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Mini review

Deciphering the loop of epithelial-mesenchymal transition, inflammatory cytokines and cancer immunoediting

Antonella Sistigu[a,b,*,1], Francesca Di Modugno[a,1], Gwenola Manic[c], Paola Nisticò[a,*]

[a] Unit of Tumor Immunology and Immunotherapy, Department of Research, Advanced Diagnostics and Technological Innovation, Regina Elena National Cancer Institute, via Elio Chianesi 53, 00144, Rome, Italy
[b] Department of General Pathology and Physiopathology, Università Cattolica del Sacro Cuore, largo Francesco Vito 1, 00168, Rome, Italy
[c] Department of Biology, University of Rome "Tor Vergata", via della Ricerca Scientifica 1, 00173, Rome, Italy

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ABSTRACT

Tumorigenesis and tumor progression relies on the dialectics between tumor cells, the extracellular matrix and its remodelling enzymes, neighbouring cells and soluble cues. The host immune response is crucial in eliminating or promoting tumor growth and the reciprocal coevolution of tumor and immune cells, during disease progression and in response to therapy, shapes tumor fate by activating innate and adaptive mechanisms. The phenotypic plasticity is a common feature of epithelial and immune cells and epithelial-mesenchymal transition (EMT) is a dynamic process, governed by microenvironmental *stimuli*, critical in tumor cell shaping, increased tumor cell heterogeneity and stemness. In this review we will outline how the dysregulation of microenvironmental signaling is crucial in determining tumor plasticity and EMT, arguing how therapy resistance hinges on these dynamics.

Contents

Abbreviations: AKT1/AKT, AKT serine/threonine kinase 1; AXL, AXL receptor tyrosine kinase; Bmi1, BMI1 proto-oncogene, polycomb ring finger; CAF, cancer-associated fibroblast; CDH/CAD, cadherin; CRKL, CRK Like Proto-Oncogene; CSC, cancer stem cell; CSF-1, colony-stimulating factor-1; CTLA4, cytotoxic T-lymphocyte antigen 4; CXCL, C-X-C motif ligand; CXCR, C-X-C chemokine receptor; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial–mesenchymal transition; ESRP, epithelial splicing regulatory protein; FGF, fibroblast growth factor; FSP-1, fibroblast-specific protein-1; HDAC3, histone deacetylase 3; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor-1α; ICB, immune checkpoint blocker; IFN-γ, interferon-γ; IL, interleukin; IL-6/8 R, IL-6/8 receptor; IRAK-M, interleukin-1 receptor-associated kinase-M; JAK, Janus kinase; KRAS, Kirsten rat sarcoma viral oncogene homolog; LOX, lysyl oxidase; LOXL2, lysyl oxidase like 2; MDSC, myeloid-derived suppressor cell; MET, mesenchymal-epithelial transition; MHC-I, major histocompatibility complex-I; miRNA, micro-RNA; MMP, metalloproteinase; NF-κB, nuclear factor-κB; NLRP3, NACHT, LRR and PYD domains-containing protein 3; NSCLC, non-small cell lung cancer; PDGF, platelet-derived growth factor; PD-L1, programmed death-ligand 1; Rac1, ras-related C3 botulinum toxin substrate 1; ROS, reactive oxygen species; α-SMA, α-smooth muscle actin; SMAD2, SMAD family member 2; SNAI1/SNAIL, snail family transcriptional repressor 1; SNAI2/SLUG, snail family transcriptional repressor 2; Sox9, SRY-box 9; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; TAZ, tafazzin; TGF-β, tumor growth factor-β; TME, tumor microenvironment; TNF-α, tumor necrosis factor-α; TP53/p53, tumor suppressor p53; TWIST1/TWIST, twist family bHLH transcription factor 1; VEGF, vascular endothelial growth factor; YAP1/YAP, yes associated protein 1; ZEB1, zinc finger E-box-binding homeobox 1.

* Corresponding author at: Unit of Tumor Immunology and Immunotherapy, Department of Research, Advanced Diagnostics and Technological Innovation, Regina Elena National Cancer Institute, via Elio Chianesi 53, 00144 Rome, Italy.
E-mail addresses: antonella.sistigu@gmail.com (A. Sistigu), paola.nistico@ifo.gov.it (P. Nisticò).
[1] These authors contributed equally to this article.

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Introduction. Epithelial-mesenchymal transition at a glance

The epithelial–mesenchymal transition (EMT) is a highly conserved, naturally occurring transdifferentiation program that governs changes in cell states along the epithelial *versus* mesenchymal axis, conferring epithelial–mesenchymal plasticity. Known from embryologists as soon as 1879 [1], EMT has been of interest to the research community since Greenburg and Hay first described a mesenchymal-like transformation of epithelial cells when suspended in collagen gels [2]. From then on, EMT and the reverse process, termed mesenchymal-epithelial transition (MET) are recognized as the foremost trans-differentiation programs operating during development and ensuring a proper histogenesis and organogenesis, through plastic interconversions between epithelium and mesenchyme [3]. In adults, EMT assists tissue regeneration and regrowth during wound repair and guarantees the re-establishment of the epithelial integrity, essential for tissue homeostasis [4,5]. When repair mechanisms are not properly executed, myofibroblasts induce fibrotic extracellular matrix (ECM), altering normal cell functions and tissue homeostasis. This leads to organ fibrosis, a tissue context facilitating tumor growth and progression [6]. Noteworthy, EMT is widely recognized as a leading biological process regulating cancer invasion, metastasis and immune escape (Fig. 1).

Despite being biologically equivalent, the physiological and pathological EMT follow different mechanistic rules – the first complying with non-inflamed highly regulated spatial and temporal plans, the latter instead mainly being an inflamed stochastic and time-independent process [7].

Conventionally, epithelial cells are defined as surface barrier cells with secretory functions that show distinct apical *versus* basolateral polarity established by desmosomes, adherent, tight and gap junctions with cell-ECM integration controlling the tissue architecture [8]. Conversely, mesenchymal cells are loosely organized, able to remodel ECM and to modify the integrin-ECM axis with consequent increased expression of metalloproteinases (MMPs) and acquired migratory and invasive ability [8] (Table 1).

The transition from the epithelial to mesenchymal cell state encompasses a spectrum of inter- and intra-cellular changes most likely determined by the integration of extracellular signals perceived by the cells (Fig. 1). Indeed, the EMT program is mediated by complex signaling networks induced by different dynamic *stimuli* triggered by stromal cells and ECM components of the surrounding microenvironment and by soluble factors [epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), tumor growth factor (TGF)-β and vascular endothelial growth factor (VEGF)]. Other EMT inducers are the morphogens Wnt, Notch and Sonic hedgehog, and pro-inflammatory cytokines [*i.e.*, interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α] [3,9–11]. A paramount consequence of these pro-inflammatory and hypoxic responses is the upregulation of a number of transcriptional factors, repressors of epithelial genes or activators of mesenchymal genes, such as the snail family transcriptional

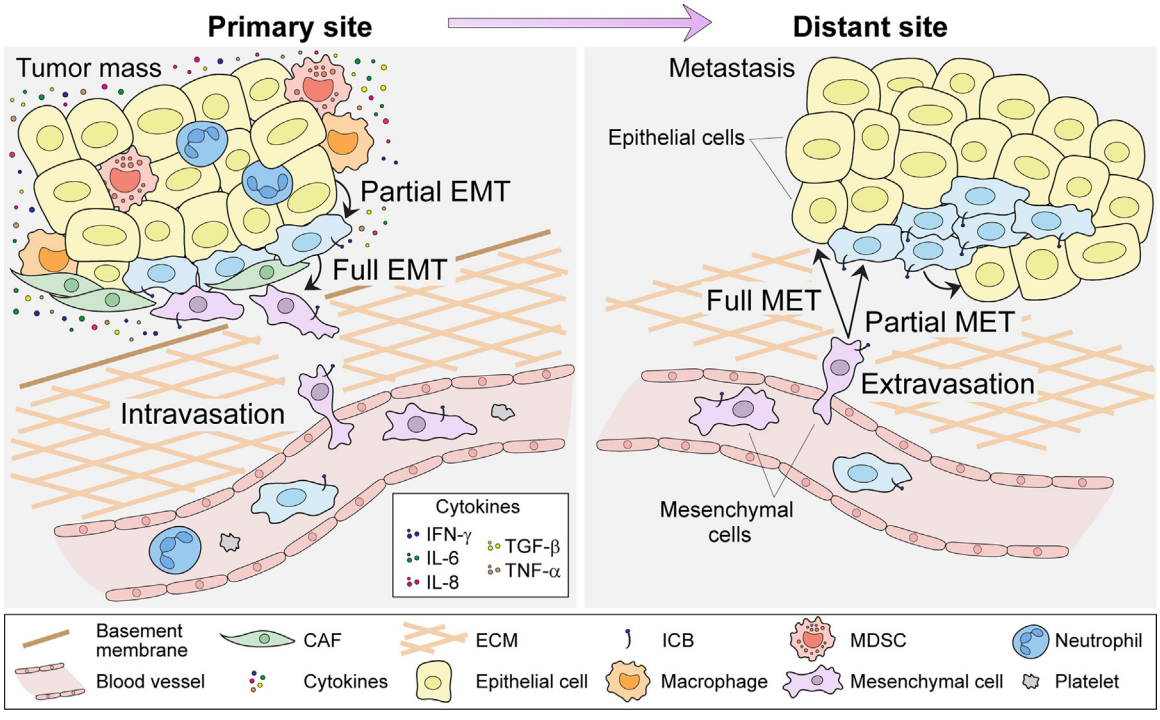

Fig. 1. Complex networks orchestrating EMT.
Soluble inflammatory mediators (IFN-γ, IL-6, IL-8, TNF-α and TGF-β), immune infiltrating macrophages, MDSCs, neutrophils, platelets and CAFs can promote an EMT program in primary tumors. Mesenchymal cells are then able to invade the surrounding stroma and eventually enter the systemic circulation. Once circulating tumor cells reach distant sites, undergo a MET program that is crucial for the outgrowth of metastases. CAF, cancer-associated fibroblast; ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; ICB, immune checkpoint blocker; IFN, interferon; IL, interleukin; MDSC, myeloid-derived suppressor cell; MET, mesenchymal-epithelial transition; TGF-β, tumor growth factor-β; TNF-α, tumor necrosis factor-α.