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Mesenchymal–epithelial transition in development and reprogramming

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During organogenesis, epithelial cells can give rise to mesenchymal cells through epithelial–mesenchymal transition. The reverse process, mesenchymal–epithelial transition (MET), can similarly generate epithelial cells. Transitions between epithelial and mesenchymal states are also critical for the induction of pluripotent stem cells from somatic cells. This Review discusses the relatively less characterized process of MET, focusing on the genesis of apicobasal cell polarity and exploring the roles of MET in development and reprogramming.

Epithelial–mesenchymal transition (EMT) and its reverse process mesenchymal–epithelial transition (MET) are fundamental evolutionarily conserved mechanisms employed at different stages of morphogenesis and organogenesis to generate the body plan of metazoans. EMT involves the progressive loss of epithelial cell polarity, downregulation of junctional complexes and reorganization of the actin cytoskeleton to confer the migratory phenotype necessary to execute the extensive cellular movements that will give rise to the germ layers and later to tissues[1]. MET is employed to generate epithelia at different developmental stages. During MET, mesenchymal cells progressively establish apicobasal polarity through an evolutionarily conserved group of proteins and distinct but well-defined mechanisms[2]: polarity-related cell-surface receptors generate different membrane domains and become stabilized with the assembly of junctional complexes, leading to the formation of tight junctions at the apex of the lateral domain and the organization of cytoskeletal structures and organelles[2]. Evidence of embryonic cells displaying attributes of both epithelial and mesenchymal phenotypes supports the existence of transient intermediate EMT and MET stages[2–5], a phenomenon that is also observed in carcinoma[1,6].

Long germ-band insects, such as *Drosophila*, assemble the first epithelium through the migration of nuclei to the periphery of the egg followed by rapid cellularization[7,8]. The newly formed epithelial blastoderm will engage in complex morphogenetic movements to elongate the embryo and simultaneously create invagination sites by the localized formation of a contractile actomyosin ring in cells within the body cavity. This process initiates gastrulation at distinct sites along the body axis[7]. Endodermal cells forming the anterior and posterior proctodaeal invaginations engage in an EMT–MET sequence and merge to give rise to the midgut. By contrast, ectodermal cells that form the foregut and the hindgut will retain their epithelial phenotype[7,8]. An EMT–MET cycle is also observed for mesodermal cells that invaginate through the ventral furrow to form the dorsal vessel gonadal sheet and the Malpighian tubules[9]. Most other metazoan development proceeds through a series of cleavages of the fertilized egg and the progressive assembly of epithelial-like structures. These embryos engage in gastrulation by activating epithelial plasticity programmes, including EMT, as soon as the blastocoelic cavity is formed[10]. Although morphogenetic movements are quite diverse in different species, they adhere to a set of general principles of epithelial cell plasticity, reviewed in detail elsewhere[11].

Embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) undergo EMT and MET to differentiate into somatic cell types. Similarly, differentiated somatic cells can be reprogrammed into pluripotent cells by a sequential EMT–MET, with MET being a critical step for the acquisition of pluripotency[12]. In addition to the establishment of epithelial polarity, MET in reprogramming is associated with metabolic switching, epigenetic modifications and cell fate changes[13], providing a unique opportunity to investigate the relationships between these cellular events.

Although morphogenesis and setting the body plan require cell plasticity and EMT–MET cycles, later postnatal development requires stabilization of epithelial tissues. EMT-associated transcription factors are rarely detectable in adult epithelial tissues[14] and several factors were recently shown to protect this epithelial state. For instance, inactivation of the Ets superfamily transcription factor ELF5 induces EMT in the normal mammary gland, affecting alveologenesis and increasing the number of mammary stem cells[15]. In vitro, ELF5 overexpression prevents transforming growth factor-β (TGF-β)-induced EMT in normal murine mammary cells and can partially revert the mesenchymal phenotype of breast adenocarcinoma cells[15]. Grainyhead-like 2 (GRHL2), a DNA-binding protein that maintains the non-neural ectodermal epithelium[16], binds to *CDH1* (which encodes E-cadherin) intron 2 and the promoter of *CLDN4* (which encodes claudin-4) to augment their transcription[17,18]. As a result, *GRHL2* suppression induces a mesenchymal-like phenotype in ovarian epithelial carcinoma cell lines. Finally, the Ovol1 and Ovol2 transcription factors maintain epithelial integrity in the embryonic epidermis[19] and Ovol2 also in the mammary gland[20], by repressing EMT-associated transcription factors. One such factor, Zeb1, is controlled by a regulatory loop involving repression directly by GRHL2 and Ovol2 or indirectly through microRNA-200 (ref. [18]).

This Review focuses on the mechanisms that drive the induction and maintenance of epithelial tissues in development, the molecular drivers that contribute to epithelial cell polarization and the role of MET in reprogramming.

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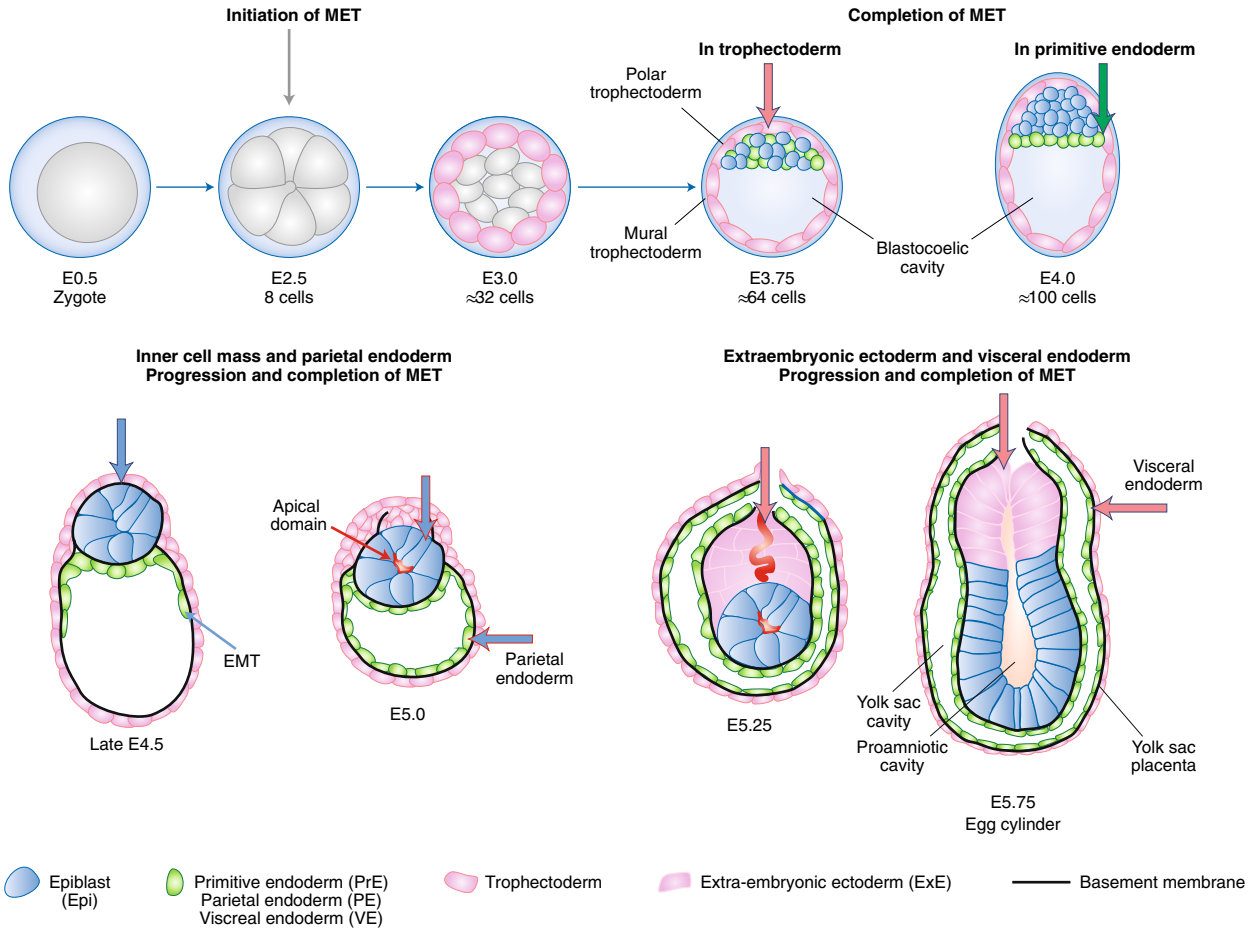

Fig. 1 | Formation of the first epithelia in the mouse embryo through MET. Following fertilization, the mouse egg enters cell division through cleavages. At E2.5, blastomeres maximize their intercellular contacts through compaction as a first step of MET. This mechanism is essential for the formation of the trophectoderm, which segregates as an outer layer at the 32-cell stage, a time at which these cells engage the MET programme. By E3.75, the trophectoderm has acquired a fully polarized epithelial structure, with functional tight junctions permitting the formation of the first cavity (the blastocoelic cavity). By E4.0, MET initiates in the primitive endodermal cells sorting them from the ICM (blue). A basement membrane is produced by the trophectoderm and the primitive endoderm, separating these two extraembryonic tissues from the ICM. By E4.5, the primitive endoderm expands along the mural trophectoderm and undergoes partial EMT at the leading edge (late E4.5). The mural trophectoderm and the parietal endoderm are separated by a basement membrane. By E4.75, cells in the ICM start reorganizing their intercellular contacts to acquire an apicobasal polarity. This polarity is initiated by acquiring a basal domain identity in contact with the newly deposited basement membrane that interacts with β_1-integrins. Par6 and aPKC accumulate at the apical domain, which is narrowing by a contractile actomyosin ring, a region that is becoming enriched in E-cadherin-based adherens junctions. These events confer a rosette-like structure to the ICM. At E5.0, MET is fully executed, with a small cavity forming at the apical domain by hollowing through the repulsive interactions of apically expressed podocalyxin. At E.5.25, a similar reorganization occurs in the extraembryonic ectoderm to generate an apicobasal polarity. The newly formed lumen in the extraembryonic ectoderm will merge with the ectoderm lumen to create the amniotic cavity at the egg cylinder stage. The thicker coloured arrows indicate the time of initiation or completion of MET in the different cell layers.

MET in development

MET is a fundamental process in histogenesis to assemble mesenchymal-like cells into cohesive structures. In the absence of MET, embryos cannot engage in gastrulation or the subsequent body plan formation.

Epithelia in eutherian mammals. *Trophectoderm.* In mammalian embryos, the need to implant at an early stage after the first round of cleavages prioritizes the formation of the trophectoderm before epithelial characteristics are acquired by the primitive endoderm and the epiblast. MET operates only after the first three cleavages (Fig. 1). The resulting 8-cell mouse embryo undergoes compaction—a well-studied process that is critical for the first lineage segregation at the next cell division. At the 16-cell stage, cells located at the periphery of the morula will be destined to form the epithelial trophectoderm, which is required for ensuring implantation in the endometrium. These cells exhibit asymmetric cell contacts compared to those cells in the inner cell mass (ICM). The trophectoderm cells become polarized at this stage, and during the next cell division, trophectodermal cells assemble adherens junctions, desmosomes, gap junctions and, most importantly, tight junctions, which permit the selective paracellular transport of ions and water to create the blastocoelic cavity. Transcripts of tight junction proteins, including junctional adhesion molecules and zonula occludens-1 (ZO-1), are already detected at the 8-cell stage, but these proteins are translated and post-translationally modified only at the 16-cell to 32-cell stage[21]. Different protein kinase C (PKC) isoforms, such as PKC-ε and PKC-δ, are critical for the proper assembly of ZO proteins and occludins[22]. At this stage, the apicobasal polarity does not require a basement membrane but is critically dependent on cell contact

asymmetry in the outer cells of the blastula[23]. E-cadherin is also essential in this process, as E-cadherin homozygous null mutants fail to form a blastocoelic cavity[24]. Despite evidence for cadherin switching in other tissues, E-cadherin cannot be substituted by N-cadherin to create a functional trophectodermal epithelial layer during blastocoelic cavity formation[25]. Between embryonic day 3.0 (E3.0) and E4.5, calcium-dependent, immature desmosomes shift to a calcium-independent, hyperadhesive state, under the control of PKC-α and PKC-β[26]. Most notably, the AP-2-γ transcription factor is essential for the formation of the first epithelium of the mouse embryo, as its gene inactivation results in the disappearance of tight junctions[27]. Specifically, AP-2-γ induces polarity genes, such as *Pard6b*, and tight junction components, such as claudin-4 and claudin-6, tight junction protein 2, aquaporin-3 and sodium–potassium ATPase1b1 (ref. [27]). By contrast, other components of the polarity complex and tight junctions are downregulated.

Primitive endoderm. A second MET occurs to generate the primitive epithelial endoderm. Progenitor cells of this transient epithelial structure appear stochastically in the ICM at the 8-cell to 16-cell stage before the cells segregate at the 64-cell stage to establish an outer epithelial layer[28] (Fig. 1). This segregation is driven by the fibroblast growth factor 4 (FGF4)–FGF receptor 2 signalling axis, promoting extracellular signal-regulated kinase and GATA6 responses[28]. Atypical PKC (aPKC) is expressed apically in this newly formed cell layer[22]. The primitive endoderm expresses tight junction components but undergoes partial EMT at its edges to form the parietal endoderm, which lines the basal surface of the trophectoderm[29]. The primitive endoderm also gives rise to the visceral endoderm, which acquires epithelial cell polarity, including the expression of tight junction components[30].

Epiblast. The epiblast is the epithelial cell layer that gives rise to the embryo proper following gastrulation. How the epiblast is formed from the ICM through MET has been analysed in great detail[31]. Although ICM cells express E-cadherin at E3.5 at the time of blastocoelic cavity formation, they acquire the characteristic features of fully polarized cells only gradually[23] (Fig. 1). At the peri-implantation stage (E4.5), the ICM cells adopt a rosette-like structure, creating a lumen through hollowing rather than through cavitation[23]. Subsequent early polarization events involve aPKC and Par6 accumulation at the centre of the rosette, accompanied by the basal localization of the nucleus, the subapical localization of the Golgi and the accumulation of the actomyosin contractile machinery apically along adherens junctions[23]. By E5.0, a lumen enlarges through the repulsive interactions of the negatively charged podocalyxin expressed on the apical domain[23]. A similar mechanism operates slightly later in the adjacent trophectoderm-derived extraembryonic ectoderm. During the post-implantation stage (E5.5), the two lumens merge as the embryo elongates to adopt a cup shape that gives rise to the proamniotic cavity. Polarization is induced by β_1-integrin signalling, which interacts with the basement membrane assembled by the trophectoderm and the primitive endoderm surrounding the ICM[23]. Epiblast cell polarity is maintained until primitive streak formation[23]; this is the site of EMT and migration of mesodermal and definitive endodermal cells. During gastrulation and neurulation, the epiblast—now called the ectoderm—undergoes intense morphogenetic movements[10,32]. Studies carried out in mouse embryos have revealed that the epiblast cells lining the primitive streak are protected from ingressing[33]. In these cells, EMT induction is abolished following glycosylation of members of the thrombospondin type-1 repeat superfamily by *O*-fucosyl transferase 2 (ref. [33]). In chick embryos, dissociation of epiblast cells adjacent to the primitive streak is prevented by the Net1 RhoA guanine exchange factor, contributing to the maintenance of a microtubule network on the basal side and preserving the epiblast basement membrane[34]. During gastrulation, newly formed mesenchymal cells migrate rostrally and laterally and subsequently form transient epithelia through MET[35]. Mesenchymal cells near the neural axis establish the paraxial mesoderm, which will form the epithelial structure of the somites[35]. More laterally, mesenchymal cells regroup into transient epithelial-like structures of the intermediate and lateral mesoderm[35]. We briefly describe these structures undergoing MET.

Paraxial mesoderm. Rho family small GTPases play important roles in MET during somite formation. In the mesenchymal paraxial mesoderm, cell division cycle protein 42 (Cdc42) and Rac1 must remain expressed at intermediate levels, otherwise the somitic epithelium becomes aberrantly organized[36]. Rac1 contributes to the induction of somitogenesis by acting post-transcriptionally on the basic-loop-helix transcription factor paraxis[36].

Intermediate mesoderm. Kidney development is another striking example of the importance of MET[37]. Cells close to the paraxial mesoderm establish the intermediate mesoderm, a separate structure along the dorsoventral axis. The definitive kidney, known as the metanephros, derives from the caudal region of the intermediate mesoderm. The caudal intermediate mesodermal region originates from mesenchymal mesodermal cells of the late gastrulating epiblast cells at the primitive streak. The intermediate mesoderm initially contains all the cells that will give rise to the metanephros. However, the intermediate mesoderm becomes segregated into two structures: the epithelial nephric duct and the metanephric mesenchyme. The kidney forms through the reciprocal interaction of the lateral buds from the nephric duct, called the ureteric bud, which induces MET in the adjacent nephric mesenchyme. In turn, this mesenchyme induces branching morphogenesis in the ureteric bud, with lateral branching induced by glial-cell-derived neurotrophic factor. Some mesenchymal metanephric cells, called cap cells, undergo MET to form a connected renal vesicle, a transient structure that first adopts a comma-shape, then an S-shape, before giving rise to part of the glomerulus[37]. Cells of the renal vesicle closer to the ureteric bud will form the proximal tubule, the loop of Henle and the distal tubule to create the mature nephron[38]. MET in the cap mesenchyme is induced by Wnt9b, which is expressed by the ureteric bud[39]. Wnt9b stabilizes β-catenin and represses the sine oculis homeobox 2 transcription factor and Cbp/p300-interacting transactivator 1 to engage cap cells into renal epithelial differentiation. This induction can be partially reproduced in vitro: human ESCs are first induced into mesenchymal cells using glycogen synthase kinase 3 (GSK3) inhibitors or high bone morphogenetic protein 4 (BMP4) and low activin A concentrations, thereby mimicking gastrulation. They are then induced to form the intermediate mesoderm through FGF9 stimulation, followed by the formation of the ureteric bud and metanephric mesenchyme, with an island of renal vesicles seen in two-dimensional (2D) cultures and nephrons in organoid cultures[40].

Lateral mesoderm. At the trunk level, the lateral mesenchyme undergoes MET to form two distinct transient epithelial layers—the somatopleure and the splanchnopleure—and undergoes hollowing to generate the coelomic cavity[41]. More rostrally, mesenchymal cells that are destined to form heart cell progenitors are incorporated into two symmetrical crescents in the splanchnopleural mesoderm. The myocardial progenitor cells specified before gastrulation acquire their restricted potential when the heart tube starts shaping through folding of the two lateral domains of the heart field. The inner layer of the splanchnopleure will then undergo EMT to generate endothelial progenitors, which will subsequently form the endocardium through MET. These two concentric epithelial-like structures—the myocardium and the endocardium—now constitute the heart tube. However, a second wave of progenitor cells that originate from the

secondary heart field will also contribute to the heart through a similar process, except that the endocardium originates from a domain that is distinct to that of the myocardium[42,43]. Despite the efforts to unravel the mechanisms controlling the specification, determination and differentiation of these two components of the heart, we do not have mechanistic insight regarding MET in these tissues, in contrast to our knowledge on EMT in the endocardium during valve formation[44].

MET is also involved in the formation of the epicardium. This single-layered epithelium originates from sinus venosus mesenchymal cells, which migrate and subsequently undergo MET at the external surface of the myocardium[44]. The zinc-finger Wilms tumour transcription factor, WT1, controls this MET but is also involved in an EMT programme in the epicardium[45,46].

Endoderm. The definitive endoderm formed during gastrulation becomes regionalized along the rostral–caudal axis to develop the lung, pancreas and liver. Here, we present the liver as an example of endoderm-derived organogenesis through cycles of EMT and MET. Gastrulating cells at the source of the definitive endoderm undergo EMT before inserting into the primitive endoderm (hypoblast) through MET[35]. A small area of the closing foregut endoderm becomes specified to hepatic lineages through its proximity to the heart rudiment, secreting FGF family members[47]. Endodermal cells that form the hepatic buds migrate into the surrounding mesenchyme (the septum transversum), which contributes to specification and promotes EMT in the hepatic bud through the GATA4-mediated induction of BMP4 and the resulting downregulation of E-cadherin[48]. Hepatoblasts invade the septum transversum, driven by prospero homeobox 1 (*PROX1*), a target gene of the T-box transcription factor TBX3, before undergoing MET to initiate liver morphogenesis[47,49]. TBX3 also induces and maintains hepatocyte nuclear factor 4-α (HNF4-α) and CCAAT/enhancer-binding protein-α (C/EBP-α) in hepatoblasts and inhibits HNF1-β and HNF6, which are critical for the formation of the cholangiocyte lineage[50]. MET in hepatoblasts leads to the differentiation and assembly of hepatocytes into cords and to differentiation into cholangiocytes, forming bile ducts. However, quite remarkably and in contrast to cholangiocytes and the periportal hepatocytes, which express E-cadherin at the adult stage, the perivenous hepatocytes express N-cadherin[51]. Periportal hepatocytes and intrahepatic cholangiocytes may be exposed to a similar microenvironment that favours E-cadherin expression. However, these hepatoblast-derived cell types differ considerably. Whereas hepatocytes exhibit a unique polarization to construct the bile canaliculus by abutting two apical domains that are sealed by tight junctions, adherens junctions and desmosomes[52], cholangiocytes organize a tubular structure lined by a single, polarized, E-cadherin-expressing cell layer[53].

Building polarity in epithelia. How MET is executed has been partly elucidated by studying apicobasal polarity, a complex programme coupled with lumen formation and regulated by a set of proteins and lipids, including Rho GTPases, polarity complex proteins[54,55] and phosphoinositides[56,57]. Polarization is initiated by cues from intercellular adhesion and interactions with the extracellular matrix (ECM), which are mediated primarily through integrins[58,59]. Dystroglycans, another type of ECM receptor, are also implicated in basement membrane assembly and cell polarity[60–65]. RhoA, its effector Rho-associated kinase 1 and myosin II also play crucial roles in orienting cell polarity by regulating actomyosin contractility[66,67]. Once the apicobasal axis is established, cortical actin becomes contractile[68], coordinating Rab-GTPase-mediated polarized endosomal trafficking to create the lumen at cell–cell contacts, the enlargement of which is controlled by cell division[69]. As in epiblast formation, lumen formation after membrane separation at the putative apical cell–cell contact is called 'hollowing' and is considered part of the MET mechanism.

Polarization generates the apical membrane, which faces the lumen, and the basolateral membrane, which ensures intercellular adhesion and interaction with the ECM[69,70] (Fig. 2). Intercellular adhesion is established through the formation of cell–cell junctions, including tight junctions, adherens junctions, desmosomes and gap junctions, along the lateral membrane[2,4].

E-cadherin clusters form in neighbouring cells through cis- and trans-interactions[71,72]. Downstream signalling events are initiated by E-cadherin binding to β-catenin, which interacts with α-catenin to indirectly recruit Rac, Rho and their effectors, thereby promoting the formation and stabilization of the cortical actin network, which in turn strengthens adherens junctions[71,73–75]. Members of the nectin family also contribute to the establishment of adherens junctions through cell–cell and cell–ECM crosstalk and are required for lumen formation[68,76,77].

Three evolutionarily conserved protein complexes are localized along the apicobasal axis. The Crumbs complex, at the apical domain, comprises Crumbs, protein-associated with Lin seven 1 (PALS1) and PALS1-associated tight junction protein (PATJ)[78]. The Par complex, consisting of Par3, Par6 and aPKC, accumulates at tight junctions, whereas the Scribble complex, comprising Scribble, discs large (Dlg) and lethal giant larvae (Lgl), localizes at the basolateral membrane[78]. The identity and boundaries (or size) of the apical and basolateral domains are established through repressive and cooperative interactions between these different complexes and through the actions of adherens junction proteins[54,55]. Par3 has been primarily associated with the formation and stabilization of ZO-1-containing tight junctions, but was recently shown to also regulate the formation and stability of adherens junctions[76]. Upstream of the Par complex are Rac1 and Cdc42, which contribute to the activation of aPKC[79–81]. aPKC phosphorylates several polarity proteins, including Crumbs[82], Lgl[83–85] and GSK3-β[86]. Par3 associates with dynein and contributes to the local regulation of microtubule dynamics at cell–cell contacts and proper positioning of the centrosome at the cell centre[87,88] and controls actin dynamics by regulating Rac1[89]. Par3 also binds to the Rac guanine exchange factor Tiam1 to inhibit its activity and thereby suppress Rac1[89]. By inhibiting Rac1 signalling and its protrusive activity at nascent cell–cell contacts, Par3 promotes a switch to Rho signalling, leading to actin cable formation and the stabilization of adherens junctions[76,90]. Par3 depletion in different systems can affect both tight junctions and adherens junctions. In mammalian cells, in which these junctions are in close proximity and share common assembly mechanisms, cross-interaction has been observed between the Scribble and Par complexes[2,90]. A direct interaction between the Crumbs and Par complexes promotes tight junction assembly[91].

Phosphoinositides also regulate polarity through their spatial restriction[57,92,93] (Fig. 2). Phosphatase and tensin homologue (PTEN) generates phosphatidylinositol (4,5)-bisphosphate (PtdIns(4,5)P_2) from PtdIns(3,4,5)P_3; PtdIns(4,5)P_2, annexin 2 and activated Cdc42 are required for the targeting and localization of Par6 and PKC to the apical domain to regulate the formation of the apical plasma membrane and lumen during epithelial morphogenesis[93,94].

Although PTEN is unlikely to be the only regulator of PtdIns(4,5)P_2 during apical membrane specification, PtdIns(4,5)P_2 on the apical surface is mainly generated by the phosphorylation of PtdIns4P by PtdInsP 5-kinase, which selectively regulates apical endocytosis[95,96]. SH2-domain-containing inositol 5-phosphatase 2 and its lipid product PtdIns(3,4)P_2 bind to Dlg homologue 1 (Dlg1) to stabilize the basolateral membrane[97] and regulate RhoA-dependent actin contractility and cell division to create the lumen[98] (Fig. 2). Phosphatidylinositol-3-OH kinase (PI3K) also controls the organization of epithelial cells by restricting liver kinase B1 signalling both

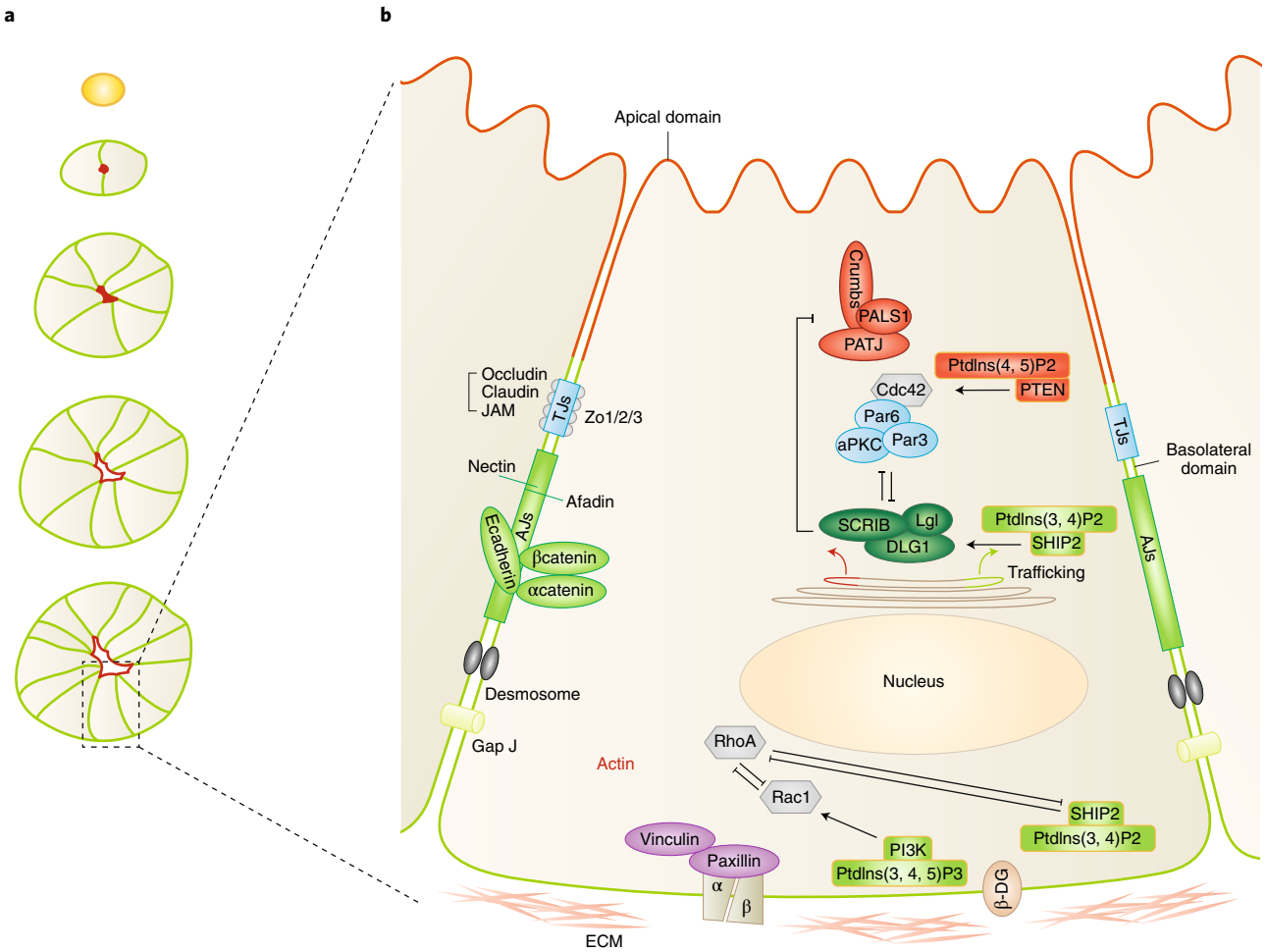

Fig. 2 | Determinants of apicobasal polarity and lumen formation in epithelial cells. During epithelial morphogenesis, the establishment of apicobasal polarity and lumen formation are controlled by polarity protein complexes, phosphoinositides and signalling pathways. **a**, The mechanisms of lumen formation have been elucidated primarily using 3D in vitro cultures of epithelial cells. Apical proteins (red) start to accumulate at the centre of cell doublets cultured in Matrigel, whereas cell–cell contacts are devoid of β-catenin (green). The lumen develops a pre-apical patch and becomes enlarged concurrently with cell division[148]. The polarized epithelial cells form a mature cyst, where a central lumen is surrounded by a monolayer of tightly associated cells. **b**, The plasma membrane of polarized epithelial cells comprises a basolateral membrane containing adherens junctions (AJs) and is associated with the basement membrane and the ECM. Tight junctions (TJs) separate the lumen-facing apical membranes (red line) from the basolateral membrane (green line). Polarity complexes are distributed asymmetrically along the apicobasal axis. The Crumbs complex (red), consisting of Crumbs, PALS1-associated tight junction protein (PATJ) and PALS1, localizes to the apical membrane. The Par complex (blue), which is composed of aPKC, Par3 and Par6, is located laterally where it interacts with tight junctions. Scribble, Lgl and Dlg comprise the Scribble complex (dark green) at the basolateral surface. Phosphoinositides and their metabolizing enzymes (rectangles outlined in yellow) are polarized and have specific subcellular localizations. PtdIns(4,5)P_2 (red) is enriched at the apical membrane, whereas PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3 (dark green) are enriched at the basolateral surface. PTEN is activated at the apical pole to generate PtdIns(4,5)P_2 and mediate lumen formation. SH2-domain-containing inositol 5-phosphatase 2 (SHIP2) produces PtdIns(3,4)P_2 at the basal pole and stabilizes polarity complex proteins such as Dlg homologue 1 (DLG1) or Scribble, which support epithelial architecture. Membrane trafficking from the Golgi ensures the correct targeting to the apical surface or the basolateral surface. β-DG, β-dystroglycan; JAM, junctional adhesion molecule. Figure adapted from ref. [149].

in *Drosophila* and in mammalian epithelial cells in 3D culture[99]. PtdIns(3,4,5)P_3, produced by the δ-isoform of PI3K (PI3K-δ) and enriched on the basolateral surface, orients the apicobasal axis, participates in building the basolateral membrane and lumen formation through ECM assembly[100,101].

Collectively, these data reveal the dynamic and elaborate cross-talk between polarity and junctional complexes, Rho GTPases and phosphoinositides for the establishment and stability of epithelial cell polarity, leading to the completion of MET.

MET in cell fate conversions and somatic cell reprogramming

Somatic cell reprogramming by a combination of Oct4, Sox2 Klf4 and Myc (hereafter OSKM factors)[102] provides an ideal in vitro model to investigate the regulation of cell fate changes. Accumulating evidence indicates that MET is essential during early somatic cell reprogramming in mouse embryonic fibroblasts (MEFs) and human fibroblasts[103,104], and that blocking this step can impair reprogramming efficiency[105]. In the initial stages of MEF reprogramming, Sox2, Oct4 and Myc suppress TGF-β–Snail

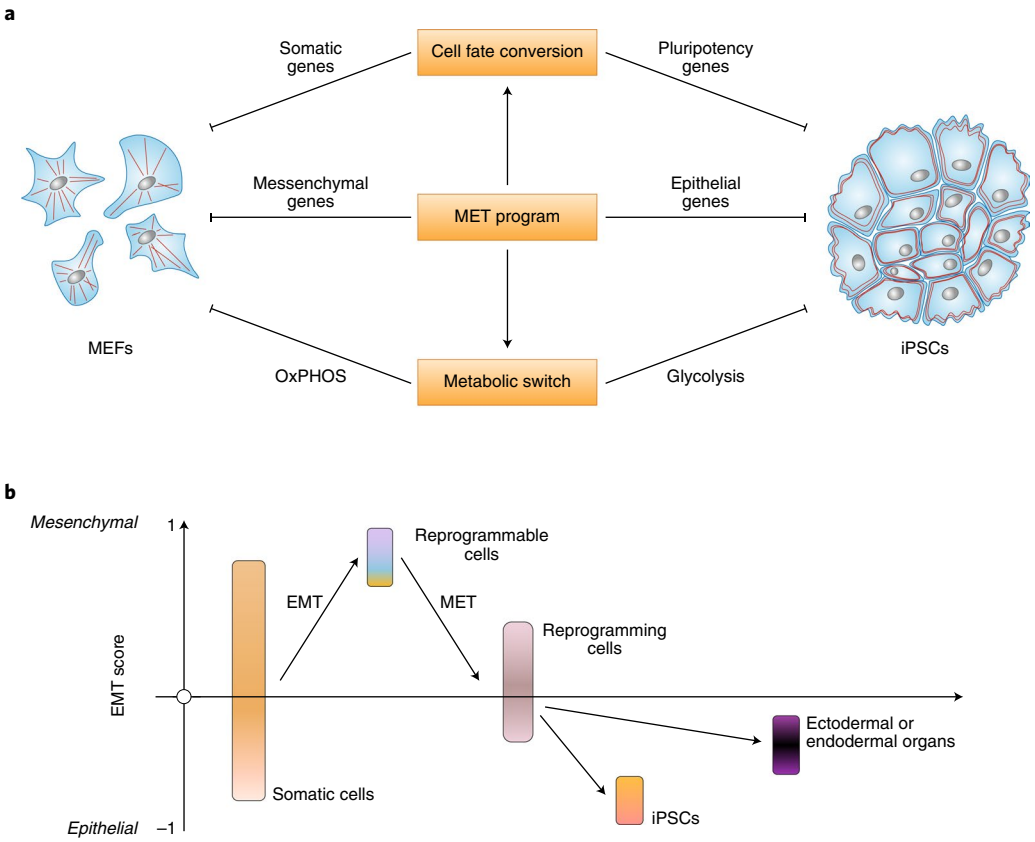

Fig. 3 | Sequential EMT and MET for reprogramming of somatic cells. a, Major changes in the somatic reprogramming of MEFs. The OSKM factors silence somatic genes in MEFs and induce pluripotency genes during the late stages of reprogramming. A metabolic switch from oxidative phosphorylation (OxPHOS) to glycolysis occurs during reprogramming. MET is an essential early step in reprogramming, as it remodels the mesenchymal cytoskeleton and cell-surface protein expression to adopt an epithelial-like morphology and facilitates metabolic and cell fate changes. **b**, Schematic outline of stemness acquisition in the EMT spectrum. Epithelial-like or mesenchymal-like somatic cells can be reprogrammed using OSKM factors and/or small molecules. The first step is to induce a quasi-mesenchymal phenotype, with stemness acquired during the early phase of MET[120], at which point cells can be reprogrammed into iPSCs or endodermal or ectodermal derivatives[150].

signalling, whereas Klf4 induces the epithelial programme[105], with a net effect of downregulating mesenchymal proteins and upregulating epithelial proteins, as confirmed by proteomics analyses[106] (Fig. 3a). BMP-driven MET can also facilitate reprogramming[107], as can the use of well-controlled MEF adhesion conditions, such as growth on microgrooved substrates or soft hydrogels[108,109]. By contrast, dual specificity testis-specific protein kinase 1 and LIM domain kinase 2 (Limk2), which promote actin polymerization in fibroblasts, impede reprogramming[110].

Recent studies indicate that MET-like changes are also involved in the reprogramming of other somatic cell types. For instance, mouse B cells can be reprogrammed into iPSCs by OSKM factors and the forced expression of C/EBP-α, leading to MET-like gene expression changes[111]. MET is also observed when reprogramming haematopoietic progenitor and stem cells[112] and spermatogonial stem cells[113], with an active mesenchymal programme functioning as a reprogramming barrier. MEFs from the Tet1/2/3 triple-knockout mice failed to be reprogrammed into iPSCs due to a failure to undergo MET[114]. Intriguingly, however, more epithelial-like neural progenitor cells and keratinocytes from the same mice could be reprogrammed efficiently in the same study. These data clearly demonstrate that the acquisition of an epithelial-like status is a prerequisite for cells to establish pluripotency.

In addition to iPSCs, MEFs can be directly converted into other epithelial-like cells, such as induced hepatocyte-like cells, by the overexpression of transcription factors, such as Myc and Klf4, and/or through treatment with small molecules[115–117]. In the chemical-induced conversion of MEFs into hepatocytes, cells first undergo MET to become endodermal progenitors and then further differentiate into cells of the hepatic lineage[118]. Similar transitions between epithelial and mesenchymal statuses are observed in the hepatic differentiation of ESCs in vitro: ESCs are epithelial cells and an EMT event occurs during ESC differentiation into the definitive endoderm, whereas MET takes place at later stages of hepatic differentiation and maturation[119,120]. In vitro hepatic differentiation mimics in vivo liver development, with a round of EMT–MET involved in the acquisition of hepatic cell fate.

Somatic cell reprogramming studies show that an epithelial or mesenchymal status of the cell at the beginning of induction affects iPSC generation. For example, pre-treatment of MEFs with the TGF-β receptor inhibitor RepSox reduces the efficiency of OSKM-induced reprogramming[121,122]. By contrast, TGF-β pre-treatment drives MEFs to a more mesenchymal state and enhances reprogramming efficiency[121]. In the same study, the sequential introduction of OSKM showed that an initial EMT is beneficial for subsequent MET in MEF reprogramming. In B cells, C/EBP-α treatment induces an EMT and promotes the efficiency of OSKM-mediated reprogramming[111]. It is possible that EMT as the initial step may synchronize and prime cells for reprogramming, although this remains to be formally demonstrated.

Epigenetic status also determines the capacity of somatic cells for iPSC reprogramming. Dynamic epigenetic changes occur during reprogramming, including DNA methylation and histone modifications[123], and MET events are also under epigenetic control[114,124–126]. For example, the failure of MEFs from Tet1/2/3 triple-knockout mice to be reprogrammed stems from disrupted DNA demethylation[114]; conversely, the histone H3K36 demethylases Kdm2a/2b enhance reprogramming, at least partially, through the promotion of MET at the initial stages[124,126]. Furthermore, blocking the H3K79 methyltransferase DOT1L downregulates mesenchymal gene expression and enhances reprogramming efficiency[125].

In addition to MET-type morphological changes, successful iPSC reprogramming from MEFs requires a metabolic switch. Whereas mesenchymal cells, such as MEFs, rely more on oxidative phosphorylation and mitochondrial functions, pluripotent stem cells, including ESCs and iPSCs, require high glycolysis levels[13,127] and rely on distinct metabolic pathways to maintain pluripotency-related epigenetic modifications (Fig. 3a). For example, a threonine catabolic pathway supplies *S*-adenosylmethionine, which is essential for H3K4 methylation and the maintenance of pluripotency in mouse ESCs[128]. The methionine–*S*-adenosylmethionine pathway functions in a similar manner in human ESCs or iPSCs[129]. α-Ketoglutarate, a metabolite of the tricarboxylic acid cycle, also contributes to the maintenance of mouse ESCs through histone and DNA demethylation[130]. Acetyl-CoA, a product of glycolysis, promotes histone acetylation and maintains ESC pluripotency[131]. Defects in these metabolic pathways can disrupt pluripotency and result in differentiation[128–131]. Thus, a MET-induced metabolic switch during reprogramming may promote global epigenetic modifications that favour either the establishment or the maintenance of pluripotency.

Concluding remarks

Early in embryogenesis, the formation and plasticity of an epithelial anlage allow cells to engage in EMT for the execution of morphogenetic events during gastrulation and organogenesis. Most of these cells will re-acquire intercellular adhesion at the onset of MET to generate different epithelial organizations[35]. However, some mesenchymal cells will never revert to an epithelial state[132]. Similarly, reprogramming somatic cells into iPSCs transiently involves a full EMT to reset the epigenetic landscape, followed by MET to acquire stemness. The transition to the stem-like state probably occurs at an intermediate EMT state before all epithelial traits are acquired[120] (Fig. 3b).

Mechanisms driving epithelial apicobasal polarity have been partially elucidated and provide an understanding of the principles driving morphological organization in early-stage embryos and in adult tissues. One critical issue is the precise estimation of 'mesenchymality' in any cell type of the body. This is technically challenging but already feasible in several tissues[3,133]. Surprisingly, epithelial tissues exhibit a range of EMT scores, with the colon being more epithelial like and the kidney more mesenchymal like. The EMT spectrum of these epithelial tissues is somewhat reflected by the average value of EMT scores in carcinoma cell lines and tumours originating from the same tissues[134].

Several avenues of research could identify the factors that strengthen the stability of epithelia. Such factors could prevent or revert the partial EMT phenotype acquired by epithelial cells of the kidney[135,136] and other organs in fibrotic disease[1]. However, inhibiting MET can also be beneficial, as in the case of granuloma formed by aggregated macrophages that mask parasites or infectious bacteria[137]. Quite surprisingly, these macrophages acquire an epithelial-like phenotype through the expression of E-cadherin, leading to adherens junction formation. Disrupting such aggregates could be beneficial against chronic infections that are resistant to antibiotics or antiparasitic drugs, such as in tuberculosis and schistosomiasis[137]. A beneficial effect may also be expected in carcinoma, given that mesenchymal-like carcinoma cells are more prone to metastasis[6,138] and are more refractory to chemotherapy and targeted therapeutics[1]. In addition, MET can suppress tumour-initiating cells[139,140], which may improve patient responses to antimitotic drugs. Most importantly, cytotoxic T lymphocytes cannot develop a functional immunological synapse in epithelial carcinoma cells acquiring a mesenchymal-like phenotype by EMT inducers. Cytotoxicity can be restored in these mesenchymal-like carcinoma cells that are rendered more epithelial like using MET inducers, such as the TGF-β receptor inhibitor A83.01 (refs [141–143]). Recently, AXL was found to form a multimolecular complex with other receptor tyrosine kinases in ovarian carcinoma cells exhibiting a mesenchymal phenotype[144]. MET can be induced by the AXL inhibitor R428 (ref. [144]), which abrogates tumour growth. A complementary strategy would be to leverage the fact that a mesenchymal status confers sensitivity to ferroptosis, an oxidative form of iron-dependant cell death mediated by lipid hydroperoxides[145]. Glutathione peroxidase 4 has been identified as a critical suppressor of ferroptosis by reducing the levels of allylic lipid hydroperoxides[146,147]. Drugs targeting glutathione peroxidase 4 will potentially contribute to eradicate refractory mesenchymal-like carcinoma or sarcoma cells in tumors[146].

Considering the high research activity in the field of epithelial and mesenchymal transitions, we can expect that in the coming years, we will witness the discovery of more regulators that maintain the epithelial state and the further elucidation of the mechanisms driving MET in embryonic development and cancer, to facilitate the development of new therapeutic strategies.

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Competing interests

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