

# Epithelial-mesenchymal transition

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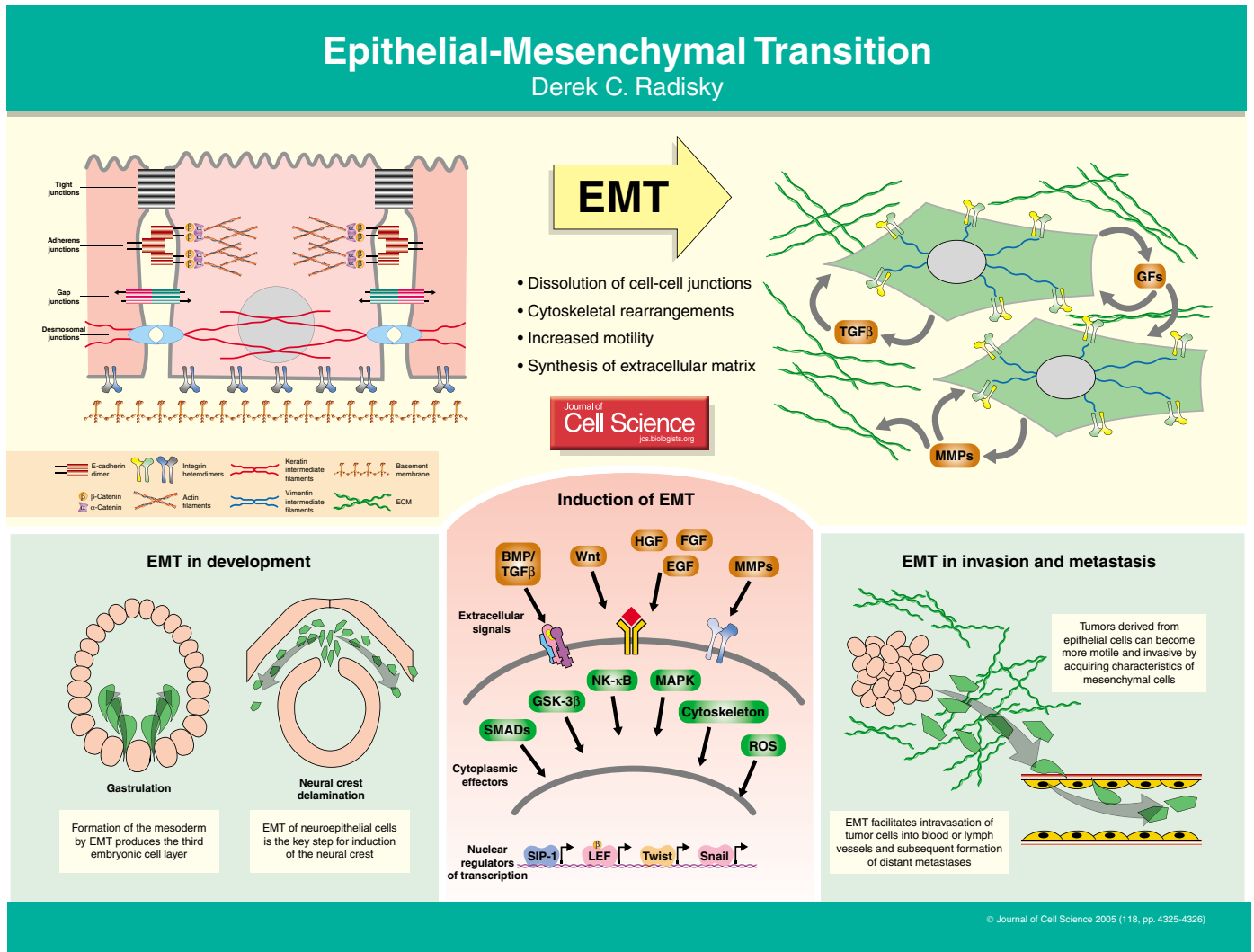
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The epithelial-mesenchymal transition (EMT) is an orchestrated series of events in which cell-cell and cell-extracellular matrix (ECM) interactions are altered to release epithelial cells from the surrounding tissue, the cytoskeleton is reorganized to confer the ability to move through a three-dimensional ECM, and a new transcriptional program is induced to maintain the mesenchymal phenotype.

Essential for embryonic development, EMT is nevertheless potentially destructive if deregulated, and it is becoming increasingly clear that inappropriate utilization of EMT mechanisms is an integral component of the progression of many tumors of epithelial tissues.

Structural integrity is a key property of epithelial tissues: external epithelia serve as protective barriers against environmental hazards, and internal epithelia create defined and physiologically controlled subdomains within the organism. Epithelial structure is maintained by cell-cell interactions. These involve tight junctions, cadherin-based adherens junctions that are connected to the actin cytoskeleton, gap junctions that allow direct chemical interactions between neighboring cells,

and desmosomes connected to the intermediate filament cytoskeleton, and cell-ECM interactions mediated by integrins and other molecules. The cell-cell and cell-ECM contacts also define tissue polarity (Yeaman et al., 1999), which allows different functions for the apical and basal surfaces. By contrast, many mesenchymal cells exist largely without direct cell-cell contacts and defined cell polarity, and have distinct cell-ECM interactions and cytoskeletal structures. Mesenchymal cells can contribute to the ECM by synthesizing and organizing new components and by remodeling the ECM through the production of matrix-degrading metalloproteinases (MMPs). Mesenchymal cells are also abundant sources of signaling proteins that act on epithelial cells, including growth factors of the epidermal (EGF), heptocyte



(HGF) and fibroblast (FGF) families, as well as transforming growth factor  $\beta$  (TGF $\beta$ ).

Induction of EMT appears to be highly tissue- and cell type-specific (Thiery, 2003), because factors that induce EMT under some circumstances can have quite different effects in others (Janda et al., 2002). Some of the cytoplasmic signal transduction pathways are fairly well defined – for example, the activation and nuclear translocation of SMAD proteins following association of TGF $\beta$  with its cell surface receptors (Shi and Massague, 2003). In other cases, activation of EMT involves more pleiotropic signals, as in the case of reactive oxygen species (ROS) produced in response to exposure to matrix metalloproteinases (MMPs) (Radisky et al., 2005). ROS can influence a number of signaling pathways (Finkel, 2003; Hussain et al., 2003), and can also directly induce EMT (Mori et al., 2004). Inducers of EMT can directly alter cytoskeletal structure and lead to breakdown of cell-cell and cell-ECM interactions (Janda et al., 2002; Ozdamar et al., 2005), but an important component of the EMT pathway involves activation of key transcription factors (Huber et al., 2004; Nieto, 2002; Peinado et al., 2003). Many of the EMT-responsive genes activated by these transcription factors encode proteins involved in induction of EMT, and so create feedback loops that may help sustain the mesenchymal phenotype.

EMT plays a role in many stages of development, including gastrulation, in which the embryonic epithelium gives rise to the mesoderm, and in delamination of the neural crest, which produces a population of highly mobile cells that migrate to and are incorporated into many different tissues (Nieto, 2001; Shook and Keller, 2003). Having migrated to their target destinations, the cells may revert to their original epithelial phenotype through a process known as mesenchymal-epithelial transition (MET). Investigations have revealed that tissue morphology plays a role in the induction of developmental EMT (Shook and Keller, 2003). In some cases, epithelial cells are located at the place where they undergo EMT. In

others, areas of epithelium are rearranged prior to detachment from the surrounding cells and acquisition of the ability to break through the basement membrane.

Induction of EMT can compromise the mechanical and physiological integrity of the tissue, and inappropriate induction of this process can have disastrous consequences. Chronic inflammation or conditions that promote sustained tissue disruption can stimulate fibrosis, a condition in which excess EMT compromises tissue integrity and organ function (Iwano et al., 2002; Kalluri and Neilson, 2003). Moreover, the defining property of cells that undergo EMT – the ability to separate from neighboring cells and penetrate into and through surrounding tissues – is particularly dangerous when acquired by tumor cells, and EMT processes identified in developmental studies are now being found to be involved in key steps of tumor metastasis (Kang and Massague, 2004; Yang et al., 2004). EMT also acts in tumor progression by providing increased resistance to apoptotic agents (Maestro et al., 1999; Vega et al., 2004), and by producing supporting tissues that enhance the malignancy of the central tumor (Petersen et al., 2003).

Although much has been learned about individual extracellular factors and the pathways they induce that regulate EMT, very little is known about how these factors are integrated with each other in the tissue context, and even less well-understood are the mechanisms involved in MET. Integration of data obtained from developmental studies with the detailed information obtained from culture assays, a process already underway, will provide key insights into these questions.

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