JULS

Perspectives

The Mesenchymal-Epithelial Transition and Metaplasia

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Introduction to the Mesenchymal-Epithelial Transition (MET)

A mesenchymal-to-epithelial transition (MET) and its reverse process epithelial-to-mesenchymal transition (EMT) are evolutionarily conserved programmes involved in embryogenesis[1,2], wound healing[2,3], and cancer metastasis[2,4]. MET is characterized by a complex phenotypic change from motile, spindle-shaped mesenchymal cells into sheets of polarized epithelial cells[5].

MET involves upregulation of junctional complexes required for cell adhesion to other cells and to the extracellular matrix (ECM)[1]. Intercellular adhesion is established through the formation of adherens junctions, tight junctions, gap junctions, and desmosomes along the lateral membrane[1,6], while interaction with the ECM is primarily mediated through upregulation of integrins existing at the basal membrane (Figure 1)[1,6,7].

Together, intercellular adhesion and cell-ECM interactions initiate the process of polarization during MET[5]. Reorganization of the actin cytoskeleton coordinates endosomal trafficking, helping to establish apical-basal polarity[1]. Specifically, apical-basal polarity refers to unequal distribution of proteins and intracellular organelles between the apical and basal sides of epithelial cells[5]. For example, cells undergoing MET localize the Golgi apparatus to the apical cytoplasm and situate their basal cell surface on top of the basement membrane[7].

MET ultimately replaces loose mesenchymal cells with sheets of connected epithelial cells that bear a distinct phenotype[1,2,5]. Due to polarization and upregulation of junctional complexes, cells undergoing MET downregulate mesenchymal markers such as neural cadherin (N-cadherin), collagen type I and III, and vimentin[8]. Instead, cells upregulate their expression of epithelial surface markers such as epithelial cadherin (E-cadherin), collagen type IV and VII, tight junction protein 1 (TJP1/ZO-1), and laminin[9].

Metaplasia and MET

The term ‘metaplasia’ was originally created based on anatomical observations of foreign tissues existing at ectopic sites[10]. Today, metaplasia is defined as the replacement of one differentiated cell type with another differentiated cell type not normally expressed in a specific tissue[11]. A subset of metaplasia known as transdifferentiation (TD) refers to the direct conversion between differentiated cell types without going through a dedifferentiated “intermediate” (i.e., an intermediate pluripotent state or progenitor cell type)[12].

The process of MET, which is crucial to both embryogenesis[2] and the metastasis of secondary tumors[6], bears similarities to TD. Recently, Wang et al. demonstrated that culturing metastatic breast and prostate cancer cells on nanostructures significantly promoted MET[13]. However, these researchers also found that nanostructure-cultured cells acquired expression of both epithelial and mesenchymal markers[13]. Other evidence also shows embryonic and cancer cells displaying attributes of both epithelial and mesenchymal phenotypes, supporting the existence of a transient intermediate existing in the process of MET[14,15,16,17]. Likewise, an intermediate cell phenotype has also been discovered in the process of TD, with researchers finding that TD can only reach completion upon passing through this intermediate state[18]. The possession of an intermediate phenotype in both MET and TD may point to similarity between the two processes.

However, TD and metaplasia both replace a differentiated cell type with another cell type derived from the same embryonic germ layer[12,19]. In contrast, MET replaces cells with cell types derived from a different germ layer[1,2,3,6]. Mesenchymal cells, derived from the mesoderm, undergo MET to be replaced by epithelial cells, which are instead derived from the ectoderm/endoderm — entirely different germ layers[20].

Additionally, MET often replaces undifferentiated

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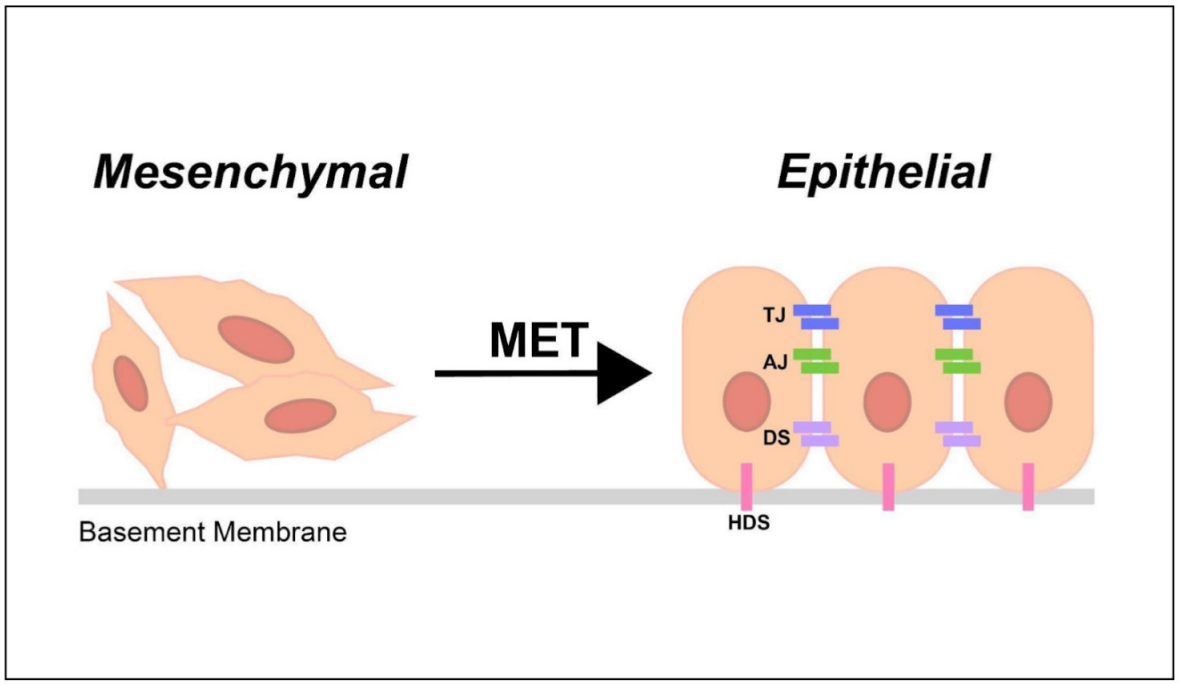

Figure 1: The mesenchymal-epithelial transition (MET). Mesenchymal cells undergoing MET upregulate epithelial junctional complexes required for cell-cell and cell-ECM adhesion. Tight junctions (TJ), adherens junctions (AJ), gap junctions (GJ), and desmosomes (DS) are formed along the lateral membrane, and hemidesmosomes (HDS) are formed along the basal membrane.

progenitors as opposed to terminally differentiated cell types[9,21,22]. MET does not usually replace one differentiated cell type with another differentiated cell type[1,9,21,22], making it difficult to explicitly define the process as a form of metaplasia. Rather, MET often involves the reprogramming of undifferentiated cells such as mesenchymal stem cells (MSCs)[21], embryonic stem cells (ESCs)[1], and cancer stem cells (CSCs)[2,22].

Numerous examples of MET occurring across embryonic germ layers have been observed. For example, bone marrow-derived mesenchymal stem cells (BM-MSCs) are adult stem cells that have been shown to populate endo/ectoderm-derived tissues and convert into epithelial cells of the liver, kidney, lung, and pancreas through MET[23,24,25,26]. Engraftment of BM-MSCs into hepatocytes (epithelial cells) following bone marrow transplantation was first observed in response to liver damage[24]. To test whether liver damage promoted the MET of MSCs into hepatocytes, researchers administered hepatotoxin (induces liver damage) and 2-acetylaminofluorine (prevents endogenous liver repair) to rats[24,27]. Using fluorescence in situ hybridization (FISH), resultant hepatocytes were confirmed to be derived from the transplanted BM-MSCs, suggesting that the developmental potential of BM-MSCs is not restricted to their germ layer of origin[24]. Even during nephrogenesis, cells of the mesenteric mesenchyme undergo MET to form the renal epithelium[2,28,29]. Likewise, carcinoma cells often undergo MET to efficiently metastasize at distant tissue sites, changing from mesenchymal to epithelial cells[30]. In each of these examples, MET is shown to occur across germ layers or involve stem cells, features that do not comply with consensus definition of metaplasia[11].

Moving Forward with Understanding MET

The mechanism of MET is poorly characterized compared to EMT[1-5], and several unknowns still exist in the field of epithelial and mesenchymal transitions. It is poorly understood how epithelial cells derived from different types of mesenchymal cells differ on the molecular level. MSCs and fibroblasts (FB) represent two distinct types of mesenchymal cells that are both known to undergo MET[9,21]. An experiment that could help elucidate the differences between MSC-derived and fibroblast-derived epithelial cells could be done by culturing MSCs and FB separately on nanostructures known to promote MET[13]. After MET is induced by the nanostructures, cells could be incubated with an antibody that binds to E-cadherin, a marker specific to epithelial cells[9]. Then, antibody-bound cells could be isolated using fluorescence-activated cell sorting (FACS). Genetic and transcriptomic analyses such as next-generation sequencing (NGS) and single-cell RNA sequencing (RNA-seq) could be conducted on these isolated epithelial cells to observe molecular differences existing between epithelial cells derived from either MSCs or fibroblasts. However, substantial

research will be required to properly translate current knowledge on MET to a clinical setting.

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COMPETING INTERESTS

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