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1 Epithelial-to-Mesenchymal Plasticity from development to disease: an  
2 introduction to the special issue.

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10

11 **Abstract**

12 Epithelial-Mesenchymal Transition (EMT) refers to the ability of cells to switch between  
13 epithelial and mesenchymal states, playing critical roles in embryonic development, wound healing,  
14 fibrosis, and cancer metastasis. Here, we discuss some examples that challenge the use of specific  
15 markers to define EMT, noting that their expression may not always correspond to the expected  
16 epithelial or mesenchymal identity. In concordance with recent development in the field, we emphasize  
17 the importance of generalizing the use of the term Epithelial-Mesenchymal Plasticity (EMP), to better  
18 capture the diverse and context-dependent nature of the bidirectional journey that cells can undertake  
19 between the E and M phenotypes. We highlight the usefulness of studying a wide range of physiological  
20 EMT scenarios, stress the value of the dynamic of expression of EMP regulators and advocate,  
21 whenever possible, for more systematic functional assays to assess cellular states.

22

23 **Main Text**

24 The term “Epithelial-Mesenchymal Transformation” was introduced by Elizabeth Hay to define  
25 the phenomena that cells can switch from epithelial to mesenchymal states during tissue  
26 morphogenesis and homeostasis. The term “transformation” is later replaced by the more accurate  
27 word “transition” to better reflect the non-binary nature of the process (see (Hay, 2005) and references  
28 therein). EMT is indeed a staple of embryonic development as cells must proliferate and move in three  
29 dimensions to form and rearrange tissues and organs at the right place and time. For that, they  
30 frequently toggle between relatively cohesive and stable epithelial states and more dynamic and loose  
31 mesenchymal arrangements (Nieto et al., 2016). In many cases, and as discussed below, EMT occurs in

32 cells that will eventually migrate. However, one should not systematically associate EMT with migratory  
33 behavior. During fibrosis, there are several examples of cells adopting partial E/M phenotypes that do  
34 not undertake migration but nonetheless contribute to disease progression via this phenotypic change  
35 (see (Liu et al., 2022) for discussion).

36 Classical examples of EMT include gastrulation and neural crest development. Mesoderm is  
37 induced at the interface between ectoderm and endoderm. Initially epithelial, mesoderm progenitor  
38 cells undergo a conversion towards mesenchymal states to ingress, migrate and intercalate between  
39 ectoderm and endoderm during gastrulation. At the cervical and trunk level, the most axial of these  
40 migratory mesodermal cells re-epithelialize into repetitive structures called somites on either sides of  
41 the neural tube (Benazeraf & Pourquie, 2013). These somites will then undergo another round of  
42 mesenchymalization at their ventral side to form the sclerotome, which later produces vertebrae, and  
43 at their dorsal side to produce the dermis and muscle progenitors. Neural crest cells are multipotent  
44 stem cells induced at the lateral border of the prospective central nervous system (Gouignard et al.,  
45 2018). As neurulation proceeds, neural crest cells emerge from the neuroepithelium by converting into  
46 highly migratory mesenchyme cells, many of which will later re-aggregate to form solid structures  
47 ranging from condensed connective tissue, such as ganglia of the peripheral nervous system, to  
48 epithelial cells of the corneal endothelium of the eye (Dupin et al., 2006). Other examples of EMT  
49 during development occurs in the lateral mesoderm, the liver diverticulum, the pancreatic buds or the  
50 endocardium (Lim & Thiery, 2012).

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

63 We all hope for the right marker (or set of markers) whose expression could discriminate  
64 between cells that have not yet undergone EMT and the ones that are engaged in EMT. Ideally at the

65 earliest possible moment, so that these expressions might have predictive value regarding to what cells  
66 will do next. However, the overwhelming diversity of EMTs in physiological settings suggests that the  
67 search for the right markers may be a wild goose chase. This is why we think that the previously  
68 suggested term “Epithelial-Mesenchymal Plasticity (EMP)” (Haerinck et al., 2023; Yang et al., 2020)  
69 should be used to define the framework within which cells’ journeys around E and M status are studied.  
70 This makes it possible to think about and address plasticity between epithelial and mesenchymal cell  
71 states as a whole without being limited to the simplistic and reductive definitions often linked to the  
72 EMT/MET terminologies. The terms EMT and MET are still valid but they represent specific cases of  
73 unidirectional changes between E and M that take place at a smaller time scale within the global long-  
74 term EMP context. This framework puts less pressure on the use of markers as proof of a cell status  
75 and more importance on cell behavior and overall capabilities of cells to interact with one another.

76 One telling example is that of cadherins. The expressions of these calcium-dependent cell  
77 adhesion molecules are often used as definitive markers of epithelial versus mesenchymal identities  
78 such that cells expressing E-cadherin (Cadherin-1, CDH1) are considered epithelial while those  
79 expressing N-cadherin (Cadherin-2, CDH2) are thought to be mesenchymal. However, neural crest  
80 development gives a different perspective on this idea. In *Xenopus*, pre-migratory cephalic neural crest  
81 cells are epithelial and turn into mesenchymal migratory cells via an E to N cadherin switch (Scarpa et  
82 al., 2015). However, it should be noted that these cells maintain some expression of E-cadherin (Huang  
83 et al., 2016). During migration of *Xenopus* neural crest cells, E-cadherin is no longer involved in cell-cell  
84 junctions and its loss of function impairs adhesion to fibronectin (Huang et al., 2016). Interestingly, the  
85 role of maintaining cell-cell junctions during migration is performed by N-cadherin whose loss-of-  
86 function impairs cell-cell adhesion (Theveneau et al., 2010). Therefore, *Xenopus* neural crest cells  
87 display an intermediate E/M phenotype but this is due to the fact that these cells maintain some  
88 transient junctions while migrating, not because they have some residual level of E-cadherin  
89 expression. In other cell types, E-cadherin has been shown to be involved in cell-cell adhesions allowing  
90 collective motion (Bazellieres et al., 2015). By contrast, in chicken embryos, cephalic neural crest cells  
91 emerge from a neuroepithelium that expresses both E and N-cadherin. These cells become  
92 mesenchymal and initiate migration while expressing E and N-cadherin (Dady et al., 2012; Dady &  
93 Duband, 2017; Rogers et al., 2018; Theveneau et al., 2007). Whereas, at trunk level, chicken neural  
94 crest cells depart from a neuroepithelium that only expresses N-cadherin and their  
95 mesenchymalization occurs while maintaining N-cadherin expression (Shoval et al., 2007). These three  
96 examples demonstrate that mesenchymalization of neural crest cells can occur concomitantly with an  
97 upregulation, a stable expression or a loss of N-cadherin expression at mRNA level and a subsequent  
98 complex dynamics at protein level. Thus, the change from E-to-M in neural crest cells cannot be simply

99 attributed to a cadherin switch. Similar observations can be made in other cell types. In gastrulating  
100 paraxial mesoderm, N-cadherin is used for epithelialization of the somites from the mesenchymal  
101 presomitic mesoderm (Chal et al., 2017). In adults, N-cadherin is endogenously expressed in multiple  
102 organs under normal conditions (i.e liver, testis, adrenal gland and cardiomyocytes). These different  
103 examples highlight the fact that high expression levels of N-cadherin at mRNA level may correspond to  
104 very different situations in terms of stability of the N-cadherin protein and cell behavior (i.e. migration,  
105 active epithelialization or stable differentiated organ). This is true for the neuroepithelium and  
106 migratory neural crest cells. In the former, N-cadherin is involved in stable junctions and maintains the  
107 epithelium. In the latter, the N-cadherin protein is cleaved and endocytosed, thus preventing neural  
108 crest cells from forming stable cell-cell adhesions (Kuriyama et al., 2014; Shoval et al., 2007). Overall,  
109 this indicates that expressions of cadherins by themselves are not indicative of a mesenchymal or  
110 epithelial status and that the context in which these expressions occur has to be taken into account.

111 Another example is that of transcription factors that act upstream of the EMP programs during  
112 development such as Snai, Twist, and Zeb family members. Developmental studies highlighted the  
113 critical roles that many of these genes play in destabilizing epithelial features by repressing cadherin  
114 expressions, upregulating proteases and modifying extracellular matrix. When examining EMP  
115 transcription factors in the Human Protein Atlas (Human Protein Atlas [proteinatlas.org](https://www.proteinatlas.org); (Karlsson et al.,  
116 2021; Uhlen et al., 2015)), one cannot help noticing that several of them also have normal expression  
117 in certain cell types. One extreme example is that of the specialized epithelial cells of the male gonads,  
118 known as Sertoli cells. These cells have an endogenous expression of Twist1, Zeb1, MMP14 and N-  
119 cadherin. By all measures, a cell expressing simultaneously these four proteins would be considered a  
120 highly invasive migratory cell by most developmental and cancer biologists. Yet, Sertoli cells are  
121 epithelial and non-migratory. Another example is the expression of Snai1 and Snai2 in breast  
122 adipocytes, cells with limited migratory potential under normal physiological conditions. The same  
123 observation can be made for metalloproteinases whose expression is often used as a sign of invasive  
124 behavior. While such enzymes can degrade extracellular matrix, generate tracks for migration and  
125 invasion, numerous epithelia express metalloproteinases without displaying signs of EMP. During  
126 neural tube development, MMP14 mRNA is strongly detected throughout the entire tissue (Andrieu et  
127 al., 2020). However, MMP14-dependent EMP only occurs in the neural crest (Andrieu et al., 2020) while  
128 the rest of the neural tube maintains an epithelial organization and a continuous basement membrane.  
129 Therefore, while MMPs are involved in invasion, expression of MMPs alone cannot define invasiveness,  
130 a trait only assessed via functional assays such as assessing motility, matrix degradation or the ability  
131 to intermix with other cells. Finally, in some cell types E-cadherin is co-expressed with known repressors  
132 of its expression under normal circumstances. Such examples include the co-expression of E-cadherin

133 and Snai2 in migratory cephalic neural crest cells in chicken embryos (Rogers et al., 2018). This shows  
134 that levels of regulation other than gene expression, post-transcriptionally and post-translationally, are  
135 relevant as well.

136         What do we learn from all of this? First, that the dynamic of expression, taking into  
137 consideration the actual protein level, is likely to be more informative than a single measure at the RNA  
138 level. Unfortunately, expression analyses at multiple time points in pathological contexts is often  
139 technically challenging to achieve and/or initial control expression level in each patient/tissue may not  
140 be known. When possible, such analyses may yield seemingly surprising results if only a small set of  
141 factors is considered, such as the described reduction of Snai2 expression in malignant prostate cancer  
142 compared to normal prostate (Esposito et al., 2015). If taken *stricto sensu* in the classical EMT  
143 framework, such loss of Snai2 expression may be interpreted as an absence of conversion from E to M  
144 associated with prostate cancer progression. A more likely situation is that of a progressive change of  
145 transcription factor signature as seen in melanoma where the progression from proliferation to  
146 invasion is associated with a change from Snai2/Zeb2 to a Twist1/Zeb1 profile (Caramel et al., 2013).  
147 Interestingly, such transitions are also observed in neural crest development. In *Xenopus* cephalic  
148 neural crest cells, Snai1/Snai2 are expressed in pre-migratory cells (Aybar et al., 2003). Then, several  
149 hours later, Twist expression starts (Hopwood et al., 1989). As migration proceeds, Twist expression is  
150 maintained and increased while those of Snai1 and 2 are lost. Functional evidence further indicate that  
151 Twist physically interact with Snail proteins to inhibit their function (Lander et al., 2013). Second, that  
152 the context plays a crucial part in interpreting the data. EMP gene expression in cells that do or do not  
153 express such genes under normal physiological conditions will not carry the same weight. Third, part  
154 of that context may be the subcellular localization of some of the putative EMP regulators themselves.  
155 In the case of metalloproteinases, while they obviously can affect the matrix, they need to be presented  
156 at the cell surface or released extracellularly to do so in the first place. We now know that many of such  
157 proteins have complex subcellular trafficking and can be kept intracellularly (Jobin et al., 2017), in some  
158 cases to promote EMP, as seen in *Xenopus* neural crest (Gougnard et al., 2023). Transcription factors  
159 also traffic between the cytosol and preventing entry into the nucleus can block their function as shown  
160 for TWIST1 in response to different extracellular matrix rigidities (Fattet et al., 2020; Wei et al., 2015).  
161 Fourth, some EMP regulators may have additional functions beyond regulating EMP. Snail for instance  
162 can influence cancer progression without triggering E-cadherin downregulation and EMP (Paul et al.,  
163 2023) and Snai2 is required for normal hematopoiesis (Pioli & Weis, 2014). Twist1 is known as an  
164 important factor for mesoderm development and differentiation most likely by modulating FGF and  
165 Shh signaling as well as Hand proteins (Qin et al., 2012) but some of these targets might still be related  
166 to EMP. Overexpression of Sox10 is sufficient to promote partial or complete mesenchymalization in

167 the neuroepithelium (McKeown et al., 2005). However, during normal neural crest development it  
168 promotes pigment cell formation (Aoki et al., 2003) whereas its inhibition does not affect EMT and  
169 migration (Aoki et al., 2003; Honore et al., 2003). Therefore, in some cases, expression of some EMP  
170 genes may be related to cell identity/lineage rather than cell behavior. These observations require us  
171 to rethink the framework associated with the initial definition of EMT by proposing a more flexible  
172 paradigm, where the plasticity between E and M states is tissue and context-dependent and cannot be  
173 reduced to a few key markers.

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

191         When people discuss EMP from development to diseases, they usually mean that EMP can be  
192 found in a large spectrum of biological systems from the most physiological (i.e., development, healing)  
193 all the way up to pathological settings (i.e., fibrosis and cancer). This, however, maintains the various  
194 fields of investigation on parallel trajectories with researchers comparing systems, drawing similarities,  
195 and searching for correlations. But we may be ignoring another level of analysis that could be more  
196 relevant. Should we actually follow cells from development to disease? Thus, considering the life of  
197 cells from development to normal homeostasis to the pathology? Organs are composed of cells that  
198 have a history through which they have acquired a given gene expression profile, a given morphology  
199 and a given set of interactions with their neighboring cells in their organs and with adjacent organs.  
200 While some organs are formed from cells that never underwent EMP (epidermis), other went through

201 one (i.e. ganglia of the peripheral nervous system), two (i.e. dermis, skeletal muscle) or three (i.e.  
202 cushion mesenchyme of the heart) round trips between epithelial and mesenchymal states. Should we  
203 treat the variations in gene expression profiles and protein levels differently when dealing with cells  
204 from various tissues that experienced one, two, three or no EMT at all throughout their lives? Or when  
205 considering cells that display different endogenous expression of genes with EMP potential? Plasticity  
206 around E/M states is known to impact stemness and survival, in addition to migratory and invasive  
207 properties. Are cells durably affected by a chronic exposure to signals triggering EMP? Genome-scale  
208 epigenetic modifications have been documented during EMP (Malouf et al., 2013; McDonald et al.,  
209 2011). Do they have long-lasting effects in terms of competence to toggle between E, M and  
210 intermediate states? We hope that future systematic studies could address the long term effects (if  
211 any) of successive EMT-MET events on cells and their putative impact on subsequent EM plasticity  
212 events.

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

220

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228

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