Received: 29 June 2023 | Revised: 3 November 2023 | Accepted: 7 November 2023

DOI: 10.1002/dvg.23581

EDITORIAL

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Epithelial-to-mesenchymal plasticity from development to disease: An introduction to the special issue

The term "Epithelial-Mesenchymal Transformation" was introduced by Elizabeth Hay to define the phenomena that cells can switch from epithelial to mesenchymal states during tissue morphogenesis and homeostasis. The term "transformation" is later replaced by the more accurate word "transition" to better reflect the non-binary nature of the process (see [Hay, 2005] and references therein). EMT is indeed a staple of embryonic development as cells must proliferate and move in three dimensions to form and rearrange tissues and organs at the right place and time. For that, they frequently toggle between relatively cohesive and stable epithelial states and more dynamic and loose mesenchymal arrangements (Nieto et al., 2016). In many cases, and as discussed below, EMT occurs in cells that will eventually migrate. However, one should not systematically associate EMT with migratory behavior. During fibrosis, there are several examples of cells adopting partial E/M phenotypes that do not undertake migration but nonetheless contribute to disease progression via this phenotypic change (see [Liu et al., 2022] for discussion).

Classical examples of EMT include gastrulation and neural crest development. Mesoderm is induced at the interface between ectoderm and endoderm. Initially epithelial, mesoderm progenitor cells undergo a conversion towards mesenchymal states to ingress, migrate and intercalate between ectoderm and endoderm during gastrulation. At the cervical and trunk level, the most axial of these migratory mesodermal cells re-epithelialize into repetitive structures called somites on either sides of the neural tube (Benazeraf & Pourquie, 2013). These somites will then undergo another round of mesenchymalization at their ventral side to form the sclerotome, which later produces vertebrae, and at their dorsal side to produce the dermis and muscle progenitors. Neural crest cells are multipotent stem cells induced at the lateral border of the prospective central nervous system (Gouignard et al., 2018). As neurulation proceeds, neural crest cells emerge from the neuroepithelium by converting into highly migratory mesenchyme cells, many of which will later re-aggregate to form solid structures ranging from condensed connective tissue, such as ganglia of the peripheral nervous system, to epithelial cells of the corneal endothelium of the eye (Dupin et al., 2006). Other examples of EMT during development occurs in the lateral mesoderm, the liver diverticulum, the pancreatic buds or the endocardium (Lim & Thiery, 2012).

Importantly, EMT is not specific to embryonic development but also occurs during various conditions, including wound healing, fibrosis and cancer metastasis (Yang et al., 2020). Molecular and cellular mechanisms controlling EMT are evolutionally conserved due to their physiological importance. Therefore, these settings provide knowledge databases on how EMT is controlled, what signals may trigger EMT and how cells change their E/M characteristics over time. The range of EMT possibilities and variations is huge. For instance, gastrulation occurs in all animals, except Porifera (sponges) and Placozoa (Lanna, 2015; Martindale, 2005). While the basic principles are conserved, EMT during gastrulation happens at different initial conditions in each species (i.e., number of cells, topology etc.). As for neural crest delamination, there are variations from species to species but also among neural crest subpopulations in each animal. Therefore, by studying the wide diversity of physiological EMTs in multiple experimental models, we can build a catalogue of various possible scenarios for cells to undergo EMT and its reverse transition, MET.

We all hope for the right marker (or set of markers) whose expression could discriminate between cells that have not yet undergone EMT and the ones that are engaged in EMT. Ideally at the earliest possible moment, so that these expressions might have predictive value regarding to what cells will do next. However, the overwhelming diversity of EMTs in physiological settings suggests that the search for the right markers may be a wild goose chase. This is why we think that the previously suggested term "Epithelial-Mesenchymal Plasticity (EMP)" (Haerinck et al., 2023; Yang et al., 2020) should be used to define the framework within which cells' journeys around E and M status are studied. This makes it possible to think about and address plasticity between epithelial and mesenchymal cell states as a whole without being limited to the simplistic and reductive definitions often linked to the EMT/MET terminologies. The terms EMT and MET are still valid but they represent specific cases of unidirectional changes between E and M that take place at a smaller time scale within the global long-term EMP context. This framework puts less pressure on the use of markers as proof of a cell status and more importance on cell behavior and overall capabilities of cells to interact with one another.

One telling example is that of cadherins. The expressions of these calcium-dependent cell adhesion molecules are often used as definitive markers of epithelial versus mesenchymal identities such that cells expressing E-cadherin (Cadherin-1, CDH1) are considered epithelial while those expressing N-cadherin (Cadherin-2, CDH2) are thought to be mesenchymal. However, neural crest development gives a different perspective on this idea. In Xenopus, pre-migratory cephalic neural crest cells are epithelial and turn into mesenchymal migratory cells via an E to N cadherin switch (Scarpa et al., 2015). However, it should be noted that these cells maintain some

expression of E-cadherin (Huang et al., 2016). During migration of Xenopus neural crest cells, E-cadherin is no longer involved in cell–cell junctions and its loss of function impairs adhesion to fibronectin (Huang et al., 2016). Interestingly, the role of maintaining cell–cell junctions during migration is performed by N-cadherin whose loss-of-function impairs cell–cell adhesion (Theveneau et al., 2010). Therefore, Xenopus neural crest cells display an intermediate E/M phenotype but this is due to the fact that these cells maintain some transient junctions while migrating (via N-cadherin), not because they have some residual level of E-cadherin expression. In other cell types, E-cadherin has been shown to be involved in cell–cell adhesions allowing collective motion (Bazellieres et al., 2015). By contrast, in chicken embryos, cephalic neural crest cells emerge from a neuroepithelium that expresses both E and N-cadherin. These cells become mesenchymal and initiate migration while expressing E and N-cadherin (Dady et al., 2012; Dady & Duband, 2017; Rogers et al., 2018; Theveneau et al., 2007). Whereas, at trunk level, chicken neural crest cells depart from a neuroepithelium that only expresses N-cadherin and their mesenchymalization occurs while maintaining N-cadherin expression (Shoval et al., 2007). These three examples demonstrate that mesenchymalization of neural crest cells can occur concomitantly with an upregulation, a stable expression or a loss of N-cadherin expression at mRNA level and a subsequent complex dynamics at protein level. Thus, the change from E-to-M in neural crest cells cannot be simply attributed to a cadherin switch. Similar observations can be made in other cell types. In gastrulating paraxial mesoderm, N-cadherin is used for epithelialization of the somites from the mesenchymal presomitic mesoderm (Chal et al., 2017). In adults, N-cadherin is endogenously expressed in multiple organs under normal conditions (i.e., liver, testis, adrenal gland, and cardiomyocytes). These different examples highlight the fact that high expression levels of N-cadherin at mRNA level may correspond to very different situations in terms of stability of the N-cadherin protein and cell behavior (i.e., migration, active epithelialization or stable differentiated organ). This is true for the neuroepithelium and migratory neural crest cells. In the former, N-cadherin is involved in stable junctions and maintains the epithelium. In the latter, the N-cadherin protein is cleaved and endocytosed, thus preventing neural crest cells from forming stable cell–cell adhesions (Kuriyama et al., 2014; Shoval et al., 2007). Overall, this indicates that expressions of cadherins by themselves are not indicative of a mesenchymal or epithelial status and that the context in which these expressions occur has to be taken into account.

Another example is that of transcription factors that act upstream of the EMP programs during development such as Snai, Twist, and Zeb family members. Developmental studies highlighted the critical roles that many of these genes play in destabilizing epithelial features by repressing cadherin expressions, upregulating proteases and modifying extracellular matrix. When examining EMP transcription factors in the Human Protein Atlas (Human Protein Atlas proteinatlas.org; [Karlsson et al., 2021; Uhlen et al., 2015]), one cannot help noticing that several of them also have normal expression in certain cell types. One extreme example is that of the specialized epithelial cells of the male gonads, known as Sertoli cells. These cells have an endogenous expression of Twist1, Zeb1, MMP14, and N-cadherin. By all measures, a cell expressing simultaneously these four proteins would be considered a highly invasive migratory cell by most developmental and cancer biologists. Yet, Sertoli cells are epithelial and non-migratory. Another example is the expression of Snai1 and Snai2 in breast adipocytes, cells with limited migratory potential under normal physiological conditions. The same observation can be made for metalloproteinases whose expression is often used as a sign of invasive behavior. While such enzymes can degrade extracellular matrix, generate tracks for migration and invasion, numerous epithelia express metalloproteinases without displaying signs of EMP. During neural tube development, MMP14 mRNA is strongly detected throughout the entire tissue (Andrieu et al., 2020). However, MMP14-dependent EMP only occurs in the neural crest (Andrieu et al., 2020) while the rest of the neural tube maintains an epithelial organization and a continuous basement membrane. Therefore, while MMPs are involved in invasion, expression of MMPs alone cannot define invasiveness, a trait only assessed via functional assays such as assessing motility, matrix degradation or the ability to intermix with other cells. Finally, in some cell types, E-cadherin is co-expressed with known repressors of its expression under normal circumstances. Such examples include the co-expression of E-cadherin and Snai2 in migratory cephalic neural crest cells in chicken embryos (Rogers et al., 2018). This shows that levels of regulation other than gene expression, post-transcriptionally and post-translationally, are relevant as well.

What do we learn from all of this? First, that the dynamic of expression, taking into consideration the actual protein level, is likely to be more informative than a single measure at the RNA level. Unfortunately, expression analyses at multiple time points in pathological contexts is often technically challenging to achieve and/or initial control expression level in each patient/tissue may not be known. When possible, such analyses may yield seemingly surprising results if only a small set of factors is considered, such as the described reduction of Snai2 expression in malignant prostate cancer compared to normal prostate (Esposito et al., 2015). If taken *stricto sensu* in the classical EMT framework, such loss of Snai2 expression may be interpreted as an absence of conversion from E to M associated with prostate cancer progression. A more likely situation is that of a progressive change of transcription factor signature as seen in melanoma where the progression from proliferation to invasion is associated with a change from Snai2/Zeb2 to a Twist1/Zeb1 profile (Caramel et al., 2013). Interestingly, such transitions are also observed in neural crest development. In Xenopus cephalic neural crest cells, Snai1/Snai2 are expressed in pre-migratory cells (Aybar et al., 2003). Then, several hours later, Twist expression starts (Hopwood et al., 1989). As migration proceeds, Twist expression is maintained and increased while those of Snai1 and 2 are progressively lost. Functional evidence further indicate that Twist physically interacts with Snail proteins to inhibit their function (Lander et al., 2013). Second, that the context plays a crucial part in interpreting the data. EMP gene expression in cells that do or do not express such genes under normal physiological conditions will not carry the same weight. Third, part of that context may be the subcellular localization of some of the putative EMP regulators

themselves. In the case of metalloproteinases, while they obviously can affect the matrix, they need to be presented at the cell surface or released extracellularly to do so in the first place. We now know that many of such proteins have complex subcellular trafficking and can be kept intracellularly (Jobin et al., 2017), in some cases to promote EMP, as seen in Xenopus neural crest (Gouignard et al., 2023). Transcription factors also traffic between the cytosol and preventing entry into the nucleus can block their function as shown for TWIST1 in response to different extracellular matrix rigidities (Fattet et al., 2020; Wei et al., 2015). Fourth, some EMP regulators may have additional functions beyond regulating EMP. Snail for instance can influence cancer progression without triggering E-cadherin downregulation and EMP (Paul et al., 2023) and Snai2 is required for normal hematopoiesis (Pioli & Weis, 2014). Twist1 is known as an important factor for mesoderm development and differentiation most likely by modulating FGF and Shh signaling as well as Hand proteins (Qin et al., 2012) but some of these targets might still be related to EMP. Overexpression of Sox10 is sufficient to promote partial or complete mesenchymalization in the neuroepithelium (McKeown et al., 2005). However, during normal neural crest development it promotes pigment cell formation (Aoki et al., 2003) whereas its inhibition does not affect EMT and migration (Aoki et al., 2003; Honore et al., 2003). Therefore, in some cases, expression of some EMP genes may be related to cell identity/lineage rather than cell behavior. These observations require us to rethink the framework associated with the initial definition of EMT by proposing a more flexible paradigm, where the plasticity between E and M states is tissue and context-dependent and cannot be reduced to a few key markers.

These observations stress the importance of monitoring expression of putative EMP regulators across multiple time points and to perform functional assays to assess the cells' EMP state and potential. In the context of cell and developmental biology studies multiple assays can be (and often are) implemented alongside expression analyses: migration/invasion assays, cell–cell and cell-matrix adhesion assays, collision assays, matrix remodeling/degradation assays, and so forth. Given the wealth of information that can be extracted from such experiments it would be greatly beneficial if the diagnosis/prognosis workflow in the clinical context could integrate such approaches as routine procedures from patients' biopsies. Currently, oncology centers in which there is a functional daily integration of clinical and research departments are the exception rather than the norm. There have been promising attempts to harness the power of classical embryology techniques in the context of oncology via, for instance, modified migration/invasion assays using patients' cells grafted in avian embryos (Delloye-Bourgeois et al., 2017; Jarrosson et al., 2021; Jarrosson et al., 2023). Still very marginal a few years ago, the use of these chimeras is expanding, both in the academic world and biotech companies. Organoid development, from embryonic or adult stem cells, may also help to recapitulate the features and dynamic of EMP during organogenesis, in physiology and pathologies. It allows to access and assess processes that may be difficult to observe and to quantify either in vivo or in vitro in 2D cell culture systems.

When people discuss EMP from development to diseases, they usually mean that EMP can be found in a large spectrum of biological systems from the most physiological (i.e., development, healing) all the way up to pathological settings (i.e., fibrosis and cancer). This, however, maintains the various fields of investigation on parallel trajectories with researchers comparing systems, drawing similarities, and searching for correlations. But we may be ignoring another level of analysis that could be more relevant. Should we actually follow cells from development to disease? Thus, considering the life of cells from development to normal homeostasis to the pathology? Organs are composed of cells that have a history through which they have acquired a given gene expression profile, a given morphology and a given set of interactions with their neighboring cells in their organs and with adjacent organs. While some organs are formed from cells that never underwent EMP (epidermis), other went through one (i.e., ganglia of the peripheral nervous system), two (i.e., dermis, skeletal muscle) or three (i.e., cushion mesenchyme of the heart) round trips between epithelial and mesenchymal states. Should we treat the variations in gene expression profiles and protein levels differently when dealing with cells from tissues that experienced one, two, three or no EMT-MET at all throughout their lives? Or when considering cells that display different endogenous expression of genes with EMP potential? Plasticity around E/M states is known to impact stemness and survival, in addition to migratory and invasive properties. Are cells durably affected by a chronic exposure to signals triggering EMP? Genome-scale epigenetic modifications have been documented during EMP (Malouf et al., 2013; McDonald et al., 2011). Do they have long-lasting effects in terms of competence to toggle between E, M and intermediate states? We hope that future systematic studies could address the long-term effects (if any) of successive EMT-MET events on cells and their putative impact on subsequent EM plasticity.

This Editorial only scratches the surface of the complexity of EMP and the multiple questions it raises. EMP is a rapidly expanding a field of research and our understanding of its molecular and cellular implementation as well as its functional relationship with normal and pathological processes is a work in progress. In this special issue, we have assembled a collection of reviews and research articles looking at EMP in a wide range of contexts such as lateral plate mesoderm and neural crest development, cancer cell dormancy or kidney fibrosis. We hope that readers will find the content of the Special Issue to be intellectually stimulating.

ACKNOWLEDGMENTS

Hervé Acloque is an INRAE senior researcher supported by funding from ANR PluS4PiGs (ANR-19-CE20-0019). Jing Yang has been supported by grants from NCI (1RO1CA262794, 1R01CA174869, 1R01CA206880, and 1R01CA236386) and CDMRP DOD Breast Cancer Program BC170283. Eric Theveneau is a research director at the French National Research Center (CNRS) and supported by grants from ANR SingleCrest (ANR-21-CE13-0028-02), the Association pour la Recherche contre le Cancer (ARC, ARCPJA22020060002084), the Fondation pour la Recherche Médicale (FRM AJE201224).

FUNDING INFORMATION

Agence Nationale de la Recherche, Grant/Award Numbers: ANR-19-CE20-0019, ANR-21-CE13-0028-02; Association pour la Recherche sur le Cancer, Grant/Award Number: ARCPJA22020060002084; Congressionally Directed Medical Research Programs, Grant/Award Number: BC170283; Fondation pour la Recherche Médicale, Grant/Award Number: FRM AJE201224; National Cancer Institute, Grant/Award Numbers: 1RO1CA262794, 1R01CA174869, 1R01CA206880, 1R01CA236386

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