (Ybot-Gonzalez et al., 2007; Wang et al., 2006), whereas the somites in Wnt/PCP-defective zebrafish embryos (e.g. *vangl2* mutants) become laterally expanded as a result of the defective convergence movement of mesoderm/somite progenitors (Jessen et al., 2002; Topczewski et al., 2001). However, in mouse, axial notochord progenitors undergo CE movements to trigger notochord elongation by cell intercalations (Yamanaka et

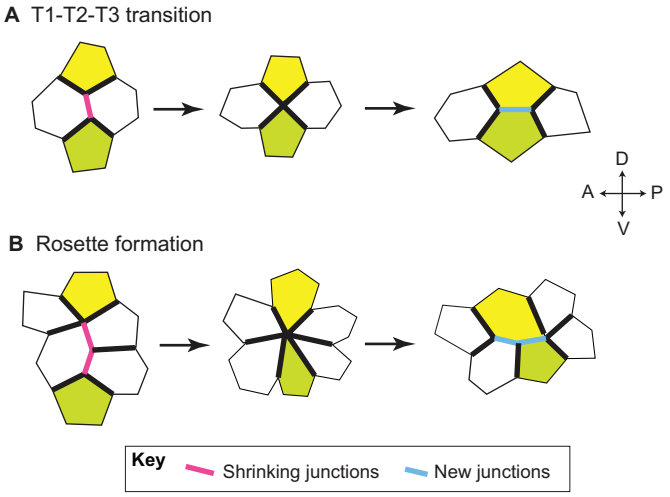

Fig. 3. Cell rearrangement and junctional remodeling during CE in *Drosophila*. The germband narrows along the DV axis and extends along the AP axis. T1-T2-T3 transitions (**A**) involve four cells, whereas rosette formation (**B**) involves 5-12 cells. In both processes, at Myosin II-positive boundaries (red) apical junctions shrink along the DV axis and thus two cells (yellow and green) meet at the vertex of a forming rosette along with neighboring cells (white). Then, new apical junctions form at new boundaries (blue) and expand along the AP axis, thus distributing the white cells anteriorly or posteriorly. Therefore, these processes contribute to the elongation of the germband.

al., 2007; Yen et al., 2009). Similar to notochord progenitors, epithelial cells in the mouse neural plate also undergo CE before the onset of neurulation, and this process is disrupted in Wnt/PCP mutants (Ybot-Gonzalez et al., 2007). Defects in neural plate CE lead to failure in neural tube closure, reminiscent of phenotypes associated with craniorachischisis in humans (reviewed by Copp and Greene, 2010). It is still unclear whether CE defects in notochord progenitor cells secondarily affect CE in overlying neuroepithelial cells or whether CE movements in these two tissues are independently regulated. Recent work suggests that PCP-mediated midline convergence and bending of the neural plate at early stages of neural tube closure is largely independent of the underlying notochord (Nishimura et al., 2012).

Conserved and divergent mechanisms of CE

In this section we discuss the extent to which the key mechanisms underlying CE are conserved and how they are implemented among different species.

Cell polarization

Wnt/PCP signaling is thought to play a key role in cell polarization during CE (reviewed by Gray et al., 2011). However, despite its requirement for cell polarization during CE in vertebrate gastrulation, there is no direct evidence yet that Wnt/PCP signaling directly polarizes cells in this process. Instead, both prechordal plate and lateral mesendoderm progenitors in zebrafish might be polarized by other factors, such as downstream target genes of the transcription activator Stat3 (Yamashita et al., 2002; Miyagi et al., 2004), as abrogation of *stat3* causes non-cell-autonomous defects in prechordal plate/lateral mesendoderm cell polarization and collective migration.

In contrast to the situation in vertebrate gastrulation, cell polarization and CE of epithelial cells during *Drosophila* germband extension have been proposed to be independent of Wnt-Frizzled/PCP signaling (Zallen and Wieschaus, 2004). Interestingly, PCP during germband extension has been shown to be controlled by pair-rule segmentation genes that are expressed in DV stripes along the AP axis of the germband (Zallen and Wieschaus, 2004). This points to the possibility that, analogous to the situation in the *Drosophila* germband, borders between different regions and tissues along the AP axis in the vertebrate gastrula are involved in mesoderm progenitor cell polarization, regardless of whether those processes are Wnt/PCP dependent or independent. This notion is also supported by observations in gastrulating *Xenopus* embryos showing that an AP gradient of Nodal/Transforming growth factor β (TGFβ) signaling activity triggers mesoderm cell polarization and CE in isolated animal cap explants (Ninomiya et al., 2004). The border between the prechordal plate and notochord is one possible region of polarizing activity, although very little is known about the cellular composition of this area. In zebrafish, the prechordal plate-notochord border is populated by posterior prechordal plate cells (Kai et al., 2008), in *Xenopus* by non-polar cells (Weber et al., 2012), and in mouse embryos by the anterior head process (Yamanaka et al., 2007). It remains to be elucidated whether these different, as yet uncharacterized, cell populations play a role in establishing cell polarization during CE.

Oriented cell division

During zebrafish CE, cells in the dorsal epiblast, which comprises the presumptive neural plate, preferentially divide along the AP axis (Gong et al., 2004; Quesada-Hernández et al., 2010). Similarly, oriented cell divisions occur at the midline during chick streak formation (Wei and Mikawa, 2000) and during *Drosophila* germband extension (da Silva and Vincent, 2007). Whereas Wnt/PCP signaling plays a pivotal role in regulating oriented cell division in zebrafish (Gong et al., 2004; Quesada-Hernández et al., 2010), abrogation of PCP signaling has little influence on germband extension in *Drosophila* (da Silva and Vincent, 2007). Oriented cell divisions have been proposed to contribute to tissue elongation in both vertebrates and invertebrates, but direct experimental evidence to support this claim is still awaited (Quesada-Hernández et al., 2010; Voiculescu et al., 2007; da Silva and Vincent, 2007).

Coordinating collective cell migration and cell intercalation

During zebrafish gastrulation, lateral mesendoderm progenitors simultaneously undergo collective migration and cell intercalations. How these cells coordinate collective migration with cell intercalation is not known. However, there are several features of lateral mesendoderm progenitors that distinguish them from cells undergoing either collective migration or intercalation alone. First, the microtubule-organizing center (MTOC) is positioned in posterior-medial regions of these cells, and not along the axis of cell migration as described for other cell types undergoing directed migration (Sepich et al., 2011). Second, the localization of core Wnt/PCP components at the anterior and posterior sides of these cells does not correlate with their ML elongation and polarization (Yin et al., 2008). This differs from the situation observed, for example, in *Drosophila* epithelial cells, where core PCP components typically co-localize with the axis of cell polarization. How this discrepancy between MTOC and Wnt/PCP component localization and cell polarization relates to the ability of lateral mesoderm progenitors to undergo both collective migration and cell intercalation remains to be answered.

Cell intercalations: junctional remodeling versus ML cell intercalation behavior

During CE, cells rearrange by ML cell intercalation behavior or junctional remodeling. ML cell intercalation behavior is typically observed in mesenchymal cells and involves polarized protrusive activities of the intercalating cells, whereas junctional remodeling occurs in epithelial cells. The main difference between ML cell intercalation behavior and junctional remodeling is the type of cellular interactions driving these processes. ML cell intercalation is mediated by cells dynamically interacting with each other and with their substrate, which is typically formed by extracellular matrix components. By contrast, junctional remodeling describes the process whereby apical junctions shrink and expand, thereby changing the shape, size and position of the apex of epithelial cells. Thus, junctional remodeling causes changes in the structure of the apical surface of epithelial cells, which is thought to drive changes in the position of epithelial cells relative to each other, whereas cell intercalations between mesenchymal cells involve changes at cell-cell and cell-matrix contact sites.

However, this view is challenged by observations that ML cell intercalation behavior can also proceed in the absence of substrate adhesion (Keller and Danilchik, 1988) and that interaction of epithelial cells on their basal side with the underlying matrix can play a crucial role in epithelial morphogenesis (Vasilyev et al., 2009; Haigo and Bilder, 2011). Future studies that address the specific functions of cell-cell versus cell-substrate interaction in ML cell intercalation behavior and junctional remodeling will be needed to elucidate the differences in CE between mesenchymal and epithelial cells.

What has been learned from studies of CE movements?

The basic cellular processes underlying CE were originally described in *Xenopus* gastrulation. Subsequent genetic and molecular studies in *Xenopus* and zebrafish have shown how this process contributes to axis elongation in these organisms. In particular, such studies have dissected the regulation and function of PCP in CE. The identification of Wnt/PCP signaling as a key pathway required for collective cell migration and intercalation underlying CE during vertebrate gastrulation suggested a general molecular and cellular mechanism linking cell polarization to body axis elongation (reviewed by Gray et al., 2011). Subsequent studies have shown that these mechanisms are also key to other morphogenetic processes, such as elongation of the cochlear tube (Wang et al., 2005), jaw cartilage (Topczewski et al., 2001) and limb cartilage (Gao et al., 2011). However, it remains unclear to what extent Wnt/PCP-dependent CE contributes to elongation of these tissues. Wnt/PCP signaling is also involved in controlling processes other than cell polarization, such as cilia orientation. Whether and how these Wnt/PCP-dependent processes function in the CE that mediates body axis elongation during gastrulation remains to be elucidated.

Conclusions

CE is a complex process that involves the integration of collective migration and cell intercalation. Despite differences in the molecular and cellular regulation of CE between species, there appears to be a common set of core cellular processes, such as cell polarization, actomyosin contraction and cell adhesion dynamics, by which CE is achieved in the various contexts. Questions remain as to the instructive signals and cues that polarize cells undergoing cell intercalation and collective cell migration during CE. Future studies to identify these signals and elucidate their roles in the core cellular processes underlying CE will unravel the basic principles by which CE functions in development.

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