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Review

Giving the right tug for migration: Cadherins in tissue movements

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ABSTRACT

Dynamically regulated cell–cell adhesion is crucial for morphogenesis during embryonic development and tumor progression. The cadherins as calcium-dependent cell–cell adhesion proteins represent key molecules in these tissue movements. How cadherins serve in maintaining tissue cohesion during migration, facilitate cell–cell communication and promote signaling will be summarized in this review.

Introduction

The formation of a complex multi-cellular embryo from a fertilized egg requires the concerted regulation of cell differentiation, cell migration and cell shape changes. During embryogenesis a variety of different cell movements are observed. Whereas some cells are migrating as individuals, most others migrate collectively in groups or cohesive cell sheets, which we define here as tissue movements (Fig. 1). During recent years a growing number of reports underlined the importance of such tissue movements in early embryogenesis, organ formation and tumor progression, which are based on different types of cell behavior. For example, cranial neural crest (NC)[1] cells undergo collective migration (Fig. 1A); in gastrulation the ectoderm exhibits epiboly (Fig. 1B) and the mesoderm converges and extends (Fig. 1C); during vesicle formation an epithelium invaginates (Fig. 1D).

Interestingly, all of these different tissue movements have one in common: they change their cell and tissue polarity and show a modulated and dynamic cell–cell adhesion. Here, we will focus on a major class of cell–cell adhesion molecules, the cadherin super-family, and describe how they promote dynamic cell–cell adhesion. Additionally, we will explain how they change tissue polarity and generate motility through their signaling function.

More recently, several reviews focused on the role of cadherins in tissue remodeling and morphogenesis predominantly emphasizing the maintenance or re-organization of adherens junctions [1–3]. Tissue movements, however, require a quite different and more dynamic regulation of cell–cell adhesion, which we will discuss here.

Cadherins

Cadherins are a multigene family of transmembrane glycoproteins mediating calcium dependent cell–cell adhesion. Most of them possess intrinsic signaling activity or are part of signaling receptor complexes (reviewed in [4,5]). Dysregulation of their adhesion and signaling function leads to tumor invasion and metastasis (reviewed in [6]) or causes congenital defects in organogenesis (reviewed in [7]). In order to highlight the recent work on cadherins in tissue movements we present an overview of cadherins including their specific functions in cell migration, their contributions in signaling pathways and their binding partners (Table 1). A broad variety of pathological defects reflected in numerous cancers and inflammatory diseases are based on dysfunctions of these cadherins in tissue movements. However, in clinical research the impact of cadherins in cohesive cell migration is underestimated until now. The latter weakens the complete understanding and in long term the treatment of cadherin related diseases. To strengthen this focus we listed the diseases related to the here presented cadherins in Table 2.

In general cadherins are divided into four different sub-groups: classical (types I and II), desmosomal, atypical and protocadherins (Fig. 2). The super-family is defined by specific extracellular cadherin repeats (EC), a transmembrane domain (TM) and variable intracellular binding sequences [8]. Three highly conserved Ca^{2+}

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[1] *Abbreviations used:* NC, neural crest; EC, extracellular cadherin repeat; PCP, planar cell polarity; CIL, contact inhibition of locomotion; MO, morpholino oligonucleotide; EMT, epithelial to mesenchymal transition; PCNS, protocadherin in neural crest and somites; CE, convergent extension; PAPC, paraxial protocadherin; EVL, enveloping layer; YSL, yolk syncytial layer; RPE, retina pigment epithelium; NR, neural retina.

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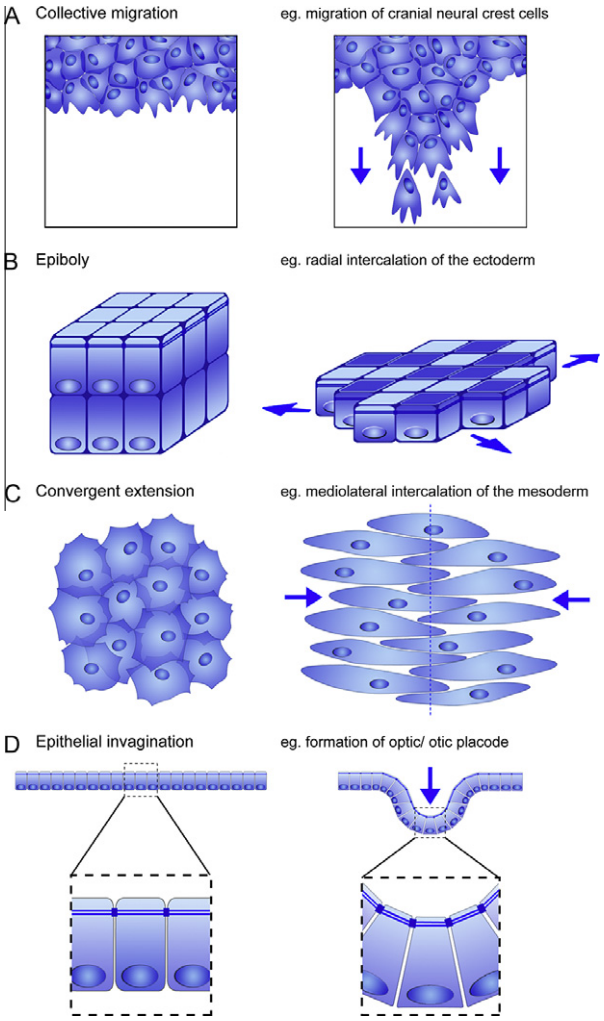

Fig. 1. Tissue movements during development. (A) Collective migration in cranial NC cells includes a transition from a cohesive sheet movement to a directed migration of cell streams with an intracellular front-rear polarization. (B) In epiboly a tissue expanses by radial intercalation and/or flattening of the cells which is, for example, observed in the ectoderm during gastrulation. (C) Convergent extension (CE) describes the mediolateral intercalation of cells towards a midline. The cell polarity changes thereby from multipolar to bipolar. Such cell behavior occurs, for example, in the mesoderm during gastrulation. (D) Epithelial invagination is based on apical or basal constriction resulting in wedge-shaped cells, examples are the invagination of the mesoderm in Drosophila or otic and optic vesicle formation.

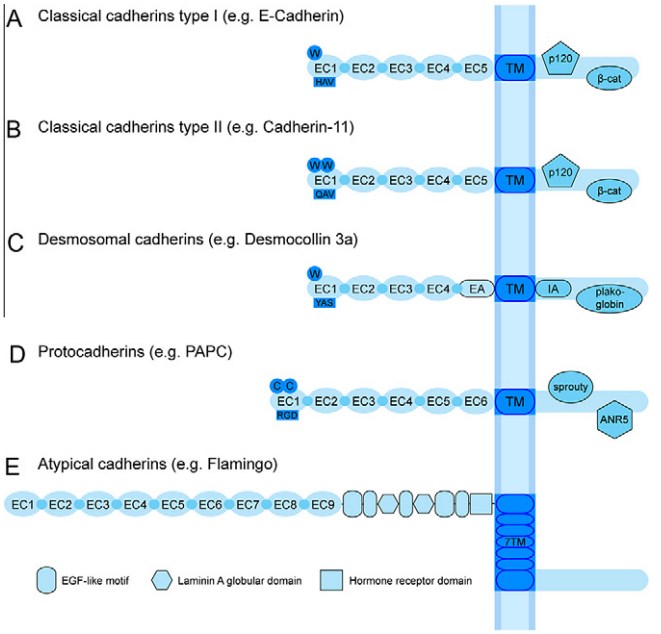

Fig. 2. Structure of the transmembrane cadherin subfamilies. (A + B) Classical cadherins (I and II) possess five extracellular cadherin repeats (EC). The EC1 domain contains the strand swap binding motifs including the Trp2/Trp4 (W) and HAV/QAV sequences, respectively. The intracellular domain of classical cadherins contains binding sites for p120- and β-catenin. (C) The desmosomal cadherins contain four highly conserved EC domains including binding motifs with Trp2 and YAT/YAS/RAL sequences in the EC1 domain. In addition, they possess a more variable extracellular anchor domain (EA). The cytoplasmic domain contains an intracellular anchor domain (IA), which is followed due to alternative splicing by different binding motifs like the plakoglobin binding site in Desmocollin 3a. (D) Protocadherins contain a Cys-$(X)_5$-Cys-motif and a binding motif for integrins in the EC1 domain. They differ in the number of EC domains (six, seven or more). The cytoplasmic domain is highly variable due to alternative splicing, which leads to binding of different interaction partners, for example, Sprouty and ANR5 in case of PAPC. (E) Atypical cadherins like Flamingo differ in their number of EC domains and contain further extracellular domains including EGF-like motifs or Laminin A globular domains. Flamingo is the only member with a seven-pass transmembrane domain and binds Frizzled (Fz) or Van Gogh (Vang). TM, transmembrane domain; CM, cytoplasmic motif; 7TM, seven-pass TM.

binding sites bridge the EC domains. The Ca^{2+}-ions are necessary for the rod-like structure and stability of the protein [9]. The intracellular domain is highly conserved within the sub-classes, but vary extremely in the composition of protein binding motifs between the sub-families (reviewed in [10]).

The mature classical cadherins possess five EC sub-domains and interact most prominently with their EC1 repeats by strand swapping (Fig. 2A and B, [11,12]). Strand swapping – also termed "strand dimer exchange" [2] – describes the insertion of the aromatic part of tryptophan-2 into a hydrophobic pocket within the EC1 domain of the other cadherin [13]. In classical cadherins of type II, a tryptophan at position four enhances this bond [14]. The hydrophobic pocket contains the alanine-residue Ala-80 within the conserved HAV-motif (type I) or the QAV-motif (type II), respectively [15,16]. While strand swapping determines the trans-interaction between cadherins of two neighboring cells, adhesion is further strengthened by lateral cadherin cis-dimerisation within the cell membrane. For cis-dimerisation the EC1 backbone interacts with the EC2 domain [13]. This is in contrast to previous models where cis-dimerisation was shown to include the complete EC domains [17–19]. The mechanistic aspects of cis-dimerization are not yet fully elucidated and are still being discussed (reviewed in [2]).

In their intracellular domain the classical cadherins contain a p120-catenin binding site in the juxtamembrane region regulating the cadherin turnover [20]. The p120-catenin binding also controls the localization of the small RhoGTPases RhoA, Rac1 and Cdc42 (reviewed in [21]). The c-terminus of the intracellular domain contains the β-catenin binding site. β-Catenin links the classical cadherins to the actin cytoskeleton via α-catenin in a dynamic manner [22,23].

The desmosomal cadherins like desmogleins and desmocollins contain four EC domains and an additional extracellular anchor domain (EA) that is less highly conserved (Fig. 2C, [24]). Their trans-interaction is mediated by strand swapping of tryptophan-2 and the alanine-residue Ala-80 of the hydrophobic pocket (YAT, YAS and RAL motifs) [11,25]. In contrast to classical cadherins, the desmosomal cadherins contain a more diverse cytoplasmic domain due to alternative splicing. They share a common intracellular anchor domain (IA), but differ in their additional binding motifs (reviewed in [24]).

The protocadherins are classified regarding to their genetic loci in clustered (α-, β- and γ-PCDH) and non-clustered (δ- and other PCDH) protocadherins. The clustered protocadherins contain six EC domains, whereas the non-clustered possess seven or more