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meeting report

The physiology and pathology of the EMT

Meeting on the Epithelial–Mesenchymal Transition

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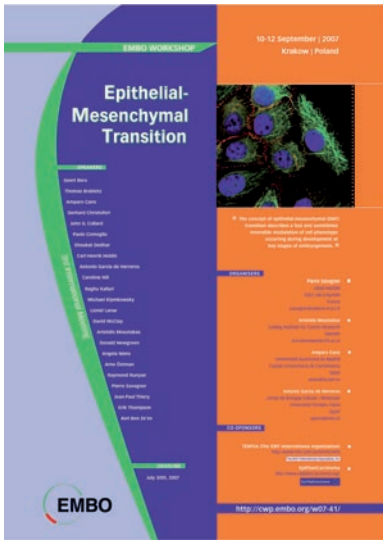

The third international symposium on the Epithelial–Mesenchymal Transition was an EMBO workshop organized by TEMTIA (The International EMT Organization) and the European network EpiPlastCarcinoma. It took place between 10 and 12 September 2007, at the Larisha Palace in Krakow, Poland, and was organized by P. Savagner, A. Moustakas, A. Garcia de Herreros and A. Cano.

Keywords: EMT; embryonic development; cancer; fibrosis

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Introduction

Epithelial–mesenchymal transitions (EMTs) have been described primarily during embryonic development when tissue remodelling and cell migration shape the future organism. In addition, they have also been described in pathological situations such as tumour progression. During EMT, epithelial cells lose the adherent and tight junctions that keep them in contact with their neighbours; they can also break through the basal membrane and migrate over long distances owing to profound changes in their cytoskeleton architecture.

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Although EMT has been recognized as a crucial process during embryonic development, its potential role in the progression of carcinoma was neglected for many years. Recent data from embryos of various species and different human pathologies, including fibrosis and cancer, are helping us to understand the physiological and pathological aspects of EMTs. In addition to somatic mutations and the control of gene expression, crosstalk between signalling pathways and regulatory elements such as microRNAs (miRNAs), natural antisense transcripts, sophisticated transcription complexes and the control of protein transport and stability, have fuelled increasing interest in this exciting field.

This EMBO workshop in Krakow, Poland, brought together around 80 people working on EMTs, and was an excellent opportunity to discuss recent advances in a relaxed and friendly atmosphere. However, the meeting began on a sad note as we expressed our condolences on the recent loss of Elizabeth Hay, who was scheduled to open the workshop. Betty Hay was the founder of the epithelial-to-mesenchymal transformation concept (Fig 1), and, in her memory, R. Kalluri (Harvard, MA, USA) and J.P. Thiery (Proteos, Singapore) opened the meeting describing her outstanding contribution to the field. In 1967, Hay realized that the EMT was of crucial importance during gastrulation (Trelstad *et al*, 1967). This seminal study was followed by other papers, culminating in 1982 with the publication of a model to study EMT in three-dimensional collagen cultures (Greenburg & Hay, 1982). Throughout her scientific life, Hay remained an extremely rigorous and passionate investigator in her quest to understand how cells assemble into functional tissues to shape the embryo. Her last co-authored paper—showing that transforming growth factor β3 (TGFβ3) induces EMT during palatal fusion through the activation of the Wnt signalling target LEF1—was presented at the meeting by A. Nawshad (Lincoln, NE, USA; Nawshad *et al*, 2007).

E-cadherin repressors and EMT

E-cadherin is essential for the maintenance of epithelial integrity of many embryonic and adult tissues. Consequently, its repression is a crucial step of the EMT, both during embryonic development and in pathological situations in the adult. *Snail* genes were the first direct repressors of E-cadherin expression to be described (Batlle *et al*, 2000; Cano *et al*, 2000). However, additional E-cadherin repressors have since been identified, including basic helix–loop–helix transcription

factors such as E47 and Twist, and the Zeb factors, ΔEF1/Zeb1 (Zeb for zinc finger E-box binding homeobox) and Sip1/Zeb2 (Sip for Smad interacting protein; Peinado *et al*, 2007). At the meeting, A. Cano (Madrid, Spain) presented E2-2, another basic helix–loop–helix transcription factor that is able to induce full EMT in Madine–Darby canine kidney cells by directly repressing E-cadherin promoter activity.

The activity of E-cadherin repressors is tightly regulated at various levels, as reflected by several recent studies that were presented in Krakow. Snail1 (Snail) was shown to control Zeb2 activity by the splicing of a 5'UTR fragment in the *Zeb2* mRNA. This produces a natural antisense transcript that leads to an increase in the protein levels of Zeb2 (A. Garcia de Herreros, Barcelona, Spain). Another way to enhance the activity of E-cadherin repressors was presented by H. Peinado (Madrid, Spain), who showed that the lysine oxidase, LoxL2, increases the stability and activity of Snail1 (Peinado *et al*, 2005). Indeed, the co-expression of Snail and LoxL2 in tumour models and human squamous cell carcinomas correlates with malignancy or local recurrence. LoxL2 silencing augments E-cadherin expression and induces epithelial differentiation. With respect to the control of Snail subcellular localization, M.A. Nieto (Alicante, Spain) identified specific amino-acid residues in the Snail1 protein that are required for the binding of several importins to mediate its nuclear translocation and function as a transcription factor.

New EMT inducers

Various posters and talks at the meeting presented new proteins that induce full EMT. One example is Pez, a protein tyrosine phosphatase that induces TGFβ expression and EMT in Madine–Darby canine kidney cells (Wyatt *et al*, 2007). The interleukin-like EMT inducer (ILEI) is also able to induce tumour growth and metastasis in various cell lines (Waerner *et al*, 2006), whereas functional interference with ILEI reverts TGFβ-induced EMT. This work, from the laboratory of H. Beug (Vienna, Austria), was the worthy recipient of the first Elizabeth Hay poster prize awarded to A. Csiszar. Another interesting study showed that the high mobility group protein, HMGA2, is required for the induction of EMT by TGFβ (Thuault *et al*, 2006), which is mediated primarily by *Snail* induction through the Smad proteins (A. Moustakas, Uppsala, Sweden).

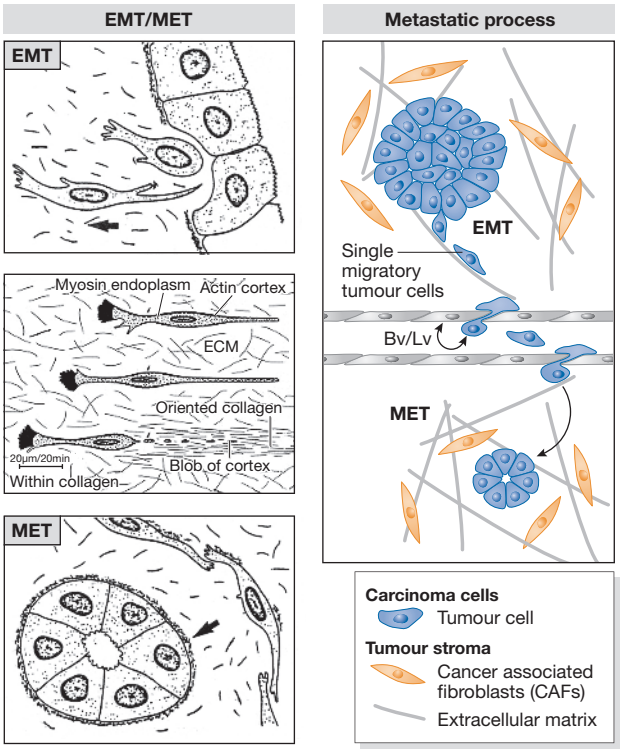

Fig 1 | The epithelial–mesenchymal transition in cancer: past, present and future perspectives. Betty Hay coined the term epithelial-to-mesenchymal transformation some 40 years ago and left us beautiful drawings that not only show the transformation to mesenchyme, but also the transient nature of the process and the reversion to the epithelial character (MET; Hay, 1968, 1995). This is why the preferred term is now epithelial-to-mesenchymal transition (EMT). The EMT, as an initial step in the metastatic cascade, has until recently remained a matter of debate; however, powerful imaging tools have convincingly shown that individual cells delaminate from primary tumours (Condeelis & Segall, 2003). Bv, blood vessels; ECM, extracellular matrix; Lv, lymphatic vessels.

New insights into cell adhesion, polarity and migration

By measuring the strength of cadherin-mediated cell adhesion, Thiery showed that cells expressing Type I cadherins adhere more rapidly and more strongly than those expressing Type II cadherins, which are often present in migratory cells (Chu *et al*, 2006). In addition, he showed that the strength of E-cadherin adhesion also depends on the cortical actin cytoskeleton, p120 interaction and the presence of an activated integrin pathway, suggesting that cadherins and integrins reciprocally control adhesive forces.

The dynamic behaviour of desmosomal cadherins also involves two adhesion states. Desmosomes in normal epidermis or confluent cells are hyper-adhesive and calcium independent, whereas those that are active in the early embryo, in subconfluent cultures or during wound healing are less adhesive and calcium dependent (D. Garrod, Manchester, UK). These different adhesion states could have implications for EMT, as an initial step in mesenchymal transition might involve a desmosome switch owing to changes in protein kinase C activity (Kimura *et al*, 2007). During wound healing, cells maintain some desmosomal proteins and they establish an intermediate state between the epithelial and mesenchymal states, referred to as the metastable phenotype (P. Savagner, Montpellier, France). This phenotype corresponds to a partial EMT characterized by the maintenance of cell–cell adhesion structures that do not preclude active cell migration. In relation to this, Nieto provided evidence that the function of *Snail* genes in regulating adhesion might or might not be associated with the induction of a full EMT, depending on the cellular context. Snail2 (Slug) induces a full EMT in the mesoderm of the early chick embryo, whereas two Snail1 proteins—snail1a and snail1b—cooperate in the migration of the axial mesendoderm in the zebrafish embryo by decreasing adhesion without inducing EMT (Blanco *et al*, 2007). In both cases, E-cadherin is downregulated, but in the latter, Snail-positive cells move and push Snail-negative/E-cadherin-positive neighbouring cells, which act as pioneers. This movement might parallel that of the leader cells during the collective migration of the epithelial monolayers (Poujade *et al*, 2007). Indeed, collective cell migration of pioneer cells can occur in the absence of cadherin downregulation both *in vitro* and *in vivo*, as shown by G. Christofori (Basel, Switzerland). This process is regulated by a mucin-like molecule called podoplanin, which induces cytoskeletal changes and the formation of filopodia (Wicki *et al*, 2006). The

combination of different cell movements has also been described in *Drosophila* embryos, in which the use of a photoactivatable green fluorescent protein has allowed M.J. Murray (Canberra, Australia) to resolve the behaviour of mesodermal cells in live embryos. In this case, some cells migrate as a group over the ectoderm, whereas others disperse independently (Murray & Saint, 2007).

Surprisingly, the changes in cell polarity concomitant with EMT had not been addressed until recently. The homologues of the *Drosophila* genes that establish cell polarity have now been analysed in vertebrates, and these studies have implicated the Scribble polarity complex in regulating polarity and migration during development and tumorigenesis (P.O. Humbert, Melbourne, Australia; Dow *et al*, 2007). Polarity genes are targeted by E-cadherin repressors in conjunction with the induction of EMT. Indeed, Snail and Zeb1 directly repress *Crumbs3* transcription (E. Whiteman, Ann Arbor, MI, USA; A. Eger, Vienna, Austria), and ZEB1 also downregulates *Lgl2* (lethal giant larvae 2) in colorectal and breast cancer human cells (T. Brabletz, Freiburg, Germany and A. Eger; Aigner *et al*, 2007; Spaderna *et al*, 2008). Interestingly, the Par complex establishes long-lasting apico–basal polarity in contacting keratinocytes in conjunction with Tiam 1 (T-cell lymphoma invasion and metastasis 1, an activator of Rac), whereas chemotactic migration is favoured in non-contacting cells by stabilizing front-to-rear polarization (J. Collard, Amsterdam, The Netherlands; Pegtel *et al*, 2007).

Signalling pathways in EMT

Although important questions linking TGFβ signalling and EMT were recently addressed at a meeting in Tucson, AZ, USA (Padgett & Reiss, 2007), new data were also presented in Krakow. To understand the dual role of TGFβ in growth inhibition and EMT, C. Hill (London, UK) has studied the function of Smad3 in two distinct cell systems: one undergoing EMT in response to TGFβ (EpH4 cells), and another resistant to TGFβ-induced growth arrest (EpRas cells). She showed that Smad3 is necessary for TGFβ to induce EMT in EpH4 cells, but that it is dispensable for the maintenance of the mesenchymal phenotype. Interestingly, Smad3 is more stable in quiescent cells than in cycling cells, and its stabilization in EpRas cells restores the inhibitory growth response to TGFβ without affecting the induction of the EMT. Together, these results indicate that the level of Smad3 protein modulates the cellular response to TGFβ. R.B. Runyan (Tucson, AZ, USA) focused on the functions of different TGFβ isoforms in promoting either EMT or cell invasion and migration (Mercado-Pimentel & Runyan, 2007). By using the atrio–ventricular canal as an experimental system, he showed that TGFβ2 and TGFβ3 act through the receptors TGFβRIII and RII, respectively, to activate Smad2/3 sequentially and induce EMT and cell spreading, and through Alk2 to promote cell invasion by Smad1/5 signalling.

Other groups focused on the crosstalk between TGFβ and other signalling pathways. A. Östman (Stockholm, Sweden) showed the importance of the platelet-derived growth factor (PDGF) pathway in the tumour microenvironment in inducing EMT. PDGF acts synergistically with TGFβRII and the vascular endothelial growth factor (Ostman & Heldin, 2007). Savagner focused on the importance of the epidermal growth factor (EGF) and Snail2 for wound healing, during which signalling through the EGF receptor preferentially activates extracellular signal-regulated kinase (ERK) pathways. He found that the Erk5 pathway specifically enhances *Snail2* promoter activity and controls *in vitro* wound healing in keratinocyte-derived HaCaT cells.

The hepatocyte growth factor (HGF)/Met signalling pathway is also involved in inducing EMT and in growth invasion. P. Comoglio (Turin, Italy) presented a microarray screening of cells exposed to HGF and identified two coagulation genes—plasminogen activator inhibitor, type I (*Pai-1*) and cyclooxygenase 2 (*Cox2*)—which are induced by HGF/Met, and the overexpression of which induces thrombohaemorrhagic syndrome and precedes the onset of hepatocarcinomas in mice. These data confirm the observations of Trousseau in 1865 that thrombophlebitis migrans is a sign of occult malignancy (Boccaccio & Comoglio, 2006). This provoked an interesting discussion as to whether the HGF signalling pathway, similar to many other developmental pathways, is part of a genetic programme controlling physiological processes that is usurped by cancer cells. Indeed, many questions relating to this issue remain unresolved; for example, the observation that HGF seems to induce the inverse mesenchymal-to-epithelial transition in some cellular contexts (M. López-Cabrera, Madrid, Spain).

Much effort has been devoted to understanding NF-κB activation during EMT. The data available show that NF-κB activates *Snail* expression both *in vitro* and *in vivo*. M. Klymkowsky (Boulder, CO, USA) showed that the induction of *Snail2* and *Twist* expression by NF-κB is necessary for mesoderm formation in *Xenopus* (Zhang *et al*, 2006). *Snail1* expression is also activated by NF-κB in human squamous carcinoma cells through the insulin-like growth factor receptor and Akt pathways (L. Larue, Orsay, France; Julien *et al*, 2007), and during the induction of EMT in mesothelial cells (R. Strippoli, Madrid, Spain).

Regulating the β-catenin pool

β-Catenin interacts with E-cadherin at adherens and tight junctions to maintain the epithelial phenotype. In response to exogenous signals, β-catenin is translocated from the cell membrane to the cytoplasm where it is either ubiquitinated and degraded, or directed to the nucleus where it can regulate gene transcription and induce EMT. In Krakow, several studies were presented that highlighted the importance of nuclear β-catenin in controlling cell invasion and growth inhibition. It is worth noting that cell density modulates adhesion through the turnover of β-catenin and E-cadherin (Conacci-Sorrell *et al*, 2003). At low cell density, β-catenin translocates to the nucleus and activates the repression of *E-cadherin* transcription by Snail2. Indeed, this process also occurs in colon cancer cells and at the invasion front of tumours where β-catenin activates the L1 cell adhesion molecule, a disintegrin and metalloprotease 10 (Adam10) and Fascin, thereby promoting EMT and metastasis (A. Ben Ze'ev, Rehovot, Israel, in collaboration with Brabletz; Gavert *et al*, 2007).

Nuclear β-catenin induces EMT and growth arrest in hepatocytes by increasing the levels of the cell-cycle inhibitor p16ink4a (Fischer *et al*, 2007). Attenuating cell proliferation seems to be a conserved characteristic associated with EMT because SIP1/ZEB2 represses *Cyclin D* expression (G. Berx, Ghent, Belgium; Mejlvang *et al*, 2007), as previously shown for Snail1 (Vega *et al*, 2004).

The relationship between the pools of E-cadherin and β-catenin is crucial for the induction and maintenance of the mesenchymal phenotype. The overexpression of E-cadherin sequesters β-catenin and maintains its association with the cell membrane, preventing its role as a transcription factor important for EMT. E-cadherin also helps to maintain the epithelial phenotype by decreasing NF-κB activity, which impairs Snail1 activation and, consequently, the induction of *ZEB1* genes and other mesenchymal markers (Garcia de Herreros).

EMT and organ fibrosis

Until recently, fibrosis and, in particular, renal fibrosis was thought to be mediated by the activation of interstitial fibroblasts that deposit an excess of collagen fibres. It now seems clear that renal tubular epithelial cells can also undergo EMT and become collagen-producing myofibroblasts (Iwano *et al*, 2002; Boutet *et al*, 2006). Kalluri has shown previously that bone morphogenetic protein 7 (Bmp7) can revert renal fibrosis by inhibiting TGFβ signalling in mice (Zeisberg *et al*, 2003). At the meeting, he discussed that Bmp7 can also revert the TGFβ-induced endothelial-to-mesenchymal transition during cardiac fibrosis (Zeisberg EM *et al*, 2007) and that EMT is also involved in liver fibrosis (Zeisberg M *et al*, 2007). Other examples of the pathological involvement of EMT were presented, including the participation of bronchial EMT in asthma (S. Letuve, Paris, France) and of mesothelial cells during peritoneal dialysis (López-Cabrera), indicating that EMT is a common process during tissue development and organ fibrosis.

A molecular signature for EMT in development and cancer

In the past few years, much effort has been devoted to identifying a molecular signature for cancer and for the metastatic potential of tumour cell lines and human tumours (Chin *et al*, 2006; Neve *et al*, 2006; Nguyen & Massague, 2007). At the meeting, E. Thompson (Melbourne, Australia) elaborated on the identification of a molecular signature for EMT that might be useful in prognosis and therapy. The characterization of a molecular signature for EMT during embryonic development could provide insight into the participation of EMT in physiological processes such as a wound healing, or in pathological circumstances such as cancer progression or organ fibrosis. Therefore, the use of genome-wide analyses and/or high-throughput screening to reveal EMT-inducing signals and their cellular response in embryos will be welcomed by the EMT community. Both M. Morkel (Berlin, Germany) and Hill presented screening strategies to identify new EMT regulators *in vivo* in mouse and *Xenopus* embryos, respectively. These animal models offer distinct opportunities to evaluate cell behaviour and molecular networks. An impressive study—as part of a long-term collaboration with E.H. Davidson (Pasadena, CA, USA)—allowed D. McClay (Durham, NC, USA) to present the pre-EMT gene regulatory network that controls endomesoderm specification in the sea urchin embryo (see Ben-Tabou de-Leon & Davidson, 2007). Conversely, a functional analysis in the sea urchin embryo of known inducers of EMT such as Snail and Twist, revealed new data indicating that Snail is involved in E-cadherin protein transport, as well as in its transcriptional repression (Wu & McClay, 2007).

MicroRNAs and EMT in cancer

MiRNAs are short non-coding RNAs involved in many developmental processes, as well as cell proliferation and differentiation. Although they have only recently been implicated in cancer, some intriguing relationships have been identified between miRNAs and tumours of diverse origins. Interesting data were presented to show that five members of the miR-200 family are repressed during TGFβ-induced EMT (G.J. Goodall, Adelaide, Australia). Indeed, it seems that their normal function is to downregulate the repressors of E-cadherin, Zeb1 and Sip1/Zeb2, and thus reinforce the epithelial phenotype. Conversely, J. Zavadil (Stony Brook, NY, USA) showed that miR-21—which is upregulated in human carcinomas—is induced during TGFβ-mediated EMT in a model of renal injury and fibrosis. Accordingly, miR-21 seems to target the tissue inhibitor of metalloproteinase-3 (TIMP-3), augmenting the degradation of the extracellular matrix. Together, these results suggest that the upregulation or downregulation of various miRNAs is fundamental for the regulation of the epithelial phenotype, as well as for EMT and tumour progression. This is in agreement with recent data obtained in breast cancer cells and tumours (Ma *et al*, 2007).

EMT and tumour progression

In deciphering the role of *Snail* genes during tumour progression, Cano showed that growth is impaired in tumours derived from keratinocyte and mammary tumour cell lines in which *Snail1* and/or *Snail2* were knocked down, and that they had a lower metastatic potential in nude mice (Olmeda *et al*, 2007). By contrast, the complementary gain-of-function approach adopted by Berx showed an increase in the sensitivity to chemical carcinogens when ectopic *Snail1* expression was driven by the keratin14 promoter in the skin. These results highlight the importance of Snail in epidermal tumour progression.

Östman discussed cancer-associated fibroblasts (CAFs) and the interaction between malignant cells and the stroma. CAFs are activated myofibroblasts that can be of bone marrow origin—the so-called mesenchymal cancer stem cells (Karnoub *et al*, 2007)—or generated by the activation of local fibroblasts, or they might originate from cancer cells after EMT (Brabletz *et al*, 2005). These are not necessarily mutually exclusive scenarios, as different CAFs might co-exist (Fig 1). Therefore, it is crucial to distinguish the CAFs within and around the tumour to decipher the origin of the different mesenchymal cells. This will significantly advance our knowledge of tumour biology and the design of anti-invasive drugs.

Conclusions and future perspectives

The use of sophisticated animal models and high-throughput technologies are helping us to understand the EMT that occurs during the formation of many organs, and to reveal the associated cellular processes and molecular networks. Powerful imaging techniques are unveiling the behaviours of migratory cells in physiological conditions such as embryonic development and wound healing, and also confirm that EMT is important in the first step of the metastatic cascade in carcinomas. Indeed, single non-dividing migratory cells delaminate from primary tumours. The characterization of authentic markers will undoubtedly help to identify the nature and origin of all mesenchymal cells found in the stroma and in the vicinity of the primary tumour.

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