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Mechanisms of boundary formation by Eph receptor and ephrin signaling

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ABSTRACT

The formation of sharp borders, across which cell intermingling is restricted, has a crucial role in the establishment and maintenance of organized tissues. Signaling of Eph receptors and ephrins underlies formation of a number of boundaries between and within tissues during vertebrate development. Eph–ephrin signaling can regulate several types of cell response—adhesion, repulsion and tension—that can in principle underlie the segregation of cells and formation of sharp borders. Recent studies have implicated each of these cell responses as having important roles at different boundaries: repulsion at the mesoderm–ectoderm border, decreased adhesion at the notochord–presomitic mesoderm border, and tension at boundaries within the hindbrain and forebrain. These distinct responses to Eph receptor and ephrin activation may in part be due to the adhesive properties of the tissue.

Introduction

The complex organization of the adult body arises progressively during development by the generation of distinct tissues at different locations, many of which become subdivided into domains with a specific regional identity. In order for precisely organized patterns to be generated, it is important that each tissue, or region within it, is not intermingled with its neighbors. This is reflected by the formation of a sharp border of the adjacent cell populations that have distinct tissue or regional identity (Batlle and Wilkinson, 2012; Dahmann et al., 2011; Fagotto, 2014; Winklbauer, 2009). In some cases, sharp borders also act to localize specialized signaling cells which regulate the local pattern of cell differentiation (Dahmann and Basler, 1999; Dahmann et al., 2011). Sharp borders form and are maintained despite the extensive intermingling of cells that can occur during growth and morphogenesis. The specific inhibition of such mixing across borders has a crucial role in stabilizing many tissues, not only during development but also in the adult, and when disrupted can contribute to disease, such as the metastasis of tumor cells (Batlle and Wilkinson, 2012).

Three classes of mechanisms have been uncovered which can inhibit the intermingling of cells across borders (Fig. 1): differences in cell-to-cell stickiness mediated by cell adhesion molecules (Steinberg, 1970); the generation of cortical tension at the interface of the distinct cell populations (Harris, 1976; Landsberg et al., 2009; Monier et al., 2010); and cell repulsion (Abercrombie, 1979). Although these mechanisms are often thought of as independent, in practice there is a biochemical interplay, for example between adhesion and cortical tension (Fagotto, 2014). Important evidence for roles of these mechanisms comes from experiments in which cells with different amounts of adhesion (Steinberg, 1970; Steinberg and Takeichi, 1994) or cortical tension (Krieg et al., 2008) are mixed and found to sort out from each other. Such segregation is likely a corollary of how these mechanisms restrict cell intermingling, and occurs locally during normal development in the sharpening of borders which are initially ragged. However, differential adhesion or tension alone may not account for the extent to which borders are sharpened. For example, the Drosophila Echinoid protein can drive cell segregation through differential adhesion, but border sharpening requires actomyosin cable formation (Chang et al., 2011). Border sharpening may thus require cooperation of multiple mechanisms.

Members of the Eph receptor and ephrin families are widely expressed in vertebrate tissues and have emerged to have major roles in establishing and maintaining tissue organization. In many contexts, there is complementary expression of interacting Eph receptors and ephrins (Gale et al., 1996), but overlapping expression also occurs (Sobieszczuk and Wilkinson, 1999) and has important roles (Carvalho et al., 2006; Marquardt et al., 2005). Cells ectopically expressing Eph receptor or ephrin segregate in vivo (Cavodeassi et al., 2013; Xu et al., 1999) and in vitro (Cortina et al., 2007; Mellitzer et al., 1999; Poliakov et al., 2008; Tanaka et al., 2003), and as discussed below Eph–ephrin signaling is essential for the formation of specific borders between tissues or regional domains. Eph receptor and ephrin signaling has been found to control cell adhesion, repulsion and tension, raising the

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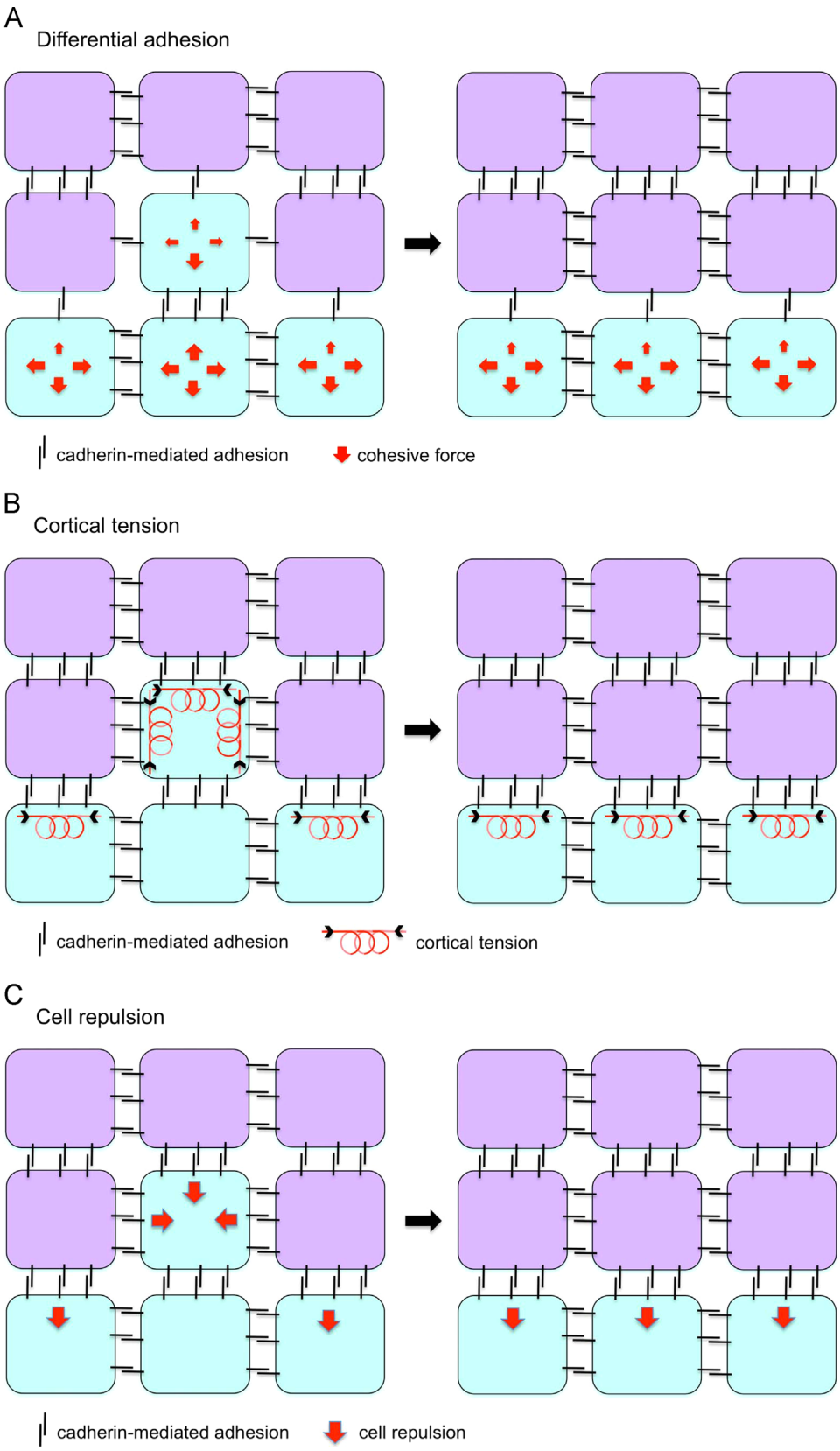

Fig. 1. General mechanisms that can underlie border sharpening. The three mechanisms depicted are not mutually exclusive and may be biochemically interlinked and/or act in parallel in some tissues. In each of the mechanisms there is dynamic adhesion which enables cells to rearrange. For simplicity, cell responses are depicted for one of the cell populations, but may occur in both. (A) Decreased cell–cell adhesion at heterotypic compared to homotypic contacts creates interfacial tension due to an imbalance in cohesive forces. This will cause the interface to flatten. (B) Increased cortical tension due to local actomyosin contraction occurs at heterotypic contacts and straightens the border. Such tension requires a linkage between actomyosin and cell–cell adhesion such that tensile forces are generated in the tissue. (C) A cell repulsion response occurs at the heterotypic interface, with localized depolymerization of actin and repolarization of the cell. This response is seen most clearly for mesenchymal cells which actively migrate away from the site of heterotypic contact. In this model, although cell repulsion leads to decreased adhesion, differential adhesion is not the driving force for border sharpening.