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Asymmetry at cell-cell interfaces direct cell sorting, boundary formation, and tissue morphogenesis

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ABSTRACT

During development, cells of seemingly homogenous character sort themselves out into distinct compartments in order to generate cell types with specialized features that support tissue morphogenesis and function. This process is often driven by receptors at the cell membrane that probe the extracellular microenvironment for specific ligands and alter downstream signaling pathways impacting transcription, cytoskeletal organization, and cell adhesion to regulate cell sorting and subsequent boundary formation. This review will focus on two of these receptor families, Eph and Notch, both of which are intrinsically non-adhesive and are activated by a unique set of ligands that are asymmetrically distributed from their receptor on neighboring cells. Understanding the requirement of asymmetric ligand-receptor signaling at the membrane under homeostatic conditions gives insight into how misregulation of these pathways contributes to boundary disruption in diseases like cancer.

1. Introduction

Identifying how cells distinguish themselves from their neighbors allowing for segregation and boundary formation is essential to understanding embryogenesis and organ morphogenesis. These mechanisms are also important in adult tissues by maintaining tissue compartmentalization, which can breakdown in diseases like cancer.

The first mechanistic concepts of tissue separation and boundary formation emerged from observations that were made during sponge death. As a sponge dies, a subset of undifferentiated cells are spared and able to form aggregates that possess regenerative capacities and differentiate to produce an entire new sponge [1]. Similar cell aggregation and sorting processes have been seen throughout development, beginning as an early embryo transforms into a gastrula containing three germ layers. Compartmentalization is key throughout neurogenesis as the midbrain-hindbrain boundary (MHB) forms between the anterior and posterior segments of the neural tube. This is followed by the formation of seven or eight rhombomeres that are each separated by distinct boundaries [2]. The mechanisms governing boundary formation play a vital role in segmenting tissues and maintaining cellular compartments to support diverse organ functions [3].

During these stages of development, cells have the ability to communicate, recognize, and sort themselves out from their neighbors according to inherent differences in their adhesion properties [4,5]. This can be caused by differences in cadherin expression, which are homophilic adhesion molecules. Differential expression of cadherins initiates cell sorting by generating compartments of like cells that segregate from neighboring cells with distinct cadherin subtypes [6].

As a boundary forms between two diverse populations of cells, mechanisms that help identify like and non-like cells in order to allow for clustering and segregation must also be activated [7]. An important factor found to play a role in this process is a biomechanical feature known as the differential adhesion hypothesis (DAH) [8]. The DAH proposes that cells have a liquid-like behavior that allows them to reorganize within a compartment and the major feature that governs their organizational pattern is mechanical force determined by the binding strength of the cell adhesion proteins expressed by the respective cell populations [9]. Consequently, increasing adhesive strength by changing the expression level of cadherins can directly impact cell aggregation and sorting. For example, mixing fibroblast cells that express different levels of N-cadherin results in aggregates

Abbreviation: ADAM, a disintegrin and metalloproteinase; Ap, apterous; BM, basement membrane; Cx43, connexin-43; CFNS, craniofrontonasal syndrome; Dll, delta-like ligand; DAH, differential adhesion hypothesis; DITH, differential interfacial tension hypothesis; DV, dorsoventral; EGFR, epidermal growth factor receptor; Eph, erythropoietin-producing hepatoma; FGF, fibroblast growth factor; GEF, guanine nucleotide exchange factor; MMP, matrix-metalloprotease; MHB, midbrain-hindbrain boundary; NICD, notch intracellular domain; RTK, receptor tyrosine kinase; Ser, serrate; SCC, squamous cell carcinoma; SHP2, tyrosine-protein phosphatase non-receptor type 11; VEGFR, vascular endothelial growth factor receptor

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with higher N-cadherin levels in the center and cells that have lower N-cadherin levels on the outer surface of colonies [10].

Since cadherins provide a link to the actin cytoskeleton, it has been suggested that adhesion strength works in combination with the cytoskeleton to generate changes in cell contractility that help compartmentalize tissues. This led to the differential interfacial tension hypothesis (DITH) that posits cells with similar surface tension will aggregate together [7,11]. The DITH is supported by atomic force microscopy experiments quantifying differences in surface tension of zebrafish germ layers. These cells cluster according to their surface tension. Lower tension aggregates surround the higher tension aggregates, corresponding with the endoderm and mesoderm having a higher surface tension compared to ectoderm cells [12]. Interestingly, increasing the expression levels of cadherins in fibroblasts that lack endogenous cadherins directly increases cell surface tension, suggesting that adhesive strength and tension cooperate to direct cell segregation [10].

Tissue morphogenesis requires dynamic boundaries implying there must be a balance between pro-adhesive cadherins and repulsive signaling during this process. This equilibrium can be accomplished by integrating cadherin-mediated adhesion with signals from other membrane receptors, like erythropoietin-producing hepatoma (Eph) receptors, Notch, fibronectin and leucine-rich repeat proteins, and epithelial cell adhesion molecules [7,13,14]. These receptors help to form tissue boundaries by several non-mutually exclusive mechanisms including altering the cytoskeleton, activating transcriptional cell fate pathways, and directly modulating the adhesion strength of cadherins. In addition, there is often crosstalk between these receptor families to maintain cell segregation and tissue organization events.

This review will go into the mechanisms driving boundary formation from two major cell-cell signaling networks involved during development, tissue maintenance, and disease, namely Eph and Notch receptors. Both of these receptor families are distinguished by their non-adhesive character and asymmetrical distribution of ligand and receptor in neighboring cells that lends well for directing cell segregation and tissue formation (Fig. 1). These receptors, along with cadherins, have points of convergence when tissue boundaries are formed [15]. The contribution of Eph and Notch pathways in the regulation of tissue morphogenesis may help us better understand scenarios where physical or functional boundaries are compromised in adult tissues and disease.

2. Signaling through Eph receptors and their ephrin ligands regulate tissue patterning and boundary formation

Eph receptors and their ephrin ligands are the largest family of receptor tyrosine kinases (RTKs) in mammals and are asymmetrically expressed at cell-cell contacts. The Eph receptors are subdivided into A and B subfamilies; EphA receptors have a higher affinity for glycosylphosphatidylinositol-linked ephrin-A ligands, whereas EphB receptors preferentially bind ephrin-B ligands that have a transmembrane domain with a cytoplasmic tail containing a PDZ-domain. The Eph family is comprised of nine EphA receptors, five EphB receptors, five ephrin-A ligands, and three ephrin-B ligands in humans [16]. Ephrin interaction with an Eph receptor on a neighboring cell can activate both forward and reverse signaling through the receptor and ligand, respectively. Although, there is promiscuity in Eph receptors binding to the alternative ephrin family, each receptor-ligand combination is formed by distinct binding affinities for one another and depending on the tissue there can be a variety of receptor-ligand combinations expressed at boundaries [17,18]. Interestingly, this asymmetric expression pattern of receptor and ligand helps initiate and maintain cell segregation and boundary formation during development and once a tissue has reached homeostasis.

Upon activation by ephrins, Eph receptors alter their conformation resulting in receptor dimerization then oligomerization and can directly phosphorylate targets or act as a scaffold to alter downstream signaling for a variety of processes that enhance boundary formation [19–21]. Ephrin stability at the membrane can also modulate adhesive and transcriptional pathways that impact early stages of tissue morphogenesis. As early as gastrulation, the expression of XLerk, the Xenopus laevis ortholog of human ephrin-B1, increases and is important in the formation of mesoderm [22]. Initiation of ephrin-B1 signaling can activate RhoA and JAK2-induced STAT3 transcriptional activity, which can modulate the expression of genes involved in cell migration and invasion [23–25] (Fig. 1). Concordantly, activation of STAT3 has been shown to be required for cell movement during gastrulation in zebrafish embryos [26]. These coordinated events initiated by ephrin reverse signaling result in early tissue separation events that lay the path for precise morphogenetic outcomes later in development.

As embryonic development progresses, there is differential expression of Ephs and ephrins at the ectoderm-mesoderm boundary [27]. The ectoderm has high expression of EphB3, EphB4, and ephrin-B3, whereas the mesoderm contains EphA4 and ephrin-B2. The separation between the mesoderm and ectoderm relies on the asymmetry of these receptor-ligand pairs in their distinctive compartments [28]. At this interface, there is a continuous cycle of cell repulsion, detachment, and attachment between receptor and ligand bearing cells. For example, forward signaling through EphB4 activates RhoA and Rac resulting in cell repulsion, but once this receptor signal decays at the membrane the boundary stabilizes allowing time to restore juxtamembrane presentation of receptor-ligand pairs that then set off another round of repulsive events [29].

The complementary expression of Eph/ephrins is a common theme that drives tissue patterning and organization in the blastula, formation of stripes of the presumptive hindbrain in zebrafish embryos, and in patterning of the developing nervous system. For example, there is abundant expression of EphB4 in the presomitic mesoderm and ephrin-B2 in the notochord. EphB4 forward signaling results in activation of the RhoA/ROCK/MLCK signaling axis causing an accumulation of filamentous actin stress fibers within the mesoderm. This leads to the formation of contractile structures with high tension at the mesoderm-somite boundary interface [13] (Fig. 1). Similarly, during neuroepithelial cell segregation, ephrin-B1 induces EphB2 forward signaling resulting in a ROCK-mediated increase in cortical actin within the EphB2 expressing cell population. This causes differential tension between the two cell populations based on their expression of receptor or ligand and resulting in cell segregation, providing a complementary molecular mechanism beyond cadherins that contributes to the DITH [30].

There is also a requirement of EphA4 and ephrin-B2a in opposing rhombomere-restricted domains allowing for the formation of asymmetric receptor-ligand pairs at these boundaries [31,32]. Intermingling between EphA4 and ephrin-B2a expressing cells causes repulsion, however, contact among the EphA4 expressing cell cluster leads to increased cell-cell adhesion [32]. These differences in adhesion of cells with differential EphA4 and ephrin-B2a expression are critical in the segregation of rhombomeres. Similarly, blocking EphA4 activity or knocking down its ephrin-A1 ligand in the neuroectoderm causes defective gastrulation in Xenopus embryos and interferes with tissue separation between the involuting mesoderm and the non-involuting ectoderm [33]. This complementary expression of Eph receptors and their ephrin ligands thus guides tissue morphogenesis throughout embryonic development.

The topographic mapping of the visual system is largely dependent on complementary gradients of Eph/ephrins [34]. In the retina and superior colliculus, EphA receptors and ephrin-A ligands are expressed, respectively, along a gradient. Retinal neurons with the highest abundance of EphA receptors target regions in the superior colliculus that have the fewest ephrin-A ligands [35–38]. The high expression level of ephrin-A in the posterior colliculus repels retinal

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