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Twenty Years of Epithelial-Mesenchymal Transition: A State of the Field from TEMTIA X

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Abstract
This report summarizes the 10th biennial meeting of The Epithelial Mesenchymal Transition International Association (TEMTIA), that took place in Paris on November 7–10, 2022. It provides a short but comprehensive introduction to the presentations and discussions that took place during the 3-day meeting. Similarly to previous TEMTIA meetings, TEMTIA X reviewed the most recent aspects of the epithelial-mesenchymal transition (EMT), a cellular process involved during distinct stages of development but also during wound healing and fibrosis to some degree. EMT has also been associated at various levels during tumor cell progression and metastasis. The meeting emphasized the intermediate stages of EMT (partial EMT or EM hybrid cells) involved in the malignant process and their potential physiological or pathological importance, taking advantage of advancements in molecular methods at the single-cell level. It also introduced novel descriptions of EMT occurrences during early embryogenesis. Sessions explored relationships between EMT and cell metabolism and how EMT can affect immune responses, particularly during tumor progression, providing new targets for cancer therapy. Finally, it introduced a new perception of EMT biological meaning based on an evolutionary perspective. The meeting integrated the TEMTIA general assembly, allowing general discussion about the future of the association and the site of the next meeting, now decided to take place in Seattle, USA, in November 2024. This report provides a comprehensive introduction to the presentations and discussions that took place during the 10th biennial meeting of

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TEMTIA, that occurred in Paris on November 7–10, 2022. It includes all the sessions and follows the chronological order during the 3-day meeting. A general purpose of the meeting was to explore the boundaries of the EMT process, including new concepts and developments, as illustrated by our leitmotiv for the meeting, inspired by the proximity of the Cluny Museum in Paris.

Fig. 1. 2022 TEMTIA's quest for EMT took place in Paris, home to the 15th-century unicorn tapestries (Cluny Museum, Paris), an evocation of EMT with multiple faces observed through the mirror of TEMTIA, and a leitmotiv for the symposium.

TEMTIA, the Story

The Epithelial Mesenchymal Transition International Association (TEMTIA) tenth biennial meeting (TEMTIA X) opened with the Betty Hay Oration, a historical retrospective of the 20 years of TEMTIA jointly prepared by initial co-founders Don Newgreen (Melbourne, Australia) and Rik Thompson (Queensland University of Technology [QUT], Brisbane, Australia), and is available in the "members" section of the TEMTIA website.

Founded to promote exchange between major disciplines affected by epithelial-mesenchymal transition (EMT) (development, cancer, pathology), TEMTIA was initiated (incorporated in NSW, Australia, 2001) with a heavily international 1st meeting (Port Douglas, Australia, 2003) program guided by a prominent international committee led by EMT pioneer Prof Elizabeth (Betty) Hay. Subsequent meetings were held in America, Europe, and Australasia, with the next meeting planned for Seattle, USA, in November 2024, led by Caroline Hookway, Allen Institute for Brain Science. Betty Hay's health was already in decline by the 2003 2nd TEMTIA meeting in Vancouver, and the 2005 meeting in Prague saw heartfelt memorial presentations by close colleagues Raghu Kalluri and Jean Paul Thiery, the implementation of the Betty Hay Award (currently AUD 1,000) for newly independent female EMT researchers, and the Betty Hay Oration, a plenary lecture, both awarded at each subsequent meeting. An evolving constitution of TEMTIA has progressively incorporated a growing executive committee and an international committee for each conference. A dedicated website (www.TEMTIA.org) was set up, providing announcements and information and preparing the organization for the challenges of the next decades. Recently, a consensus statement was published on behalf of TEMTIA to provide guidelines for EMT-related definitions [1]. Following this retrospective, scientific talks were distributed in sessions focusing on current and emergent aspects of both cancer-associated and physiological EMTs (Fig. 1).

Metabolism Meets EMT

One emerging topic in the domain of cell plasticity is the link between metabolism and cell phenotype. Several examples were provided in a dedicated session. First, Sarah Fendt (KU Leuven, Belgium) described an intriguing integrin modulation in cancer cells deprived of phosphoglycerate dehydrogenase, resulting in early cancer cell dissemination. Phosphoglycerate dehydrogenase expression pattern was found to be a marker for metastasis emergence. More generally, she is currently investigating nutrient dependencies in metastases and exposing organ-specific features [2]. Raphael Rodriguez

(Institute Curie, Paris, France) focused on a new role for CD44 glycoprotein in mediating copper and iron uptake by the cell. These metals were found to regulate cell plasticity through mechanisms that could be targeted by new classes of drugs and inhibit EMT in cancer cells [3]. Bob Weinberg (MIT, Cambridge, USA), a strong figure in the EMT field, singled out ferroptosis as a new target, preferentially impacting mesenchymal-like carcinoma cells. Similarly, a very distinct pathway involving short fatty acids including propionate was shown by P. Ceppi (U Southern Denmark, Denmark) to reduce EMT occurrence in non-small cell lung cancer, as well as metastases. This pathway involved chromatin configuration and histone acetylation, a more usual component of EMT pathways (in press in EMBO Molecular Medicine). Overall, these lectures emphasized the very comprehensive nature of the EMT process, defining a whole new cell identity in structural and functional aspects during developmental stages [4] as well as in cancer progression.

New Developmental and Physiological Perspectives

The EMT process was first described in vivo during specific stages of development, which strongly contributed to the establishment of EMT archetypical characteristics. One revealing observation is the increasing number of developmental stages during which EMT constitutes a necessary step. Several new EMT occurrences were detailed during the developmental sessions, starting with the EMT stage implicated in mesothelial cells giving rise to the chorioallantoic membrane, a critical stage during placental development (Guojun Sheng, Kumamoto University, Japan). Also in mammals, Vincent Guen (CRCI2NA, Nantes, France) showed how an EMT stage affecting mammary stem cells involves primary ciliogenesis as a necessary catalyzer for stemness and potentially tumorigenesis [5].

The role of matrix metalloproteinases (MMPs) during Xenopus neural crest cell emergence via a classic EMT was revisited by Eric Théveneau (Center for Integrative Biology, CNRS, France), showing an early and non-canonical role for MMP28 [6]. In Drosophila, Kyra Campbell (University of Sheffield, UK) exposed the role of Serpent/GATA 4/6 in coordinating cell reconfiguration and deconstructing EMT functional constituents using multiple molecular and optical approaches [7].

Endothelial cells represent a specific class of epithelial cells lining blood vessels. They can undergo an endothelial-mesenchymal transition (EndoMT) during developmental (angiogenesis, regeneration) and pathological (wound healing, atherosclerosis) events. Chris Hughes (UC Irvine, CA, USA) analyzed the role of Slug/Snai2 in angiogenic sprouting in vitro, characterizing Notch family members and specific effectors modulating endothelial cell-pericyte interactions, and describing increasing EndoMT degrees [8]. Jatin Patel (QUT, Brisbane, Australia) also studied EndoMT pathways in mouse and human endothelium in fibrosis and atherosclerosis. He described new vessel-resident stem cells activating alternatively Rbpj and Sox9 to modulate an EndoMT process [9]. These studies collectively provided new avenues for therapeutic targeting in the vasculature.

EMT Staging and Dynamics in Cancer

The EMT process is well known to participate in cancer progression and metastasis. However, it has become clear in the last few years that intermediate cell phenotypes are dominating the scene in carcinoma. The rise of in vivo imaging techniques, single-cell sequencing, and other omics has brought powerful new tools linking phenotype and tumor cell response. Jacco Van Rheenen (NCI, Amsterdam, Netherlands) used intravital microscopy in a murine mammary tumor model to compare tumor cell lifespan, stemness potential, and phenotype, demonstrating with live cell markers the lack of stem cell potential in cells expressing a fully mesenchymal phenotype [10]. In a distinct genetic mouse model of skin squamous cell carcinoma, Evgenia Pastushenko (Université Libre de Bruxelles, Belgium) identified 6 tumor cell groups associated with various EMT stages. Taking advantage of the expression of Netrin-1 by the most mesenchymal tumor cell group, she found that anti-Netrin-1 antibodies sensitized tumor cells to chemotherapy, a promising preclinical direction for therapeutic targeting [11].

EMT Pathways in Tumor Stroma and Links to Immune Response

The stiffness and nature of the tumor stroma directly impact tumor cells, as exposed by Danijela Vignjevic Matic (Institute Curie, Paris, France). Combining genetic and physical manipulations in vivo with microfabrication and force measurements in vitro, she showed the stiffness impact on tumor cells, inducing Yap delocalization and actin/myosin contractility, two functional mediators of EMT [12].

More generally, EMT processes are associated with several families of transcription factors, notably the Snail, Twist, and Zeb families, found to be expressed in all *sensu stricto* EMT cases during development, presumably in response to stroma signals. Jing Yang (U California San Diego, La Jolla, CA, USA) modulated stiffness in 3D mammary organoids by artificial means. She found Twist1 to be a key player, in partnership with the G3BP2/EphA2/LYN complex, in transmitting mechanical cues to stimulate EMT in tumor cells [13]. These factors are also linked to cell stemness. In the mammary carcinoma context, Chrysoula Tsirigoti (Uppsala University, Sweden) found that Snail-deficient tumor cells gained stemness potential and could develop differentiated acinar mammospheres in 3D culture, overexpressing the transcription factor FOXA1 and evoking the intermediary luminal progenitor-like phenotype described in triple-negative breast cancers [14].

Novel aspects of EMT-TF function came from observations that their expression is not limited to tumor cells, as they were also found to be upregulated in tumor stroma cells. Marc Stemmler (Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany) exploited a mouse model for colorectal cancer to find that Zeb1 expression drives cell plasticity also in cancer-associated fibroblasts in favor of tumor progression and immune evasion [15].

This link between EMT and immune evasion is now widely acknowledged and has been explored by other speakers. Ben Stanger (U PA, Philadelphia PA, USA) described tumor cell resistance to T-cell killing independent of antigen presentation but relying on immune checkpoints, mediated by Interferon Regulatory Factor 6 in a mouse pancreatic ductal adenocarcinoma model [16]. Anushka Dongre (Cornell University, Ithaca, NY, USA) has analyzed these links in mouse mammary tumor models, showing distinct lymphocyte and macrophage recruitment according to tumor cell phenotype. The expression of CD73 in more mesenchymal tumors was linked to decreased CD8 cytotoxic and CD4 helper T-cell infiltration, accompanied by a poor response to immune checkpoint blockade [17]. Stéphane Terry (Gustave Roussy, INSERM U1186, France) described how hypoxia promotes EMT, CTL-mediated killing and immune resistance in a non-small cell lung cancer model through the TGFβ pathway but also through AXL-mediated resistance to NK and CTL-mediated killing, suggesting therapeutic opportunities [18]. Finally, Jonathan Kurie (U PA, Philadelphia USA) described the connection between EMT and a Golgi-dependent hypersecretory process that drives pro-metastatic tyrosine kinase receptor burying inside intracellular vesicles, in link with immunosuppression in the tumor microenvironment [19].

Comprehensive Multi-Omics Approaches to EMT

Recent years have seen a surge in high-throughput multi-omics strategies to study tumor heterogeneity and dynamics, a key consequence of the EMT process. They brought unprecedented understanding on tumor microenvironment and helped bringing the EMT concept closer to the clinical field. With this goal, Karuna Ganesh (Memorial Sloan Kettering Cancer Center (MSKCC), NY, USA) has combined transcriptomics, epigenomics, and spatial/histological approaches with composite tumor organoids to analyze colorectal cancer metastasis, unveiling relevant signaling pathways involved in metastasis [20]. To link the power of single-cell analysis to the dynamics of EMT phases, Jianhua Xing (U Pittsburgh, PA, USA) designed the *Dynamo* framework to build vector fields predicting cell fate and underlying regulation by combining single-cell RNA seq with RNA velocity. Such analysis was applied in EMT cell models to reveal distinct cell transition paths involving stops at the G1/S or G2/M phase during the cell cycle [21]. The role of chromatin conformation changes in such transitions was examined at a large scale by Ruby Huang (National Taiwan University, Taiwan) using Hi-C analysis and ChIP-seq data from cancer cell lines. Her approach emphasizes the importance of topological remodeling for EMT-linked genes, with a specific enrichment of H3K27me3 in an epithelial gene-residing topologically associated domain [22]. Joseph Taube (Baylor University, TX, USA) studied chromatin accessibility dynamics to show the progressive nature of the E-cadherin gene repression in a cell line-based EMT model. EMT process was marked with an increase in global chromatin accessibility, associated with the suppression of the chromatin looping factor CCCTC-Binding Factor. This configuration supported the stability of an induced EM hybrid phenotype [23]. An EMT-MET PHENOtypic STAte MaP (Phenostamp Landscape) approach using cytoff single-cell mass-spectroscopy time course analysis of a panel of EMT markers after TGFβ treatment (EMT) then withdrawal (partial MET) was described by Loukia Karacosta (MD Anderson Cancer Center, Houston, USA), with an emphasis on MUC-1, a novel target in the MET reversal [24].

New EMT Targets for Cancer Therapy

Oncologists have followed the EMT field progress for years after years, waiting for new targets and new drugs. Recently, new candidates targeting metastasis as well as

immune response (see above) have been tested in clinical trials. Jean Paul Thiery (Guangzhou Laboratory, Guangzhou, China), a founder of the EMT concept and pioneer of targeting efforts, described his strategy to specifically target EMT process as a complementary scheme to targeted treatments [25]. With the same goal, the drug company Transcenta developed an antibody targeting Gremlin 1, a BMP antagonist member of the TGFβ superfamily and an EMT inducer expressed by cancer-associated fibroblasts as well as tumor cells. This antibody has demonstrated anti-tumor activity in prostate cancer and is now being tested in a global Phase 1 study [26]. More generally, drug companies have shown an increase in interest for drugs targeting EMT phases, especially in the context of personalized medicine. Some specific targets were mentioned throughout the talks, such as a gastrin-related peptide receptor identified in cells undergoing EMT (Veronique Delmas, Institute Curie, Paris, France) [27], and Netrin-1 and FAT-1 (Ievgenia Pastushenko, Brussels University, Belgium) [28]. Another promising approach was presented by Dana Ishay-Ronan (Sheba Medical Center, Ramat Gan, Israel) for exploiting tumor cell plasticity in the EMT program to transdifferentiate breast cancer cells into postmitotic adipocytes. Based on her findings, BRCA1 mutations influence the response to TGFβ, which might help to stratify patients for specific differentiation therapies [29]. She was awarded the Betty Hay Award for early career female EMT scientists.

A very active multidisciplinary panel led by Thomas Brabletz, including Rik Thompson (QUT, Australia), Geert Berx (Ghent University, Belgium), James Lorens (University of Bergen, Norway), Jonathan Kurie (MD Anderson Cancer Center, TX, USA), Karuna Ganesh (MSKCC, NY, USA), Pierre Savagner (INSERM/Gustave Roussy, France), and others, discussed the perspectives for incorporating EMT and related epithelial-mesenchymal plasticity (EMP) into therapy for clinical benefit. The lack of clinical translation was attributed to issues such as the biphasic nature of EMP in metastatic progression, with pro-EMT phases and pro-MET phases. Thomas Brabletz posed the question: Should the strategy be to prevent EMT, restore an epithelial state, drive to a mesenchymal state, block plasticity, directly target (standard therapy-resistant) pM state, or others? This led mostly to a preference to selectively block plasticity rather than push cells into states that may enhance other aspects of metastasis-associated EMP (e.g., plastistatic approaches, Berx) or selectively kill EM hybrid cells by targeting the unique co-expression of E and M molecules in the same cell (Thompson). Additional avenues included EM hybrid markers such as Netrin-1, FAT-1, or MUC-1, as mentioned in the talks. Perspectives were also discussed for diagnostic markers – where EMT defines subtypes (e.g., claudin-low type breast cancers/basal breast cancers), prognostic markers – where EMT defines clinical outcome such as metastasis, survival, therapy resistance, and predictive markers – where EMT is important for directing chemotherapy/immunotherapy. More targeted work is needed to identify the best markers, in which tumor types, and using which techniques (IHC, CTC, ctDNA). Treatment wise, clinical panelists discussed the need for novel trial approaches such as window-of-opportunity trials and neoadjuvant trials, where new agents could be trialed in combination with standard of care therapies. The significant financial and regulatory hurdles were discussed as was the need for partnership with the pharmaceutical industry. A noteworthy initiative is a dedicated effort since the 2019 Kumamoto meeting to focus attention and activity on clinical implementation of the abundant implications of EMT in cancer progression and therapy resistance. A special virtual meeting (TEMTIA 9.5; Targeting EMT) was held in December 2021, and this remains a key collaborative focus of TEMTIA meetings.

An Evolutionary Perspective for Physiological EMT

As EMT and its context-specific peculiarities in higher order multicellular organisms like vertebrates are very complex, important general mechanistic insight into the process and its biological meaning can be derived from much more simple multicellular organisms. Significantly, EMT stages are described in all pluricellular organisms, starting with the simplest forms. Classic EMT pathways including "classic" EMT-TF are already found in Cnideria, if not in sponges. Three speakers explored archaic animal models and pluricellular aggregates to question the biological meaning of EMT. Patrick Humbert (Latrobe Institute Medical Science, Melbourne, Australia) explored the establishment and modulation of cell polarity, early target of the EMT process, in Trichoplax, one of the simplest multicellular organisms, to identify original mechanisms, involving the Scribble polarity module. He then described a fascinating ongoing experiment involving Trichoplax cellular organization and polarization in the absence of gravity, in space rockets [30].

In the search of an evolutionary origin for EMT, we went to the edge of pluricellularity in primitive organisms such as choanoflagellates. Thibaut Brunet (Institut Pasteur, Paris, France) compared colonial forms of this

organism, involving cohesive polarized cells with an apical flagellum and temporary amoeboid forms. These forms resulted from local confinement driving a stress-induced switch, activating myosin-based motility and individual migration, a common feature with post-EMT cells [31]. This view of EMT as an ancestral escape mechanism for cells to leave an organized "epithelium" brings new perspective to cancer progression but also to the developmental occurrences of EMT, extremely conserved during evolution. This relationship between multicellularity and emergence of cellular properties [32] was finally scrutinized in cancer using several models to study the breakdown of multicellularity in cancer cells (Bertrand Daignan-Fornier, IBGC, Bordeaux, France). It might be beneficial to draw more generalized conclusions from such perspective and extraction of mechanisms that can be exploited therapeutically.

In conclusion, major scientific progress has been seen in several areas over the past two decades, involving the strong relationship between evolving cell states and EMT and providing molecular definition of developmental and disease EMT. This is being achieved by combining high-throughput multi-omic studies, including single-cell approaches, and spatial comprehension of cell plasticity in both developmental and malignancy environments. This has also provided new understanding about the disputed role of the mesenchymal phenotype in metastasis and of EM hybrid cells, which are potentially a better fit for the metastatic decathlon. These conceptual advances were also supported by more accurate mathematical modeling around the process of hysteresis and by the collaborative use of developmental systems for cancer studies. Much of this progression is chronicled in special issues of the Journal *Cells Tissue Organs*, formerly *Acta Anatomica*, from Karger Publishers, which remains a long-term partner of TEMTIA with support at each meeting.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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