<Barresi13e, Further Development_c04_01>

Type, Timing, and Border Formation

The quantitative effects of cadherins are crucial, but *qualitative* interactions—that is, the *type* and *timing* of cadherin expression—also can be important. The timing of particular developmental events can depend on cadherin expression. For instance, N-cadherin appears in the mesenchymal cells of the developing chick leg just before these cells condense and form nodules of cartilage (which are the precursors of the limb skeleton). N-cadherin is not seen prior to condensation, nor is it seen afterward. If the limbs are injected just prior to condensation with antibodies that block N-cadherin, the mesenchyme cells fail to condense and cartilage fails to form (Oberlender and Tuan 1994). It therefore appears that the signal to begin cartilage formation in the chick limb is the appearance of N-cadherin.

The type of cadherin can matter as well. Duguay and colleagues (2003) showed, for instance, that R-cadherin and B-cadherin do *not* bind well to each other. When two populations of cells expressing either R-cadherin or B-cadherin at equal levels are mixed together, they sort out into two opposing mounds of cells with a distinct border between them (Figure 1A). The formation of boundaries is a critical physical achievement necessary for many morphogenetic events. For instance, in the developing ectoderm, the expression of N-cadherin is important in separating the precursors of the neural cells from the precursors of the epidermal cells (Figure 1B). Initially, all early embryonic cells contain E-cadherin, but those cells destined to become the neural tube lose E-cadherin and gain N-cadherin. If epidermal cells are experimentally made to express N-cadherin or if N-cadherin synthesis is blocked in prospective neural cells, the border between the skin and the nervous system fails to form properly (Figure 1A; Kintner et al. 1992). Thus, through the differential expression of two different cadherin types, different tissues can become separated by the formation of a border at the cell membrane occupying the weaker heterophilic interaction (Fagotto 2014).

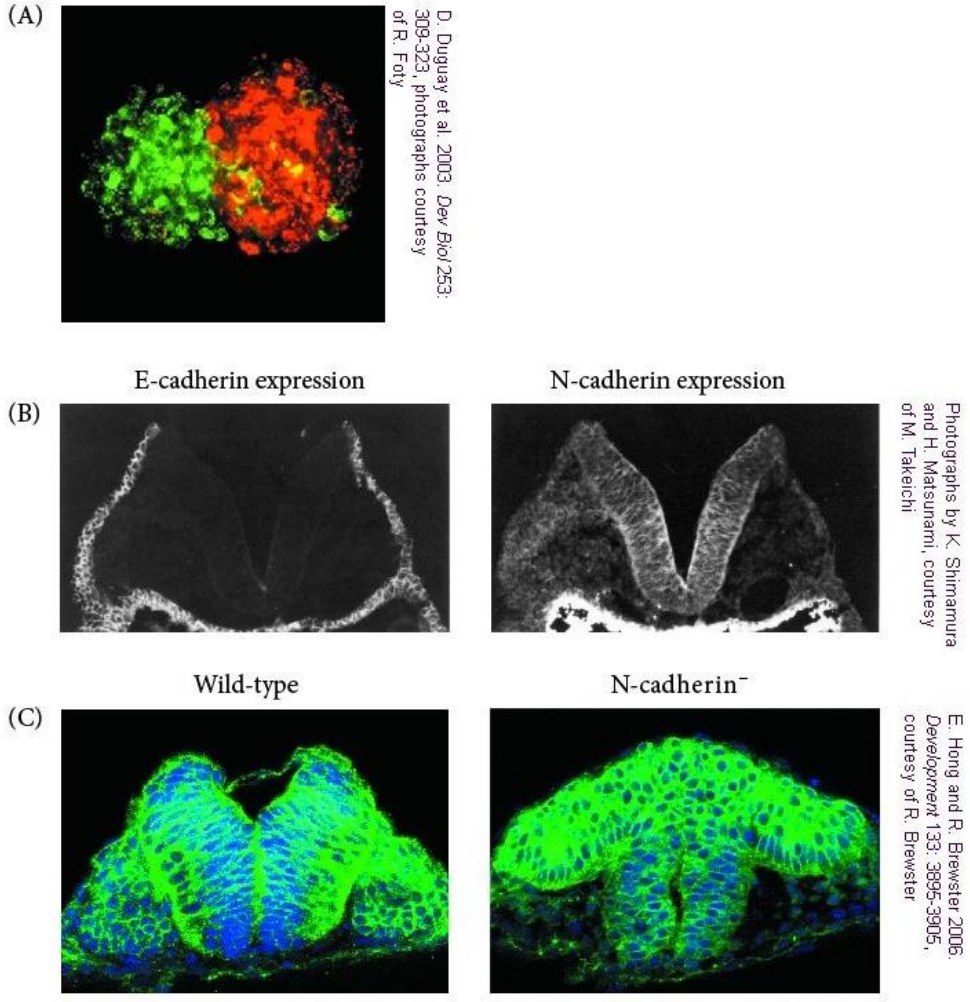

Figure 1 Importance of the types of cadherin for correct morphogenesis. (A) The type of cadherin expressed can result in different sorting behaviors, as seen when cells expressing R-cadherin (red stain) are mixed together with an equal number of cells expressing B-cadherin (green stain). The cells form two distinct mounds with one common boundary of contact. (B) Cross section of a mouse embryo showing the domains of E-cadherin expression (left) and N-cadherin expression (right). N-cadherin is critical for separation of presumptive epidermal and neural tissues during organogenesis. (C) The neural tube separates cleanly from surface epidermis in wild-type zebrafish embryos but not in mutant embryos where N-cadherin fails to be made. In these images, the cell outlines are stained green with antibodies to β-catenin, while the cell interiors are stained blue. (A from Duguay et al. 2003, photographs courtesy of R. Foty; B, photographs by K. Shimamura and H. Matsunami, courtesy of M. Takeichi; C from Hong and Brewster 2006, courtesy of R. Brewster.)

Another example of boundary formation in the embryo occurs within the mesoderm to separate the axial (notochordal) mesoderm from the paraxial (somitic) mesoderm. The primary mechanism for forming this boundary rests in the reduction of C-cadherins in the opposing membranes of the border cells (Fagotto et al. 2013). Fagotto and colleagues examined this mechanism in live *Xenopus laevis* embryos and found that actin-myosin contractile cables line up parallel to the border interface and are required for both C-cadherin reduction and boundary formation (Figure 2).

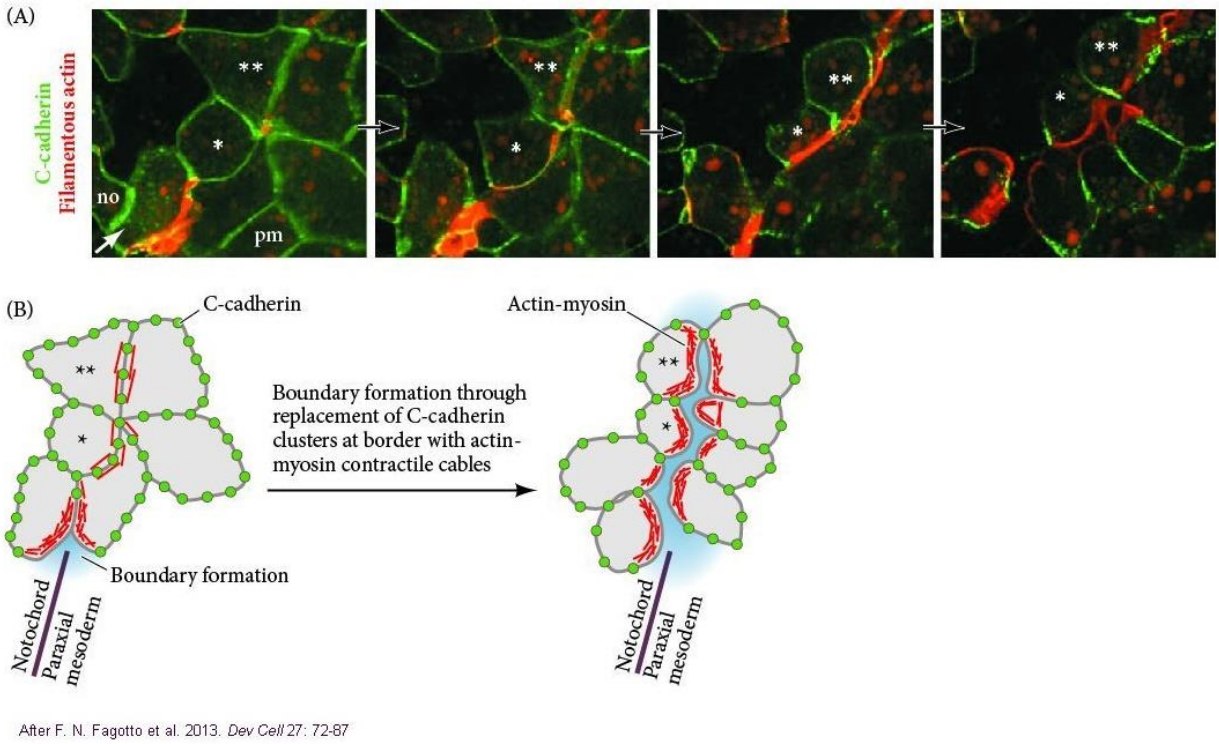

Figure 2 Boundary formation. (A) Live-cell imaging of explants of *Xenopus* dorsal mesoderm cells. Boundary formation can be seen to occur over time between notochord cells (no; asterisks) and paraxial mesodermal cells (pm) commensurate with a reduction of C-cadherin expression (green stain) and an increasing accumulation of filamentous actin (red stain) at the presumptive boundary. Boundary formation progresses from the lower left to the upper right (white arrow). (B) Schematized drawing of the cells in (A). Relative levels of C-cadherin and actin-myosin contractile units are indicated; the resulting boundary is shown in blue. (After Fagotto et al. 2013.)