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Contribution of epithelial-mesenchymal transitions to organogenesis and cancer metastasis

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The epithelial-to-mesenchymal transition (EMT) plays crucial roles during development, and inappropriate activation of EMTs are associated with tumor progression and promoting metastasis. In recent years, increasing studies have identified developmental contexts where cells undergo an EMT and transition to a partial-state, downregulating just a subset of epithelial characteristics and increasing only some mesenchymal traits, such as invasive motility. In parallel, recent studies have shown that EMTs are rarely fully activated in tumor cells, generating a diverse array of transition states. As our appreciation of the full spectrum of intermediate phenotypes and the huge diversity in underlying mechanisms grows, cross-disciplinary collaborations investigating developmental-EMTs and cancer-EMTs will be fundamental in order to achieve a full mechanistic understanding of this complex cell process.

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Introduction

The epithelial-to-mesenchymal transition (EMT) describes a cellular process during which epithelial cells transition to a mesenchymal cell state. A deceptively simple term, first coined to describe a cell behaviour observed by Elizabeth Hay during gastrulation (see Box 1) in vertebrate embryos [1], it has generated many heated debates over the years. Classically, EMT was thought of as a binary decision, involving the transition from a completely epithelial to a fully mesenchymal cell [2], which forms only transient contacts with its neighbours [3–5]. However, recent studies have pointed to a much more fluid transition, where cells may adopt a continuum of phenotypes between the 'extreme' epithelial and mesenchymal cell states (reviewed in [6–8]). Our understanding of EMT as a single program has also evolved, as we now know that there are many ways for a cell to affect an EMT. For example, the molecular mechanisms underlying developmental-EMTs varies greatly, even between different tissues within the same organism, as there is a context dependence of EMT activation with input from both cell-intrinsic and extrinsic factors. Here I will focus on key-concepts that are emerging from accumulative studies of developmental-EMTs, and how these relate to the current debate on the role of EMT in cancer.

A spectrum of EMTs occurs during development

Considering a highly differentiated epithelial cell and an individually migrating mesenchymal cell as extremes, the accumulated loss or gain of various combinations of epithelial and mesenchymal features leads to a whole spectrum or continuum of intermediate EMT phenotypes (Figure 1). There is a great morphological variation in the initial epithelial phenotype prior to EMT (reviewed in [9]), from cells which possess fully formed junctions and an underlying basement membrane such as epiblast cells (see Box 1) in amniotes [10,11], to the primitive epithelial cells that give rise to the mesendoderm (see Box 1) in *Xenopus* and fish which possess just apico-basal polarity and immature junctions (Figure 1, [12]). A common feature of the transition to a mesenchymal state is that cells lose apico-basal polarity and stable junctions, but there is a similar continuum of mesenchymal phenotypes that result from this transition. These range from cells which migrate collectively and make cadherin based cell–cell contacts, such as *Drosophila* endoderm (see Box 1) cells and zebrafish and *Xenopus* mesoderm (see Box 1) [13,14••,15,16], to cells which migrate individually, and make only transient cell contacts, such as the majority of migrating neural crest (see Box 1) cells in chicks [17].

Given its potential role in cancer progression and other diseases such as fibroses, there has been great emphasis placed on defining an EMT according to the loss and gain of molecular markers. However, cells that only transition partway towards a mesenchymal state may not repress epithelial markers such as *E-Cadherin*, nor activate mesenchymal genes such as *vimentin* or *fibronectin*. In fact, there are very few features that are unique to an epithelial or a mesenchymal cell type [7,10], and cells are often found possessing a combination of so-called epithelial and

Box 1 Glossary

Epiblast

The epiblast forms one of two distinct layers arising from the innermost cells in pre-gastrulation amniote embryos, and gives rise to the embryo proper.

Gastrulation

Gastrulation is the process during embryonic development that changes the embryo from a blastula with a single layer of cells to a gastrula containing multiple layers of cells. It is during this stage that the three germ layers, the ectoderm, mesoderm and endoderm are formed.

Endoderm and mesoderm

The mesoderm and endoderm are two of the intitial three germ cell layers (mesoderm, endoderm and ectoderm) and are formed by the process of gastrulation.

Mesendoderm

An embryonic tissue layer which differentiates into both endoderm and mesoderm.

Neural crest cells

A group of cells unique to vertebrates that arise from the embryonic ectoderm cell layer, migrate through the embryo and give rise to diverse cell lineages, including melanocytes, craniofacial cartilage and bone, smooth muscle, and peripheral and enteric neurons and glia.

Cranial neural crest

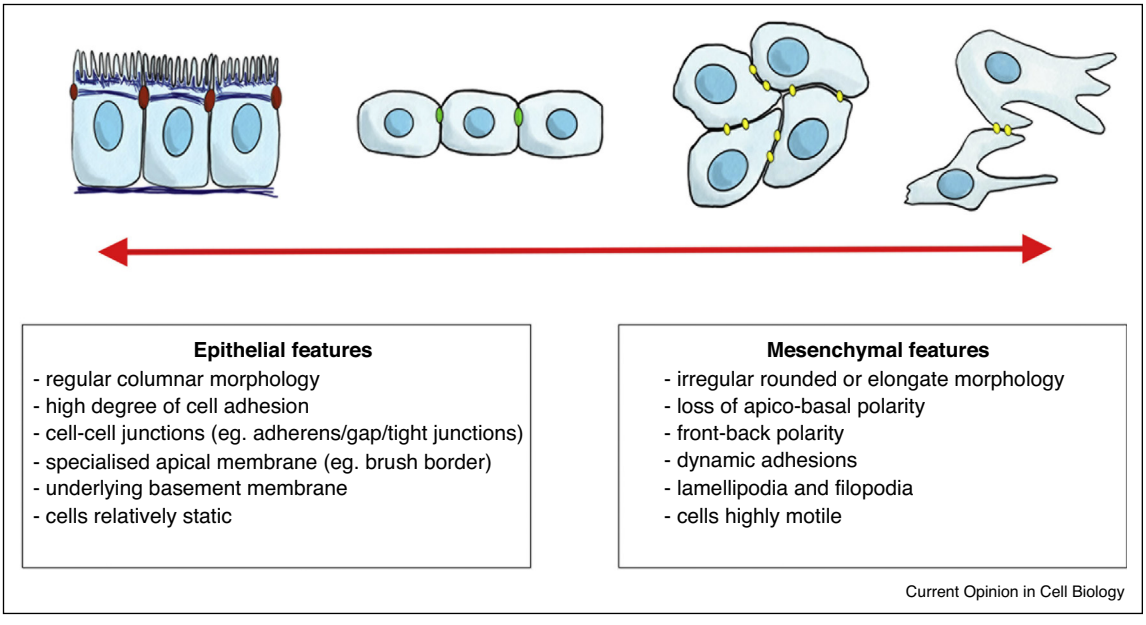
A subset of neural crest cells derived from the anterior-most part of the neural tube, and contribute to the development of most craniofacial structures in vertebrates.

mesenchymal markers [13,18•]. Thus, the classification of an EMT according to markers can be misleading. For example, while loss of apico-basal polarity and dissolution of junctions can occur downstream of the transcriptional repression of *E-Cadherin* (reviewed in [4]), it can also be driven by alternative mechanisms during which *E-Cadherin* remains transcriptionally active [13]. This suggests that it may be better to describe EMTs using morphological criteria, rather than molecular markers, and the tissue type, cell morphology and biological context all need to be taken into account.

Molecular mechanisms underlying developmental EMTs

The transcriptional repression of E-Cadherin has long been considered a critical step in, and even a landmark for, EMT [3,[14••],19]. A key component of adherens junctions, E-Cadherin plays a highly conserved role in maintaining tight adherence between epithelial cells, with transcriptional downregulation of E-Cadherin pushing cells towards a mesenchymal phenotype [20,21]. However, a number of recent findings suggest that the relationship between E-Cadherin and the mesenchymal state may be more complex. First, a number of embryonic cell types such as endoderm [13,14••], mesendoderm [12,22] and a subset of neural crest cells, cranial neural crest (see Box 1) [23], have been found to adopt many mesenchymal features, including migration, while actively transcribing E-Cadherin. Second, while

Figure 1



The 'spectrum' model for Developmental-EMTs. Almost no cell feature is unique for an epithelial, nor for a mesencyhmal cell. Instead a spectrum of cell phenotypes are seen between more differentiated epithelial and mesenchymal cell states. The accumulated loss or gain of epithelial/mesenchymal features results in a graded spectrum of cell behaviours that cells can adopt in a fluid and reversible manner. The brown junctions represent mature adherens junctions, green delineates immature junctions, and yellow show dynamic adhesions.