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Review

Cranial placodes: Models for exploring the multi-facets of cell adhesion in epithelial rearrangement, collective migration and neuronal movements

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ABSTRACT

Key to morphogenesis is the orchestration of cell movements in the embryo, which requires fine-tuned adhesive interactions between cells and their close environment. The neural crest paradigm has provided important insights into how adhesion dynamics control epithelium-to-mesenchyme transition and mesenchymal cell migration. Much less is known about cranial placodes, patches of ectodermal cells that generate essential parts of vertebrate sensory organs and ganglia. In this review, we summarise the known functions of adhesion molecules in cranial placode morphogenesis, and discuss potential novel implications of adhesive interactions in this crucial developmental process. The great repertoire of placodal cell behaviours offers new avenues for exploring the multiple roles of adhesion complexes in epithelial remodelling, collective migration and neuronal movements.

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Introduction

Adhesion molecules: Dynamic anchoring sites and signalling platforms

Cell adhesion is a major driving force in multicellular morphogenesis, and its misregulation leads to developmental defects and tumor invasion. Adhesion molecules are transmembrane glycoproteins which couple the microenvironment of cells with their internal mechanics and biology. Their extracellular domain binds to adhesive receptors of neighbouring cells (intercellular adhesion) or to components of the extracellular matrix (ECM) (cell/matrix adhesion), while cytoplasmic tails interact with cytoskeleton filaments and signalling proteins. Cadherins and integrins are the best characterised players in intercellular and cell/matrix adhesion, respectively. Cadherins engage in homophilic interactions at the level of specialised adhesive platforms, the adherens junctions. $\alpha\beta$ integrin heterodimers bind to ECM components which form 3D meshworks with various geometries and physical properties in the cell environment.

Adhesion proteins exhibit a dual function. Their first recognised role is structural: they initiate and maintain tissue cohesion, and provide anchoring sites for pushing and pulling forces required for cell shape changes and morphogenetic movements. However, it is now clear that adhesion molecules play more diverse roles, which do not only depend on their sticky properties. This can be attributed to their ability to sense and transduce mechanical cues and crosstalk with signalling pathways that regulate cytoskeleton dynamics, proliferation, survival and differentiation (Hynes, 2002; Stepniak et al., 2009; Schwartz and DeSimone, 2008). Adhesive complexes can therefore be seen as dynamic anchoring sites and signalling platforms.

The unique morphogenetic properties of cranial placodes

Neural crest (NC) cells have long been used as an experimental paradigm to study the function of adhesion molecules in cell migration and morphogenesis (McKeown et al., 2013). Here, we focus on another embryonic cell population with unique morphogenetic properties, the placodal cells. Cranial placodes are discrete patches of ectodermal cells which give rise to crucial parts of sensory organs and ganglia in the vertebrate head, including the olfactory epithelium, the lens, the entire inner ear and cranial sensory ganglia, as well as mechanosensory lateral lines in aquatic vertebrates (Fig. 1A) (Streit, 2008; Schlosser, 2010).

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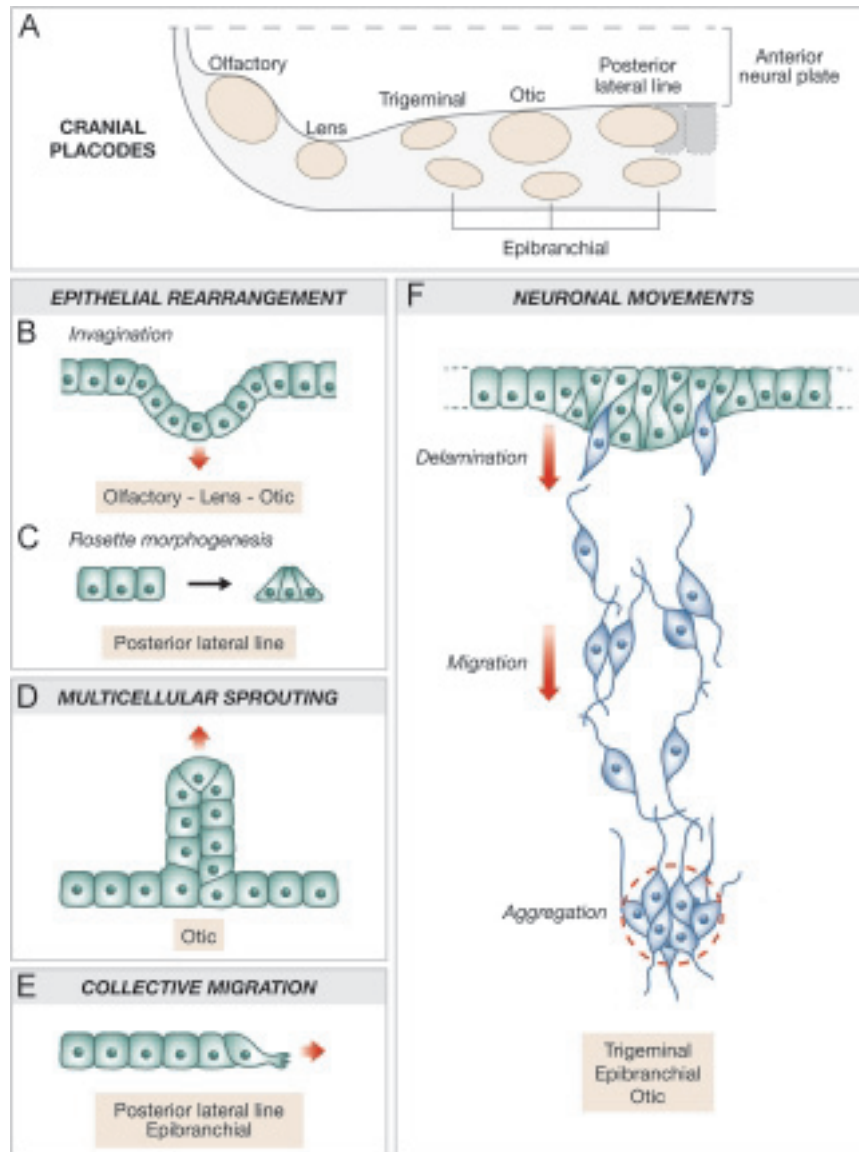E-mail address: marie.breau@upmc.fr (M.A. Breau).

Fig. 1. The repertoire of placodal cell behaviours. (A) Dorsal view of half of a theoretical vertebrate embryo, anterior to the left (adapted from Breau and Schneider-Maunoury, 2014). Placodes whose morphogenesis are not discussed in the text are not represented. After the segregation of placodal precursors and their coalescence, cranial placodes appear as discrete patches of ectodermal cells that occupy specific positions along the anteroposterior axis in the head region of the embryo, next to the brain. From this stage, these placodal tissues can undergo epithelial rearrangement such as invagination (B) and formation of rosette-like structures (C), sprouting of multicellular strands (D) or migration as cohesive groups (D). Differentiating neurons produced by neurogenic placodes delaminate from the pseudostratified epithelium of the surface ectoderm, and migrate as streams of bipolar cells towards the site of sensory ganglia aggregation (F).

Progenitors of cranial placodes are initially partially intermixed within the crescent-shaped pan-placodal domain surrounding the anterior neural plate (Streit, 2008; Schlosser, 2010). As development proceeds, three steps of placode morphogenesis can be distinguished. First, intermingled placode progenitors segregate into adjacent placodal cell domains. Second, these apposed cell populations coalesce into compact and individualised placodes occupying specific positions along the anteroposterior axis, next to the brain (Fig. 1A) (Breau and Schneider-Maunoury, 2014). Third, subsequent morphogenetic processes take place, such as invagination, delamination and diverse types of migration, giving rise to the final pattern of placodal derivatives (Schlosser, 2010). In this review, we focus on the two last steps of cranial placode morphogenesis. The mechanisms driving the first step of placodal precursor segregation, including the hypothesis of an active sorting-out mediated by differential adhesion, have been recently discussed (Breau and Schneider-Maunoury, 2014) and will not be covered here.

Placodal cells share common features with NC cells: their origin at the neural plate border, and their capacity to leave the ectoderm and move through embryonic tissues to generate a variety of internal structures. However, there are also clear differences between NC cell and placode morphogenesis. After their detachment from the neural tube through epithelium-to-mesenchyme transition (EMT), NC cells migrate as isolated or loose groups of mesenchymal cells, and differentiate into neurons or other cell types only when they have reached their final destination (Blentic et al., 2011; Strobl-Mazzulla and Bronner, 2012; Theveneau and Mayor, 2012). In contrast, placodal cells can rearrange as epithelial cells (Fig. 1B and C), move or sprout as cohesive clusters (Fig. 1D and E) and migrate as streams of differentiating neurons (Fig. 1F). These are three unique morphogenetic properties of placodal cells compared to NC cells. Such behaviours must rely on dynamic adhesive interactions with surrounding cells and ECM components. Functional studies of adhesion proteins in placode ontogeny are still relatively scarce and often lack mechanistic

investigation. We will next discuss examples of known functions for adhesion molecules in placode morphogenesis, and describe observations suggesting additional likely roles of adhesive complexes. This will shed light on placode morphogenesis as a useful model for exploring the functions and dynamics of adhesion proteins in epithelial remodelling, collective movement and neuronal migration.

Epithelial rearrangement, collective migration and multicellular sprouting in placode morphogenesis

Epithelia are cohesive sheets of cells exhibiting apico-basal polarity and adherens junctions with their neighbours. Commonly seen as stable tissues, epithelia can however undergo local rearrangements allowing morphogenesis to occur: cell intercalation results in convergence/extension, cell elongation thickens an epithelial layer, whereas apical constriction leads to epithelial invagination, or formation of rosette-like structures (Lecuit and Lenne, 2007; Guillot and Lecuit, 2013).

Collective migration and multicellular sprouting are two other dynamic behaviours of cohesive sheets observed during morphogenesis, tissue repair or tumor progression. In these processes, cells move or sprout as coherent clusters with maintained intercellular contacts (Friedl and Gilmour, 2009; Rørth, 2012). The group can contain cells with mixed epithelial and mesenchymal characters (see for example Dumortier et al., 2012), or be patterned into mesenchymal-like leaders and epithelial-like followers (Friedl and Gilmour, 2009; Rørth, 2012). Such collective behaviours thus illustrate the existence of fine-tuned partial transitions between the usually opposed epithelial and mesenchymal cell states (Revenu and Gilmour, 2009).

Placodal cells display several of these epithelial rearrangement and collective behaviours (Fig. 1B–E), in which they face the challenge of remodelling and coordinating their cell/cell and cell/matrix adhesive interactions without losing tissue cohesion.

Epithelial invagination

Invagination is the bending of an epithelial sheet to form a groove or a vesicle (Fig. 1B). This epithelial rearrangement is widely used in embryonic morphogenesis (Lecuit and Lenne, 2007), for example during neural tube formation (Suzuki et al., 2012). In placodes, invagination of the ectoderm initiates lens, otic and olfactory placode morphogenesis. Invagination is driven by coordinated apical constriction (AC), in which columnar epithelial cells shrink their apical domain to acquire a wedge-shape morphology. In fish, the lens placode is not internalised by invagination, but through the delamination of a cell mass, which appears to involve AC as well (Greiling and Clark, 2009). Canonical AC involves pulsatile contractions of apical actomyosin networks. To transform local contraction into AC, actomyosin filaments must be attached to cell/cell adhesive complexes, typically adherens junctions (Sawyer et al., 2010; Martin and Goldstein, 2014). Studies in several contexts identified a core pathway regulating AC in vertebrates, which implicates interactions at adherens junctions between Shroom3 (an actin binding protein and transcriptional target of Fgf signalling), Rock, and RhoA, the final activator of actomyosin contraction (Martin and Goldstein, 2014). This pathway is at least partially at work during lens invagination (Fig. 2) (Plageman et al., 2010, 2011; Lang et al., 2014), but has not been fully dissected in the otic placode, where myosin acts downstream Fgf signalling but in an unconventional fashion, by depleting basal domains in actin filaments (Sai and Ladher, 2008). Which adhesion proteins control AC in cranial placodes? NCad is a good candidate, although its implication in invagination appears to be species-specific for lens/otic placodes (Babb-Clendenon et al., 2006; Smith et al., 2009; Pontoriero et al., 2009; Malicki et al., 2003;

Christophorou et al., 2010; Lang et al., 2014). NCAM, which accumulates apically and controls lens invagination in chick, could fulfill this AC function (Christophorou et al., 2010). Thus, the identity of the adhesion molecules implicated in placodal AC remains to be elucidated. Also, the nature of the physical links between cell/cell contacts and actomyosin is still unclear, except for the mouse lens where β-catenin and p120-catenin are involved (Kreslova et al., 2007; Lang et al., 2014). These molecular linkers have recently regained interest in the AC field. Indeed, during *Caenorhabditis elegans* gastrulation and in *Drosophila* ventral furrow cells, actomyosin contraction preceeds AC, suggesting that the cell shape change is triggered by the tightly regulated connection of actomyosin to membrane adhesion molecules, rather than actomyosin contraction itself (Roh-Johnson et al., 2012).

Mathematical modelling suggest AC can on its own produce invagination of epithelial sheets (Sawyer et al., 2010). However, in the lens placode at least, AC appears not to be sufficient for invagination (Lang et al., 2014). Other possible driving forces likely involve cell/matrix adhesion. Indeed, the basal lamina underlying lens and otic placodal epithelia contains several ECM components including fibronectin, laminin, proteoglycans and polysaccharides, most of which are required for invagination (Gerchman et al., 1995; Moro-Balbás et al., 2000; Gato et al., 2001; Visconti and Hilfer, 2002; Huang et al., 2011). What is the precise function of cell/matrix interactions? They could mediate basal constriction (BC), which must occur in cells at the border of the invaginating layer and potentially contributes to inward tissue bending (Fig. 2). Although less studied than AC, BC has been described in several contexts where it requires cell/matrix adhesion (Gutzman et al., 2008; Martinez-Morales et al., 2009; Bogdanović et al., 2012; He et al., 2010). Alternatively, cell/matrix adhesive contacts could be important for physical interactions between lens and retina epithelia, which invaginate together in a tightly coordinated manner. Intriguing inter-epithelial filopodia are observed between invaginating lens and retina: they extend from the basal side of lens placodal cells and make contact with the optic cup (Chauhan et al., 2009). Conditional knock-out of FAK (Focal Adhesion Kinase) in lens cells results in fewer filipodia, suggesting they are anchored at their tips by integrin adhesive complexes necessary for their formation or stabilisation. Consistently, the filopodial protrusions are covered by laminin. These filopodia appear to be contractile and have been proposed to act as physical tethers assisting the invagination process and coordination between the two epithelia (Fig. 2) (Chauhan et al., 2009).

Collective migration

In collective migration, cells move as a group with maintained intercellular contacts (Friedl and Gilmour, 2009; Rørth, 2012). There are several ways adhesive contacts can be important for this process. First, at least subsets of cells in the collective need to physically interact with the environment (nearby cells or matrix) to generate traction forces that produce the movement. Intercellular contacts within the cluster must also be essential for tissue cohesion, transmission of pulling or pushing forces, and coordination of cell behaviours. Last, adhesive complexes could control collective migration through non-mechanical signalling activities.

The posterior lateral line primordium: A powerful model for collective migration

The posterior lateral line placode, found in aquatic vertebrates, generates a cohesive group of cells (the primordium) which migrates from head to tail to deposit superficial sensory organs called neuromasts (Fig. 3A) (Ghysen and Dambly-Chaudière, 2004). The directional movement of this cell cluster in zebrafish has emerged as an amenable model for collective migration (Aman
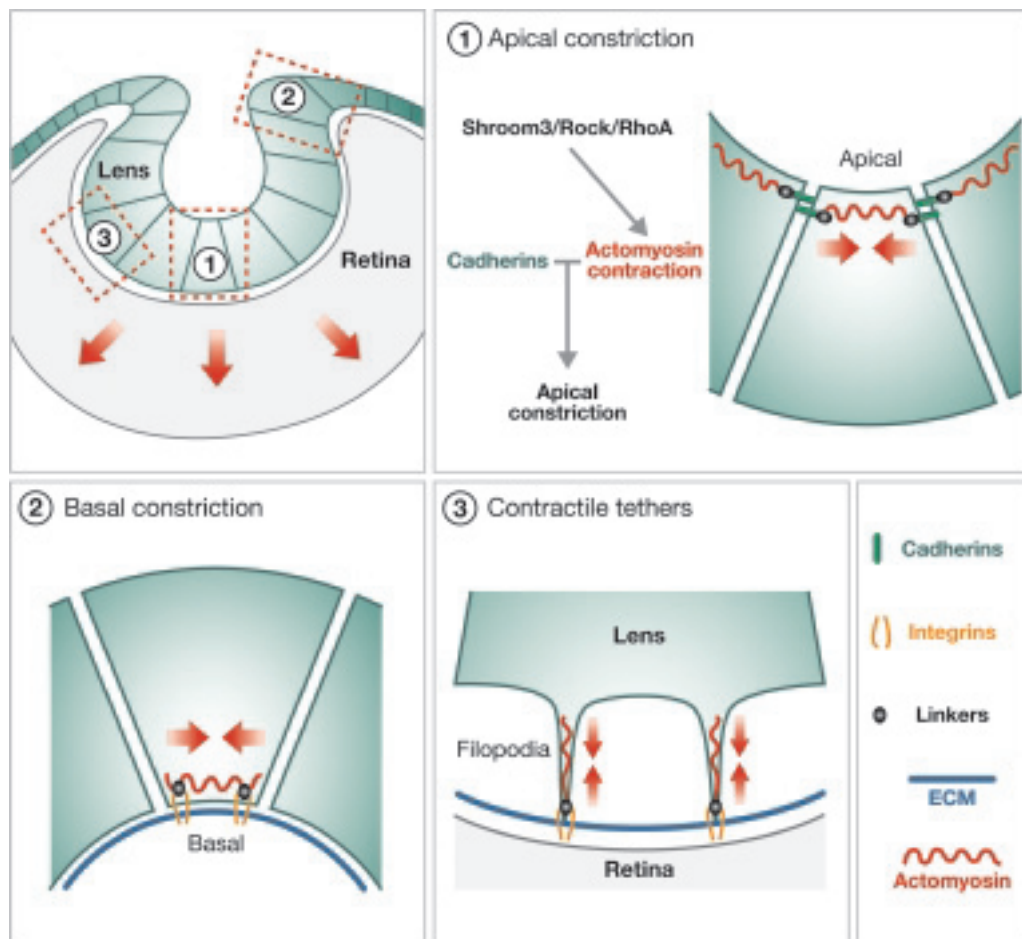
Fig. 2. Adhesion-dependent mechanisms driving epithelial invagination of the lens placode. Top left. Schematic view of lens epithelium invagination and its tight coordination with the underlying invaginating retina (adapted from Chauhan et al., 2009). Three mechanisms implicating adhesion molecules are proposed to participate in this inward epithelial movement: (1) Apical constriction of cells in the center of the invaginating layer results from the local contraction of actomyosin filaments attached to cadherin-based adherens junctions. Contraction of actomyosin networks occurs downstream of a Shroom3/Rock/RhoA signalling cascade (Plageman et al., 2010, 2011). (2) Shortening of basal domains (basal constriction) in cells at the edge of the invaginating layer may also contribute to tissue deformation. As described in other contexts, basal constriction in the lens could be mediated by integrin/ECM interactions and actomyosin contraction (Gutzman et al., 2008; Martinez-Morales et al., 2009; Bogdanović et al., 2012; He et al., 2010). (3) Inter-epithelial filopodia emanating from lens cells have been proposed to act as contractile tethers which assist the folding of the lens placode and coordinate the movement with retina invagination. Their anchoring to the retina likely depends on integrin/ECM adhesive interactions (Chauhan et al., 2009).

and Piotrowski, 2009). The migration requires the Sdf1α/Cxcl12a chemokine, present along the path, and its receptor Cxcr4b, expressed in the primordium downstream of Wnt signalling (David et al., 2002; Haas and Gilmour, 2006; Aman and Piotrowski, 2008; Breau et al., 2013). Cxcr7b-mediated sequestration of Sdf1α in the trailing primordium generates an internal chemokine gradient orienting the migration (Donà et al., 2013; Venkiteswaran et al., 2013). Strikingly, the migration phenotype of the *cxcr4b* (*ody*) mutant can be rescued by a few wild type cells located at the tip of the primordium (Haas and Gilmour, 2006), suggesting that leader cells guide followers. Follower cells could respond to chemotactic cues produced by the tip, such as Fgfs (Breau et al., 2012; Dalle Nogare et al., 2014), and/or be dragged by tip cells through mechanical coupling mediated by intercellular adhesive interactions. Recent experiments in which the primordium is laser cut into leading and trailing portions show that leading cells, in turn, need to be contacted by trailing cells to migrate (Dalle Nogare et al., 2014). Whether this physical connection induces mechanical pushing forces from the back, or trigger non-mechanical signalling activating the migration, remains however unknown.

Anosmin1 and cadherins are good candidates for mediating cohesion or transmission of pulling/pushing forces within the primordium collective. Anosmin1 is a secreted protein implicated in Kallmann syndrome (Legouis et al., 1991). It contains four fibronectin type III (FnIII) modules that are highly similar to domains found in the CAM protein family, involved in cell/cell adhesion. As it also acts as an efficient substrate for cell adhesion *in vitro* (Soussi-Yanicostas et al., 1998), it has been proposed to function as an adhesion protein through an unknown surface receptor, or linkage to other ECM components. *Anosmin1* is expressed in the primordium, and its knockdown impairs migration without altering Sdf1α and Cxcr4b expression (Yanicostas et al., 2008). The accumulation of the protein in the central region of the primordium suggests it could act as an intercellular glue holding cells together (Fig. 3C). However, cell/cell contacts are not lost upon Anosmin1 knockdown, possibly due to functional redundancies with other cell/cell adhesion molecules present throughout the primordium, such as ECad, NCad (Fig. 3C) (Liu et al; 2003, Kerstetter et al., 2004; Matsuda and Chitnis, 2010; Revenu et al., 2014), NCAM (ZFIN) and claudins, members of tight junctions (Kollmar et al., 2001). NCad loss-of-function studies report contradictory results: the migration appears affected in NCad morphants and in the *glass onion* (*glo*) NCad mutant (Kerstetter et al., 2004), but no phenotype is detected in the *parachute* (*pac*) NCad mutant (Revenu et al., 2014). The stronger defects in the *glo* mutant could be explained by the dominant
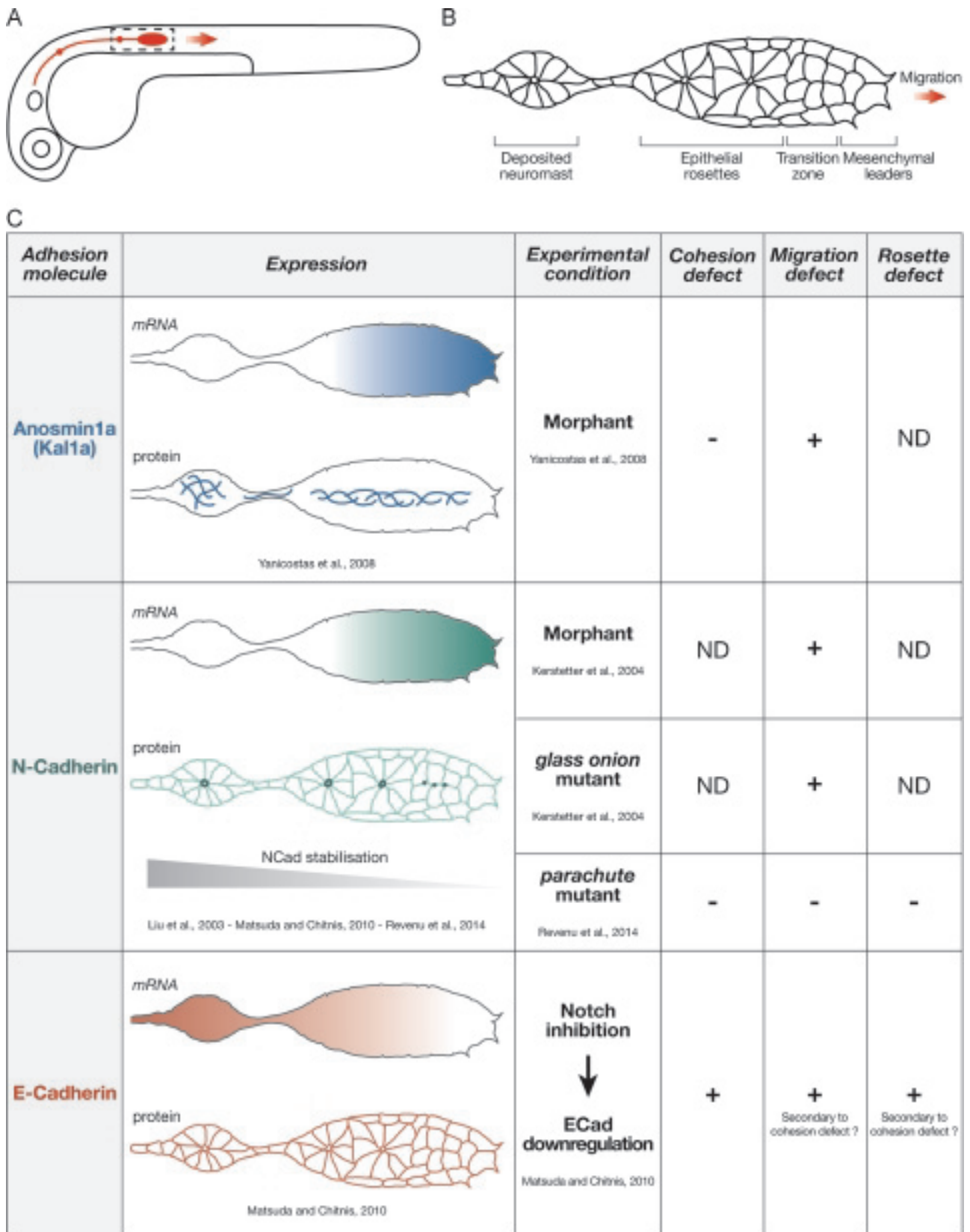
Fig. 3. Collective migration of the posterior lateral line primordium and rosette morphogenesis: expression and function of adhesion molecules. (A) Schematic view of a 28 hpf (hours post fertilisation) zebrafish embryo. Red structures represent the migrating primordium and two deposited neuromasts. The inset corresponds to the high magnification seen in (B). (B) High magnification illustration of the primordium architecture, with mesenchymal-like leader cells, a transition zone in which cells progressively acquire epithelial features to assemble in stable rosettes in the trailing region. (C) Table summarising our current knowledge about expression and function of adhesion proteins in primordium cohesion, migration and in rosette morphogenesis.

negative effect of the mutated NCad on other cadherins (Malicki et al., 2003; Harrington et al., 2007). Moreover, the morphant phenotype should be taken with caution, given known off-targets effects of morpholinos (Gerety and Wilkinson, 2011) and the lack of documented rescue experiments. Whether intercellular contacts are maintained or not in NCad morphants and *glo* mutants remains to be analysed (Kerstetter et al., 2004). The only reported condition with dissociation of primordium cells is the inhibition of Notch signalling, which results in a dramatic primordium fragmentation followed by the stalling of dissociated cells, and correlates with a reduction in ECad expression (Fig. 3C) (Matsuda and Chitnis, 2010). Although primordium disintegration is likely due to ECad downregulation, this will need to be directly tested with ECad loss-of-function experiments, which are technically challenging due to early developmental roles of ECad.

The expression of several adhesion molecules across the migrating primordium suggests that intercellular contacts and front/back force transmission are mediated by multiple redundant mechanisms that ensure the robustness of tissue cohesion. Moreover, for the cluster to move forward, at least some primordial cells have to establish anchoring sites to the environment to produce traction forces. Is this mediated by cell/matrix or cell/cell adhesion? Which molecules are involved? To elucidate the function of each individual adhesion protein will require high resolution live imaging of shapes, behaviours and protrusive activities of primordium cells upon loss- and gain-of-function experiments. The use of mechanical sensors to map tension forces exerted on cadherins or other adhesion molecules across the primordium, as it has recently been done for ECad in *Drosophila* border cells (Cai et al., 2014), will also be highly informative to better understand the dynamics of this migrating cell cohort. Finally, besides their likely role in tissue integrity and force propagation, adhesion proteins may have signalling functions. Anosmin1 may for instance interact with the Sdf1α/Cxcr4b axis, as suggested by double knockdown experiments (Yanicostas et al., 2008). In addition,

it has been proposed that NCad-based contact inhibition of locomotion (see definition below) could drive the chemotactic response of the primordium to Sdf1α, as it does for cranial NC cells (Theveneau et al., 2010), but this awaits further investigation.

Collective migration of epibranchial placodal precursors: Pushing from the back

As recently revealed by live imaging in *Xenopus* embryos, epibranchial pre-placode cells undergo directional ventral migration within the ectodermal layer, upon contact with the adjacent and more dorsal cranial NC cells (Theveneau et al., 2013). This movement is part of the coalescence step of placode morphogenesis (Breau and Schneider-Maunoury, 2014), which follows precursor segregation and preceeds delamination of epibranchial neuroblasts. Contact inhibition of locomotion (CIL) had previously been described as a mode of cell/cell interaction in which single cells change the direction of their migration upon repulsive cell/cell contacts (Carmona-Fontaine et al., 2008; Theveneau et al., 2010). Théveneau and colleagues showed that the CIL concept can be extended to repulsive interactions between two cell-populations, NC and placodes (Theveneau et al., 2013). In *in vitro* co-cultures, NC cells and placodes engage in a chase-and-run behaviour: NC cells are attracted by placodes, and placodes are in turn repelled by NC cells (Fig. 4). Cxcr4b/Sdf1α signalling mediates the chase: placodal cells play the role of the Sdf1α source that attracts Cxcr4b-expressing NC cells. In turn, contacts between NC cells and placodes push placodal cells away, a process that requires Wnt-PCP and NCad. Upon transient NCad-mediated adhesive contacts at the NC cell/placode interface, focal adhesion to the substrate and cell protrusions are destabilised in placodal cells, in an NCad-dependent fashion. This results in directional migration of the placodal cluster in the opposite direction (Fig. 4). This CIL mechanism at the cell population scale ensures a constant displacement of
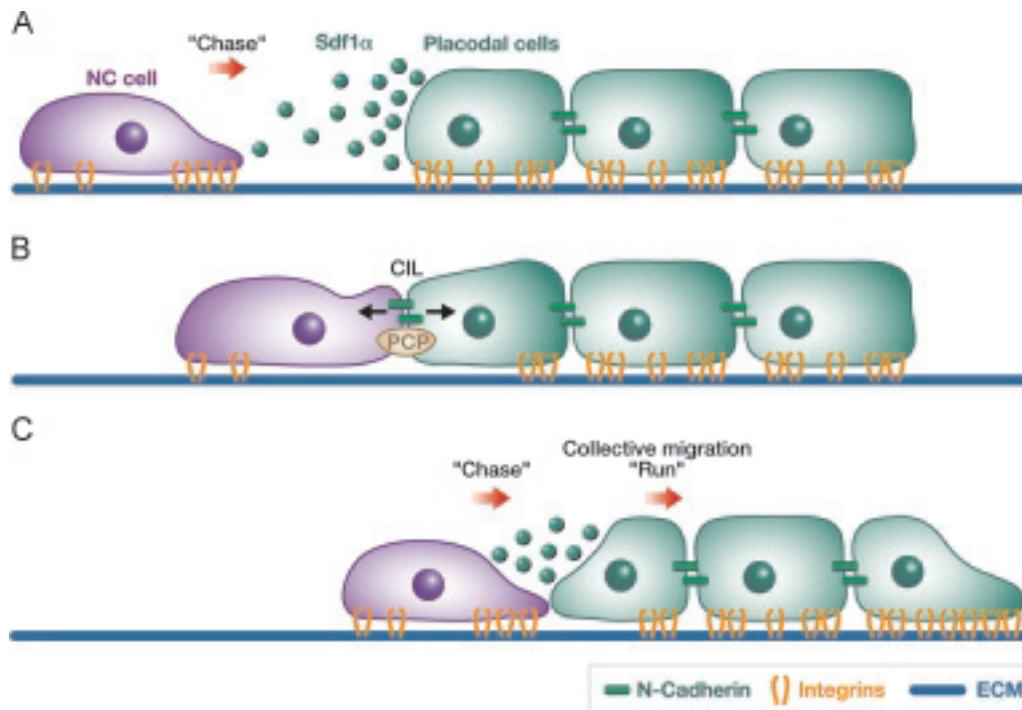

Fig. 4. NCad-dependent "Chase-and-Run" controls collective migration of epibranchial pre-placode cells. The Sdf1α chemokine secreted by placodal cells attract NC cells (A, "Chase" behaviour). Contacts between NC and placodal cells trigger the local loss of focal adhesions to the substrate and the collapse of cytoplasmic protrusions; this requires NCad and Wnt-PCP signalling (B). Force redistribution induces the migration of the placodal cells in the opposite direction: the pladodal cluster is "pushed from the back", away from the NC ((C), "Run" behaviour). This contact inhibition of locomotion (CIL) at the cell-population scale allows the coordinated movement of the two cell types within the embryo. Adapted from Theveneau et al. (2013) and Steventon et al. (2014).

the Sdf1α source and coordinated movements of the two adjacent cell types. Thus, epibranchial placodes are "pushed from the back" by repulsive interactions with NC cells, in an NCad-dependent manner (Theveneau et al., 2013).

Sprouting and fusion of multicellular strands

Multicellular sprouting is common in morphogenesis of branched organs and dissemination of solid tumors (Ochoa-Espinosa and Affolter, 2012; Friedl and Gilmour, 2009). What distinguishes the sprouting of cohesive clusters from cell groups undergoing collective migration is the maintenance of a physical contact with the tissue of origin (Rørth, 2012). In placodes, this behaviour is seen during the formation of the semi-circular canals, which are parts of the inner-ear structures controlling body balance (Bok et al., 2007). Early steps of inner ear morphogenesis include formation of the otic vesicle by epithelial invagination, and delamination of the neuroblasts forming the statoacoustic ganglion (see below). Semi-circular canal morphogenesis then starts with the evagination of multicellular buds, which grow from opposite sides in the otic cavity and fuse together (Figs. 1D and 5A). Does the sprouting process implicate proliferation, small-scale rearrangements or active cell migration? What is the epithelial/mesenchymal state of cells within the digit? Although still lacking, dynamic analysis of cell behaviours in this system will help elucidating these questions.

In the zebrafish otic placode, various ECM components are expressed by the multicellular strands (but not the surrounding otic epithelium) during their outgrowth, and downregulated after their fusion (Geng et al., 2013). Semi-circular canal outgrowth defects seen in several mutants correlate with misexpression of ECM components (Busch-Nentwich, 2004). In *Xenopus*, injection of hyaluronidase within the growing sprouts leads to their collapse, suggesting that the sprouting process requires the presence of glycosaminoglycan hyaluronan (Haddon and Lewis, 1991). Together, these data suggest that local deposition of ECM is important for the outgrowth of these evaginations. ECM could accumulate either at the bud tip to guide invasion or, as suggested for mammary gland and lung branching morphogenesis (Fata et al., 2004; Moore et al., 2005), along the flanks to stabilise and impose constraint on the growing sprout (Fig. 5B). In *Xenopus*, the sprouts contain an acellular core filled with hyaluronan. This suggests an alternative mechanism in which accumulation of ECM within this acellular core propels the evagination forward (Haddon and Lewis, 1991). The sprouting step is also dependent on NCad-mediated cell/cell adhesion in zebrafish (Babb-Clendenon et al., 2006). As discussed for collective migration, NCad could be important for transmitting pulling forces exerted by "tip cells", or pushing forces from the back produced by cell intercalation or proliferation, or have other signalling roles. Following their expansion, the buds coming from opposite sides of the otic vesicle adhere to each other and fuse (Fig. 5A). This process resembles the fusion which terminates many morphogenetic events such as neural tube closure (Pai et al., 2012). A recent report showed that the recognition and fusion of the sprouts, but not their outgrowth, involves Gpr126, a member of the G-protein coupled receptor adhesion class proposed to display adhesive functions (Geng et al., 2013; Yona et al., 2008). The mutant phenotype could result from a direct adhesive role of Gpr126 during the fusion step, or from an abnormal maintenance of ECM component expression that would prevent the fusion (Geng et al., 2013).
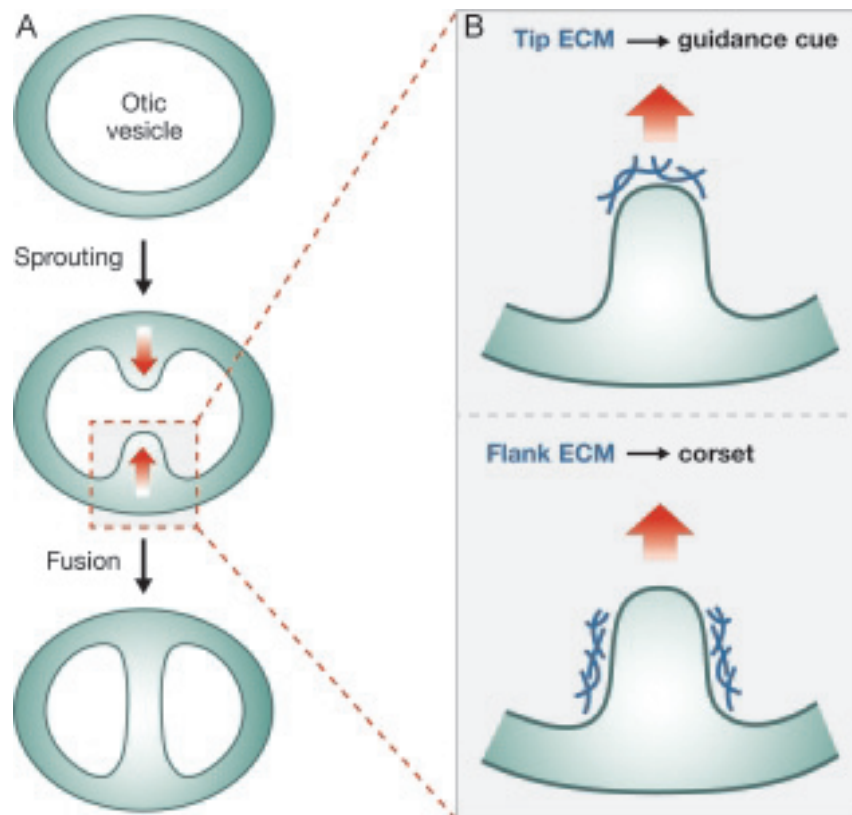

Fig. 5. Semi-circular canal morphogenesis in the otic placode involves ECM-driven multicellular sprouting. (A) Early steps of semi-circular canal morphogenesis in zebrafish involves the formation of multicellular buds which grow from opposite sides of the otic vesicle and fuse to form transverse pillars. (B) Two possible models for ECM-driven sprouting in the otic vesicle. ECM components could either accumulate at the tip and serve as guidance cues for collective invasion, or along the bud flanks to constrain growth towards the tip, like a corset.

Placodal tissues thus display collective migration and sprouting behaviours which can be likened to tumor progression. It is particularly relevant for the metastatic spreading of well-differentiated carcinomas which invade adjacent tissues as multicellular digits or clusters (Friedl and Gilmour, 2009; Friedl et al., 2012).

Rosette morphogenesis

The formation of rosettes is a frequent rearrangement of epithelial tissues undertaking morphogenesis. For instance, rosettes are observed during kidney and pancreas development, and in the closing neural tube. Epithelial rosettes can form transiently during the course of epithelial remodelling, or be maintained to prefigure the radial architecture of specialised organs (Harding et al., 2014). The latter situation is seen in the zebrafish posterior lateral line primordium, in which rosette-like structures assemble to form the future sensory neuromasts, a process regulated by Fgf signalling (Lecaudey et al., 2008; Nechiporuk and Raible, 2008; Hava et al., 2009). The migrating primordium is patterned along its anteroposterior axis: the leading zone contains mesenchymal-like cells that progressively acquire apico-basal polarity and form adherens junctions in the transition zone, to eventually organise into mature epithelial rosettes in the trailing region (Fig. 3A–C). As described for rosettes observed during neural tube closure (Nishimura and Takeichi, 2008), rosette assembly in the primordium is thought to be mediated by AC (Fig. 1C) initiating in the transition zone of the primordium, just behind the leader cells (reviewed in Harding et al., 2014). Consistently, several members of the canonical AC pathway control primordium rosette assembly downstream of Fgf signalling (Ernst et al., 2012; Harding and Nechiporuk, 2012). The AC hypothesis has however recently been challenged (Revenu et al., 2014). A dynamic analysis of NCad localisation revealed that NCad first accumulates in discrete puncta which coalesce into apical clusters in the transition zone of the primordium (Fig. 3C), a process that requires microtubules. Apical NCad junctions become stabilised in more mature pro-neuromasts in the trailing primordium. These findings suggest that rosette assembly in the primordium involves the formation, fusion and stabilisation of NCad apical adherens junctions, rather than the progressive narrowing of pre-existing apical domains expected in a canonical AC process (Revenu et al., 2014). Rosette morphogenesis is not affected in NCad *pac* mutants (Revenu et al., 2014), but primordium migration and potentially rosette formation are impaired in NCad morphants and *glo* mutants (Fig. 3C) (Kerstetter et al., 2004). Further experiments are required to clarify the requirement of NCad in rosette morphogenesis in this context. Once formed, epithelial rosettes detach from the migrating primordium at regular intervals in the back of the primordium, which generates the stereotypic alignment of sensory neuromasts along the trunk of the fish embryo (Fig. 3A and B) (Ghysen and Dambly-Chaudière, 2004). Does this deposition cycle rely on the dynamic regulation of adhesion molecules in primordium cells? Surprisingly, this fascinating question has so far remained unanswered in the lateral line field.

Besides their pre-organisation of the neuromast radial structure, could rosettes in the primordium play other roles? Rosettes are not required for primordium migration (Ernst et al., 2012), but a novel function related to cell adhesion has been recently reported: in their center, rosettes form an apical minilumen trapping secreted Fgf ligands, which locally coordinate and further enhance epithelial morphogenesis (Durdu et al., 2014). Microlumina are surrounded by tight and adherens junctions that may be important for their formation or maintenance, and the ligand trapping (Durdu et al., 2014). Two types of rosettes can be identified during epithelial morphogenesis: the first category forms by AC, while the second arises from planar polarised constriction, where the constricted region spans the entire height of the cell (Kasza et al., 2014; Harding et al., 2014). The second class of rosettes resolves rapidly and is observed in cells in the process of intercalating with each other. Their formation, but most importantly their resolution, must contribute to global changes in the tissue shape such as elongation (Harding et al., 2014). Rosettes forming by AC, like those of the primordium, are usually not resolved and rather persist to prefigure the radial organisation of organs, which makes them unlikely to play this "tension balancing" role. Rosette structures could form and have this function in
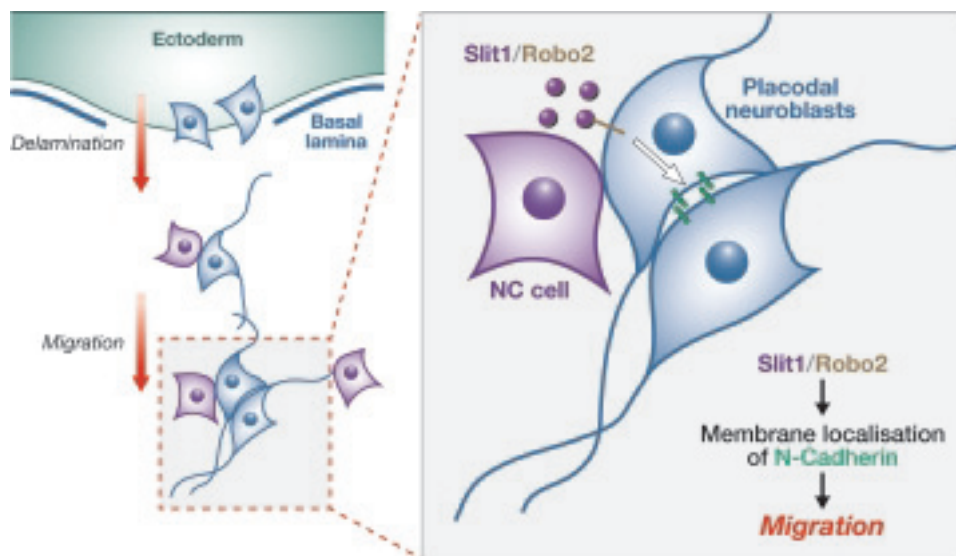

Fig. 6. Delamination and migration of neuroblasts produced by trigeminal and epibranchial placodes. (Left) Trigeminal and epibranchial neuroblasts escape from the surface ectoderm through breaches of the basal lamina ECM (Graham et al., 2007). During their migration and aggregation into sensory ganglia, differentiating placodal neurons show close interactions with each other and with surrounding neural crest (NC) cells (Shiau et al., 2008, 2011; Shiau and Bronner-Fraser, 2009). (Right) In chick embryos, interactions between placodal trigeminal neuroblasts and NC cells are required for the migration: Slit1 secreted by NC cells activates its receptor Robo2 on the surface of placodal neuroblasts. In turn, Robo2 stimulates the membrane localisation of NCad at contacts between differentiating neurons, required for neuronal migration (Shiau et al., 2008; Shiau and Bronner-Fraser, 2009).

other placodes, but this awaits further analysis of placodal tissue architecture.

Neuronal movements in placode morphogenesis

Neurogenic placodes contribute sensory neurons to the cranial peripheral nervous system; they include the olfactory, otic, trigeminal and epibranchial placodes (Schlosser, 2010). Most of our knowledge of neurogenic placode morphogenesis comes from studies of trigeminal and epibranchial placodes. These placodes are thickened and pseudostratified portions of the ectoderm epithelium which produce neuronal cells, referred to as neuroblasts or differentiating neurons in this article. Placodal neuroblasts detach from the surface ectoderm, migrate in the underlying mesenchyme and aggregate with cephalic NC cells to form the cranial sensory ganglia (Figs. 1F and 6A) (D'Amico-Martel and Noden, 1983; Lassiter et al., 2014).

Delamination in neurogenic placodes

It is tempting to compare the emigration of placodal cells from the surface ectoderm with EMT undergone by NC cells when they leave the neural tube. Placodal cells have already entered the neuronal differentiation program when they start delaminating (Lassiter et al., 2009; Blentic et al., 2011; McCabe et al., 2009; Shiau et al., 2008; Shiau and Bronner-Fraser, 2009), which suggests a possible coupling between neurogenesis and changes in their adhesive properties. This would be distinct from the ontogeny of NC which engage in EMT before their neuronal differentiation. Canonical EMT converts static epithelial cells (apico-basally polarised, glued together by adherens junctions, and stably anchored to the basal lamina by integrin-mediated adhesions) into migratory mesenchymal cells that have lost these characters and escape through breaches in the basal lamina (Thiery et al., 2009). The ectodermal basal lamina appears to be interrupted where epibranchial neuroblasts delaminate (Graham et al., 2007). This must be important for their release and suggests their ability to locally degrade basal lamina ECM components. It has been proposed that placodal neuroblast delamination is distinct from a classical EMT (Graham et al., 2007), based on morphologies of placodal neuroblasts and their lack of expression of RhoB or Snail, two EMT regulators (Thiery et al., 2009; Duband, 2010; Theveneau and Mayor, 2012). However, in this and other studies, the shape of delaminating neuroblasts looks mesenchymal (Graham et al., 2007; Shiau et al., 2011). In mouse and chick embryos, they acquire a bipolar neuronal morphology after delamination, when they reach the area underlying the ectoderm (Figs. 1F and 6) (Graham et al., 2007; Shiau and Bronner-Fraser, 2009; Shiau et al., 2011). Additional gene expression and functional studies for other key EMT players are required to reach a clear conclusion about the similarities and differences between EMT and delamination of placodal neuroblasts.

Switches in cadherin repertoire are hallmarks of EMT (Thiery et al., 2009; Wheelock et al., 2008). Delaminating neuroblasts must experience similar transitions in their cell/cell and cell/matrix adhesion complexes, which still need to be characterised in detail. Trigeminal and epibranchial placodal cells likely express ECad when still embedded in the ectodermal epithelium, as observed in other placodes (Levi et al., 1991; Liu et al., 2004). In chick trigeminal placodes, NCad is expressed in delaminating and migrating neuroblasts, suggesting that delaminating placodal neurons undergo the typical ECad to NCad transition commonly involved in EMT during tumor invasion (Wheelock et al., 2008). Although NCad is necessary for the migration (see below), it is dispensable for the delamination in this context (Shiau and Bronner-Fraser, 2009). In mouse, a similar ECad to NCad switch is observed in the otic placode, where neuroblasts detach from the otic vesicle and aggregate to form the statoacoustic ganglion, but no functional studies have been performed (Davies, 2011). In zebrafish, NCad is important for the development of the statoacoustic ganglion, but whether this phenotype results from delamination or differentiation defects is unknown (Babb-Clendenon et al., 2006). The importance of NCad and the functional relevance of the ECad to NCad transition thus remain unclear in the context of the developing neurogenic placodes, and deserve further investigation.

What other adhesion molecule could be implicated in the escape of placodal neurons? The tetraspan CD151, expressed in the ectoderm during delamination (McCabe and Bronner, 2011), is a good candidate. Given its ability to interact with integrins and regulate their activity, and its known role in renal morphogenesis and tumor invasion (Caplan et al., 2007; Sadej et al., 2014), the function or regulation of CD151 could be important for delamination, but its early requirement in neuronal specification has so far prevented the analysis of such a role (McCabe and Bronner, 2011). In addition, mechanisms acting downstream of Fgf signalling, required for the delamination (Lassiter et al., 2009), must involve yet to be discovered adhesion molecules driving the morphological changes that accompany delamination. Last, characterising the target genes of transcriptions factors implicated in neurogenic placode development (including proneural transcription factors, reviewed in Schlosser, 2010) could identify important adhesive molecules mediating delamination. Pursuing functional analysis of these candidates will certainly unravel novel mechanisms by which changes in adhesive properties convert stationary neuroepithelial cells into motile differentiating neurons.

Migration as streams of differentiating neurons

Although they harbor a mesenchymal phenotype while escaping from the ectoderm, placodal cells, at least in mouse and chick embryos, adopt a neuronal-like bipolar morphology with long processes soon after delamination, during their migration towards the site of ganglion assemby (Figs. 1F and 6) (Graham et al., 2007; Shiau et al., 2011). Consistent with this, they upregulate neuronal differentiation genes such as islet1 and neurofilament after their delamination (Graham et al., 2007; Shiau et al., 2008; Shiau and Bronner-Fraser, 2009; McCabe et al., 2009), but it is still unclear whether they migrate as post-mitotic neurons, dividing neuroblasts, or a mixed population (McCabe et al., 2009; Blentic et al., 2011; Shiau et al., 2011). Neuronal and mesenchymal cells share common migration principles (Govek et al., 2011), but differences in their morphologies and migration dynamics suggest they face distinct challenges in terms of cell biology, distribution of adhesion sites, cytoskeleton reorganisation and transmission of signals and forces between cell compartments (Cooper, 2013; Solecki, 2012). The formation of trigeminal and epibranchial sensory ganglia in chick and mouse can thus be used as a model for exploring the specific mechanisms of neuronal migration.

During their migration, placodal differentiating neurons form cell/cell contacts (Graham et al., 2007; Shiau et al., 2008; Shiau and Bronner-Fraser, 2009) that appear dynamic and transient in live imaging studies (Shiau et al., 2011; Bhat and Riley, 2011). They also intermix and closely interact with cephalic NC (Fig. 6) (Shiau et al., 2008; Shiau and Bronner-Fraser, 2009). This pattern suggests that both homotypic and heterotypic intercellular interactions can influence the migration. In chick embryos, NCad, expressed by trigeminal neuroblasts but not NC cells, localises at placodal cell/cell contacts and is necessary for their migration (Shiau and Bronner-Fraser, 2009). NCad acts downstream of Slit1/Robo2-mediated interactions between NC and placodal differentiating

neurons: Slit1 produced by NC cells activates Robo2 at the surface of placodal neuroblasts, which in turn stimulates the membrane localisation of NCad (Fig. 6). Similar expression patterns for NCad/Slit1/Robo2 in epibranchial placodes suggest a conserved mechanism in sensory ganglia formation (Shiau et al., 2008; Shiau and Bronner-Fraser, 2009). How does NCad regulate migration? As described for cranial NC cells in *Xenopus*, NCad-mediated CIL could promote overall progression of the neuronal population towards the site of ganglion assembly (Theveneau et al., 2010), but the existing live imaging data do not show repulsive behaviours between migrating placodal neuroblasts (Shiau et al., 2011; Bhat and Riley, 2011). Alternatively, NCad-mediated adhesive contacts could induce the formation of intermediate small neuronal clusters moving more efficiently, or be required for neuroblasts to pull on each other through their long protrusions during chain migration. Live imaging in NCad loss-of-function condition will clarify the underlying mechanism.

In zebrafish, trigeminal neuroblasts migrate as chains of mesenchymal-like cells (Knaut et al., 2005; Bhat and Riley, 2011). Neuroblasts express both ECad and NCad but double loss-of-function does not result in neuron mispositioning or aggregation defects (Knaut et al., 2005). ECad/NCad are thus not required for neuronal movements, but may assist Cxcr4b/Sdf1a chemokine signalling in the control of the migration (Knaut et al., 2005). Subtle defects in the shape and size of cranial ganglia were detected in NCad and Cad6-deficient embryos in other studies, but it is unclear which of delamination, migration, proliferation or differentiation is the primary affected process (Kerstetter et al., 2004; LaMora and Voigt, 2009; Liu et al., 2011). Rather than cadherins, integrin-mediated adhesion is crucial for the chain migration of trigeminal neuroblasts in zebrafish, as shown by erratic movements observed upon knockdown of the integrin α5 subunit (Bhat and Riley, 2011). Integrins may allow placodal neurons to migrate along ECM substrates produced by surrounding tissues. Alternatively, as shown for the chain migration of neuroblasts in the mouse rostral migratory stream, integrins could favor homotypic interactions through binding to interstitial matrix present at cell/cell contacts (Belvindrah et al., 2007).

The formation of cranial sensory ganglia from the neurogenic placodes therefore provide original developmental settings in which to study dynamic behaviours of differentiating neurons and the related remodelling of their adhesive complexes. Further experimental efforts are required to decipher the molecular basis underlying the function of adhesion molecules in these neuronal movements. It will be important to elucidate how changes in adhesive properties of placodal neuroblasts are coupled with the course of neurogenesis during delamination, migration and aggregation into cranial ganglia. This will help drawing comparisons with neuronal migration and differentiation occuring in the brain (Famulski and Solecki, 2013) and extract general principles ruling morphogenesis in the developing nervous system.

Concluding remarks

In conclusion, developing cranial placodes can serve as accessible systems for exploring how adhesion dynamics control epithelial remodelling, movement and sprouting of multicellular cohorts, and migration of differentiating neurons. As such, they offer an alternative and complementary model to the well-studied NC cell paradigm in which to dissect the mechanisms of EMT and mesenchymal migration. Future efforts to image the architecture of placodal tissues in available model organisms will be essential to better characterise differences between species, such as the multi-(*Xenopus*) versus mono-layered (chick and mouse) structure of the ectoderm, and their implications for placodal cell behaviour. As in other tissues, the intrinsic functions of cell adhesion molecules in placode

morphogenesis are challenging to identify, due to early developmental roles and functional compensation between different types of adhesive complexes. It is thus important to obtain a tight spatiotemporal control of functional perturbations, and use dominant-negative strategies when possible. Investigation of the molecular mechanisms underlying the functions of adhesion proteins in placode morphogenesis is still at an early stage. Future mechanistic studies will benefit from live monitoring of adhesion molecules (Revenu et al., 2014) and their interactions with the cytoskeleton, force-generating molecular motors and signalling cascades. The use of cutting edge techniques to probe forces exerted on adhesion proteins within multicellular assemblies (Cai et al., 2014) will also greatly expand our understanding of the morphogenetic movements which shape cranial placodes and their derivatives.

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