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Epithelial-to-mesenchymal transition as a central driver of tumor cell plasticity

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Epithelial-to-mesenchymal transition (EMT) is a central driver of cancer cell plasticity, enabling invasion, immune evasion, therapeutic resistance and metastasis. Rather than a binary switch, EMT comprises a continuum of transient, reversible states that endow tumor cells with distinct functional properties. Recent technological advances have revealed an unexpected diversity of EMT states across tumor contexts, with implications for disease progression and therapy response. In this Review, we synthesize emerging evidence on EMT heterogeneity and dynamics during cancer progression, examine how new methodologies have increased our understanding of the process and outline therapeutic challenges and opportunities.

EMT is a widespread process in metazoans that enables epithelial cells to acquire mesenchymal features, including front–rear polarity, motility and resistance to cell death. Originally described in the context of gastrulation and neural crest migration[1,2], EMT has since been implicated in a wide range of physiological and pathological contexts, from organogenesis and tissue repair to fibrosis and cancer[3,4]. EMT does not always entail a complete transformation into a mesenchymal state, nor does it fully erase epithelial traits, particularly in vivo. Instead, it involves an orchestrated, partial reprogramming of epithelial cells into more plastic and migratory states. In cancer, EMT has emerged as a central mechanism underlying invasion, metastasis and therapeutic resistance, not merely by enabling motility but also by unlocking a spectrum of cell states endowed with increased adaptability.

EMT is activated and strictly regulated in space and time in physiological settings, both in the embryo and in the adult. During embryogenesis, cells undergoing EMT acquire migratory properties and contribute to the formation of the mesoderm, endoderm, neural crest derivatives and other lineages, guided by precise developmental cues[5]. In the adult, transient EMT activation has a critical role in tissue repair[3] (Fig. 1a). When chronically activated, EMT becomes pathological, promoting disruption of tissue architecture, cell dedifferentiation, stromal remodeling and inflammation, leading to the development of fibrosis[6,7] (Fig. 1a).

At the core of the EMT program lies a set of transcription factors (TFs), most notably members of the SNAIL, TWIST, ZEB and PRRX families, first identified for their roles during embryonic development[8–10] and later linked to cancer progression[11–14]. These EMT transcription factorss (EMT-TFs) repress the transcription of epithelial genes and activate mesenchymal programs that remodel the cytoskeleton, modify cell–matrix interactions and disrupt cell–cell adhesion. The activity of EMT-TFs is tightly regulated at multiple levels, a topic extensively discussed elsewhere[15]. EMT-TF expression is induced by signaling pathways triggered by transforming growth factor-β (TGFβ) or WNT receptors, Notch or receptor tyrosine kinases[16], environmental factors such as hypoxia[17] and mechanical forces[18,19] or intracellular signals including response to DNA damage[20], oxidative stress[21] or metabolic reprogramming[22] (Fig. 1b). In addition, EMT is regulated post-transcriptionally via microRNAs such as the miR-200 family and miR-34 (ref. 23), alternative splicing[24] and interactions with chromatin modifiers[25]. Interestingly, systematic analysis of EMT progression across different in vitro and in vivo developmental and cancer models reveals a stereotyped sequential activation of EMT-TFs[26]. Whereas SNAIL1 acts as a pioneer regulator by repressing epithelial features, more potent mesenchymal inducers such as TWIST and PRRX1 are typically recruited at later EMT stages[26], inducing invasive properties (Fig. 1c). In agreement with this, SNAIL1 has a critical role in noninvasive partial EMT activated during kidney fibrosis, but 'late' EMT-TFs such as PRRX1 are not activated[26]. Despite the conservation of this sequential program throughout diverse contexts, it cannot be excluded that a different starting point or temporal hierarchy may occur in different cancer types, including those where the cell of origin is not a bona fide epithelial cell, as in pancreatic cancer or melanoma where nontransformed cells already express some EMT-TFs[27–29].

Although EMT is often depicted as a shift from an epithelial to a mesenchymal state, it is more accurately described as a multidimensional continuum of cell states governed by distinct regulatory modules[30]. Cells can adopt partial EMT configurations, simultaneously expressing epithelial and mesenchymal markers and displaying

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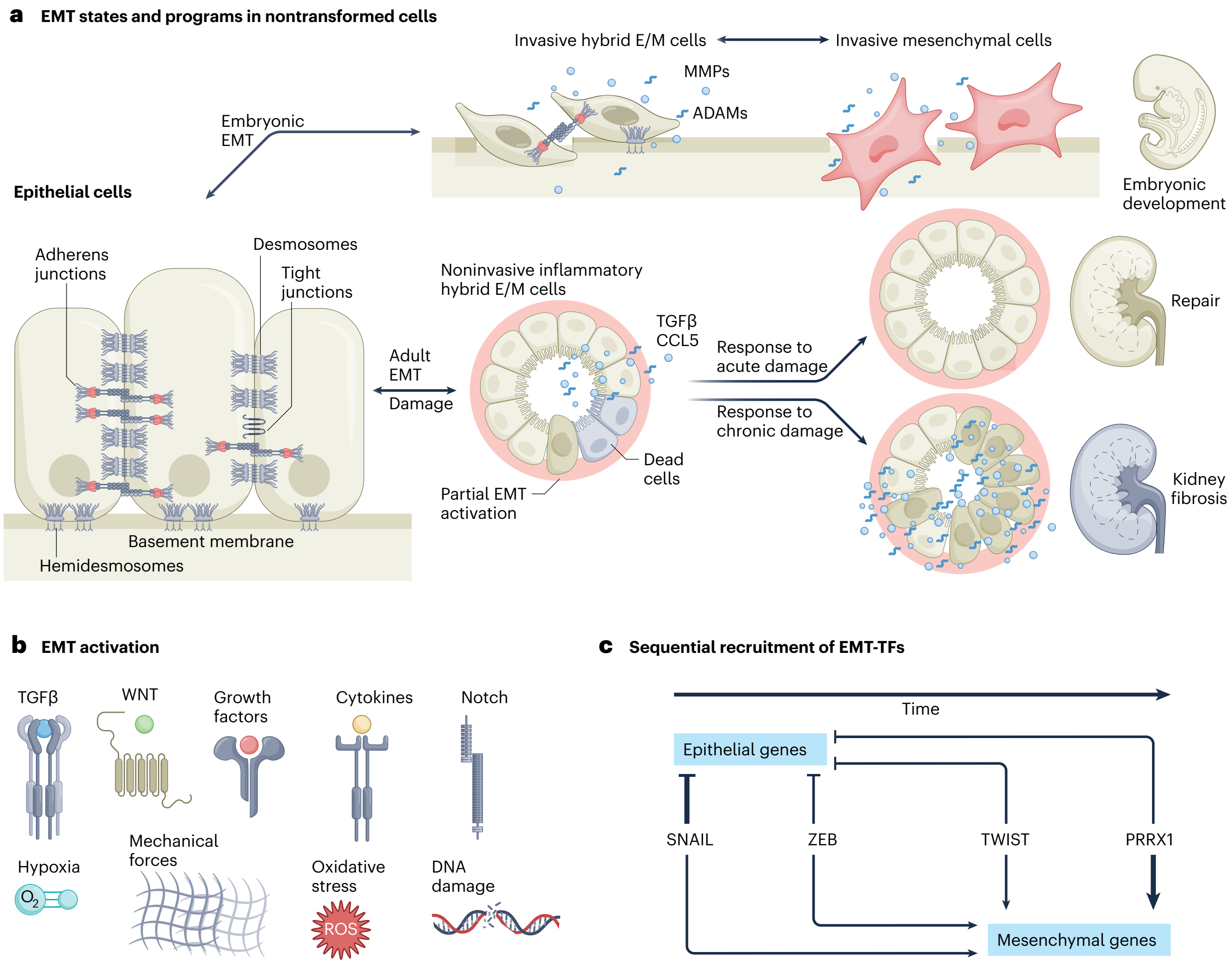


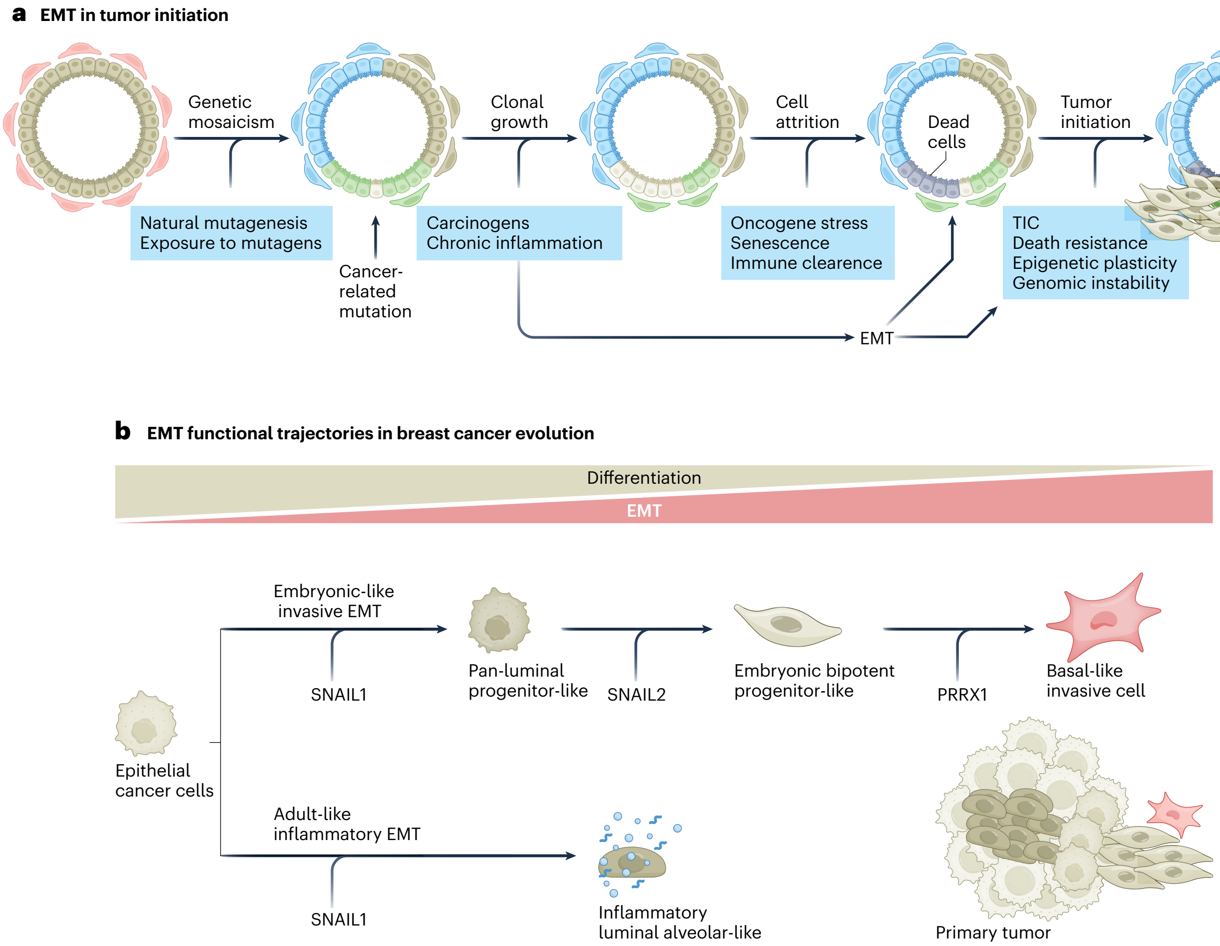
Fig. 1 | EMT overview: regulation, states and programs in nontransformed cells. a, Nontransformed epithelial cells, with clear apico–basal polarity, strong cell–cell junctions and attachment to the basal lamina, can undergo two distinct EMT programs. In the embryo, cells can engage in an invasive EMT, ranging from different hybrid epithelial/mesenchymal phenotypes to more mesenchymal states. Adult epithelial cells can activate an inflammatory EMT in response to tissue damage, represented by a noninvasive hybrid epithelial/mesenchymal state with an inflammatory profile. If the damage is acute, the partial EMT activation is transient and part of the normal repair process, whereas chronic damage leads to organ fibrosis, as exemplified by the kidney[3,6,7]; E/M, epithelial/mesenchymal; MMPs, matrix metalloproteinases. **b**, EMT is initiated by external cues such as the activation of signaling pathways, including those triggered by TGFβ, WNT, growth factors, cytokines and Notch ligands[15]; environmental factors such as hypoxia[17]; mechanical forces[18,19] or intracellular signals, such as response to oxidative stress[21] or DNA damage[20]; ROS, reactive oxygen species. **c**, The signaling pathways converge in the activation of EMT-TFs (mainly encoded by SNAIL, ZEB, TWIST and PRRX*1* gene families). They are activated in a sequential manner to repress epithelial gene expression and induce mesenchymal programs. The arrow indicates the direction of EMT-TF recruitment, and line width indicates the strength of activation or repression[26].

hybrid phenotypes (Fig. 1a). The development of technologies allowing single-cell resolution has led to a better characterization of these hybrid states, which can be stable or metastable within the EMT landscape[30,31]. Furthermore, EMT is often reversible, as cells undergo a mesenchymal-to-epithelial transition (MET). Cells can engage into sequential EMT/MET cycles throughout their history, both during development and in cancer[30], and the downregulation of EMT-TFs is essential for successful metastatic colonization[32,33].

EMT is increasingly recognized not only as a means for cells to acquire migratory properties but also as a driver of cellular plasticity, which is the capacity of a cell to adapt its identity and behavior in response to intrinsic or environmental cues and recently recognized as a hallmark of cancer[34]. EMT confers plasticity to differentiated cells by unlocking terminal transcriptional programs both in cancer and for tissue repair or degeneration[26,35,36]. For instance, during reprogramming of fibroblasts to induced pluripotent stem cells, a MET-like process[37] is required, but a transient activation of the EMT-TF SNAIL1 increases the efficiency of the process[38]. Furthermore, an ERBB2/YAP-mediated transient EMT activation promotes cardiomyocyte dedifferentiation and cell cycle re-entry, leading to heart regeneration in mice[39,40]. In contrast to genetic evolution, which depends on irreversible mutations, phenotypic plasticity enables rapid transitions that enhance cellular fitness under selective pressure. In cancer, EMT-induced plasticity is behind the progression to metastatic disease, compatible with the absence of metastasis-specific genomic alterations[41–43].

EMT-induced plasticity can be used to devise novel therapeutic strategies both in cancer, discussed later in this Review, and in nontransformed cells. For the latter, a partial reprogramming (MET-like) of cells that have undergone EMT-like processes during aging or degenerative diseases (mesenchymal drift) has been recently proposed to promote rejuvenation[44].

Complementary to recent reviews focused on an overview of EMT activation across systems[45], its detailed regulatory landscape[15] or its clinical relevance in cancer[46], this Review discusses recent findings into the role of EMT in primary tumor initiation and


a EMT in tumor initiation

b EMT functional trajectories in breast cancer evolution

Fig. 2 | EMT confers tumor-initiating properties and drives nongenetic ITH. **a**, Tissues are not genetically homogeneous but instead are composed of clonal mosaics, resulting from natural mutagenesis during tissue development, homeostasis and aging or from exposure to mutagens. Some of these clones may carry cancer-related mutations, but these are not always sufficient to initiate a tumor[51]. Some clones undergo selection and amplification, and although many of the amplified cells will die, the ones that activate EMT can acquire resistance to cell death[59,60] together with tumor initiation capacities (TIC)[57,58] and epigenetic plasticity[64] while increasing genomic instability[65]. **b**, In breast cancer, after oncogenic activation, tumor cells can activate EMT and dedifferentiate, acquiring progenitor-like phenotypes and engaging in one of two distinct EMT trajectories governed by different EMT-TFs[26] and linked to specific functional cancer hallmarks[34]. In the embryonic-like trajectory, epithelial cancer cells continue dedifferentiation and acquire invasive properties[26,81,83]. Alternatively, cancer cells are reprogrammed into an inflammatory-like state linked to antitumor immune infiltration[26]. The two populations occupy distinct positions within the same tumor.

progression, metastatic colonization and a revision of new avenues for therapeutic opportunities.

Effect of EMT activation on cancer progression

Since the discovery of the first oncogenes in the 1980s, cancer initiation and evolution have been tightly linked with mutations[47–50]. However, during the last decade, we have learned that mutations are not sufficient to trigger tumor initiation. Indeed, our body can be understood as a large clonal mosaic[51], and we harbor a multitude of clones with cancer-associated mutations in several tissues[52] (Fig. 2a). Related to the precise role of driver gene mutations, there is a huge ongoing effort to understand the mechanisms of tumor promotion by many carcinogens, which we now know do not directly cause mutations[53] but rather act as tumor promoters through clonal expansion of cells with pre-existing driver mutations[54] (Fig. 2a). In addition, epigenetic alterations can induce tumorigenesis even in the absence of detectable driver mutations[55].

EMT in tumor initiation

Clonal expansion is not enough for tumor formation, as the cells need to bypass additional bottlenecks such as oncogene-induced senescence or immune clearance[56]. The activation of EMT can endow cancer cells with tumor-initiating capacity[57,58] while conferring resistance to apoptosis or oncogene-induced senescence[59,60] (Fig. 2a). Compatible with its pioneer role during EMT activation[26], SNAIL1 is key in the transition from nontransformed to transformed cells, as demonstrated in mouse models of breast cancer[26,61–63]. In addition, through multimodal single-cell sequencing of mouse and human samples, a pretumoral state has been identified in *BRCA*-mutated breast cancers characterized by profound epigenomic dysregulation in the absence of driver mutations (Fig. 2a). This state, marked by SNAIL1 activation and a partial EMT, acts as a bridge between nontransformed and transformed cells[64].

Considering that EMT activation is an important step during malignization, a question that arises is whether it can provide a permissive or primed cellular state that cooperates with oncogenic mutations. Recent evidence suggests that EMT activation contributes to the emergence of genomic instabilityowing to increased chromatin accessibility[65]. Moreover, the ablation of mesenchymal cancer cell lineages affects genomic evolutionary trajectories, as EMT-induced chromatin remodeling increases genomic instability at very early stages[65] (Fig. 2a). Together, these data indicate that EMT-induced cell plasticity establishes epigenetic and transcriptional configurations that influence subsequent evolutionary routes. Thus, EMT activation may function as an early 'state-setting' event that cooperates with oncogenic mutations and, in some contexts, precedes them, creating a permissive cellular landscape that favors the stabilization of tumorigenic programs.

Following that idea, the inflammatory response observed following EMT activation in response to injury[3] may explain why chronic inflammation is associated with an increase in cancer risk[66] (Fig. 2a). In addition, environmental factors associated with increased cancer incidence also trigger EMT. For example, nicotine exacerbates the fibrosis induced by silica in a mouse model of pulmonary fibrosis through activation of STAT3–BDNF–TRKB signaling, which leads to the activation of TWIST in alveolar type 2 cells[67] (Fig. 2a). On the other hand, particulate matter in air pollution induces an EMT-like state through the activation of ETS-1 and NF-κB in a lung cancer cell line[68] (Fig. 2a). Similarly, systemic conditions such as obesity and natural cycling processes like the estrous cycle have also been associated with EMT activation[69,70]. Further research in these areas, requiring advanced mouse models and closer integration between oncology and other medical fields, may provide critical insights into tumor initiation and EMT that would help develop novel preventive therapeutic strategies.

EMT heterogeneity in primary tumors

Tumors display a high degree of intratumor heterogeneity (ITH), believed to be derived from genetic differences, as distinct clones carrying different mutations coexist within the same tumor[71]. Genetic ITH poses a major challenge to precision oncology[72], as key driver mutations are often not uniformly present across all cancer cells, limiting the efficacy of targeted therapies. The prevailing model of cancer evolution is based on Darwinian selection, where cancer cells accumulate genomic alterations through stochastic processes, undergoing positive or negative selection. Advances in sequencing and biopsy techniques have enabled the use of genetic data to reconstruct tumor phylogenies and track clonal evolution[71]. Consortia like TRACERx are providing new resolution in the description of cancer progression in humans through multiregional sequencing[73]. Yet, despite intensive efforts, no metastasis-specific driver mutations have been identified beyond those already present in the primary tumor[41–43], suggesting that genetic heterogeneity alone cannot fully explain metastatic behavior.

Indeed, an additional layer of ITH arises from cellular plasticity, where genetically identical cells adopt different transcriptomic programs[74], explaining why plasticity is now considered a fundamental cancer hallmark, given its capacity to enable or modulate other hallmarks[34]. Ongoing efforts to map this transcriptomic heterogeneity include the construction of tumor cell atlases[75,76] and the identification of consensus cellular metaprograms across cancer types[74]. EMT activation in a subset of tumor cells constitutes one such functional source of heterogeneity, long associated with increased invasive properties. Single-cell RNA sequencing has revealed the existence of EMT states across various cancer types, including head and neck cancer[77], melanoma[78], glioblastoma[79] and breast cancer[80,81], confirming its activation in vivo both in animal models and in individuals with cancer. Notably, intermediate EMT states are associated with increased metastatic potential[80,81]. In breast cancer, a rare basal/stem-like EMT population representing only ~1.5% of tumor cells exhibit disproportionately high metastatic capacity[82].

EMT-driven heterogeneity is observed in vivo as a range of cell plastic states distributed along the epithelial–mesenchymal spectrum. Different markers distinguish cell states along the EMT spectrum bearing different metastatic potential in mouse models of squamous cell carcinoma and breast cancer[81]. In addition, different epigenetic regulators like PRC2 and KMT2D govern different steps toward a more mesenchymal state[83]. These transitions are linked with invasion and metastasis, and at the cellular level, they resemble the EMT implemented during embryonic development. In addition, breast cancer cells can activate a noninvasive inflammatory EMT, similar to that activated in response to tissue damage in the adult[26] (Fig. 2b). The two distinct EMT programs identified in cancer are governed by different EMT-TFs, and the corresponding cells occupy distinct spatial niches within the primary tumor. Cells engaged in the invasion-related EMT program are enriched at the tumor–stroma interface[26] (Fig. 2b). This invasive trajectory is implemented through the sequential activation of EMT-TFs ending with PRRX1$^+$ cells, described as the metastatic population in melanoma[84]. Interestingly, cells in this program dedifferentiate, acquiring markers of progenitors of the mammary gland like those observed during embryonic development (Fig. 2b).

By contrast, the EMT inflammatory program, driven by SNAIL1, is activated in cells that localize internally in the tumor (Fig. 2b) and are associated with major histocompatibility complex (MHC) class II$^+$ macrophages[26], suggesting a link with antitumor immunity. In this context, functional analyses demonstrate that depletion of PRRX1, an EMT-TF specific for the invasive EMT trajectory, not only results in a marked reduction in metastatic burden but also leads to a shift toward an inflammatory EMT program, characterized by increased infiltration of antitumor macrophages[26]. These findings indicate that the two EMT programs activated in cancer are plastic and interdependent and further suggest that they are functionally antagonistic: the invasive program is protumorigenic whereas the inflammatory program exerts antitumor effects. Although the precise mechanisms underlying this EMT bifurcation in breast cancer remain poorly understood, emerging evidence suggests that differential integration of TGFβ and RAS signaling pathways determines EMT fate, with RREB1 acting as a key transcriptional hub linking EMT-TFs, particularly SNAIL1, to fibrogenic gene expression in carcinoma cells[85,86]. Further studies are required to assess whether this plasticity can be therapeutically exploited to bias EMT toward the antitumor inflammatory trajectory, thereby offering potential clinical benefit.

EMT-driven intratumoral heterogeneity adds another layer of complexity to tumor evolution, as cancer cells can occupy distinct positions along the epithelial-to-mesenchymal spectrum. As mentioned, these states reflect the activation of embryonic-like invasive programs or adult-like inflammatory programs in different tumor cell populations (Fig. 2b). Moreover, multiple studies have demonstrated functional interactions between epithelial and mesenchymal cells during tumor progression. For example, grafted mesenchymal cells can induce EMT in neighboring epithelial cells, thereby enhancing their invasive and metastatic potential[87–89]. In addition, spontaneous models of pancreatic cancer have revealed a dynamic equilibrium between epithelial and mesenchymal tumor cell populations, maintained by a paracrine signaling loop involving GREM1, an EMT inhibitor secreted by mesenchymal cancer cells, and SPP1, an EMT inducer secreted by the epithelial compartment[90,91]. Disruption of this loop through genetic deletion of *GREM1* shifts the balance toward mesenchymal cells, and it is accompanied by increased metastatic burden, whereas deletion of *SPP1* reduces both mesenchymal cell abundance and metastasis. Together, these findings underscore the cooperation and functional interdependence of cancer cells at different EMT states within the same tumor.

To distinguish between distinct EMT phenotypes, functional characterization is essential after EMT profiling relying on molecular markers. A comprehensive and authoritative description of the different EMT states, with particular focus on the hybrid epithelial/mesenchymal phenotypes can be found in a recent review[92]. Understanding the role of EMT in vivo requires careful consideration of tissue context and lineage-specific EMT programs. This heterogeneity is the main reason behind the lack of universal pan-cancer EMT markers, which should also consider the developmental history of the corresponding tissue and organ. As such, oversimplified definitions of EMT have led to conflicting conclusions in the field. For instance, early studies suggesting that EMT was dispensable for metastasis[93,94] relied on limited markers (for

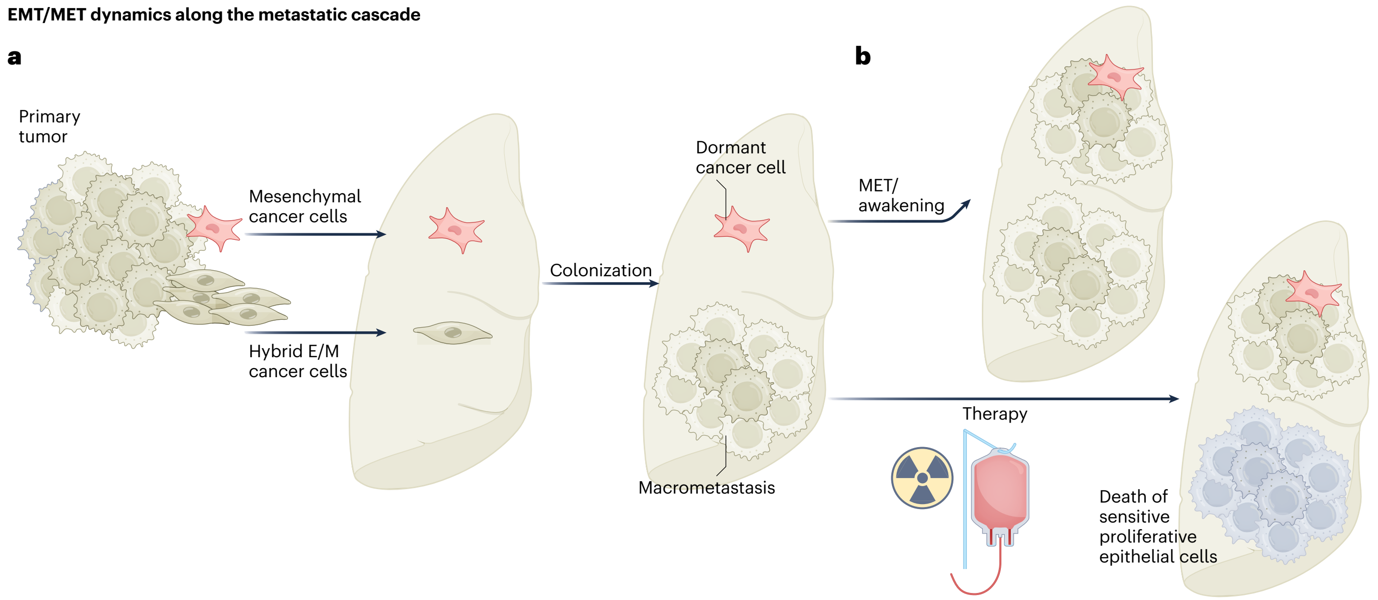


Fig. 3 | EMT dynamics during dissemination and colonization. **a**, Both mesenchymal and hybrid invasive E/M cancer cells leave the primary tumor and arrive at the metastatic site. Hybrid cells are primed for colonization[80,81,106] and can rapidly generate metastasis, whereas mesenchymal cells stay in a low proliferative/dormant state. **b**, Additional mechanisms, particularly environmentally driven, can induce MET in mesenchymal cells and with that an increase in proliferation or 'awakening' of dormant cells, giving rise to additional macrometastasis[32,33]. On the other hand, although current therapies can kill proliferating metastatic cells, they can also awaken dormant mesenchymal cells that now can become an important source of metastatic clones[93–95,114].

example, FSP1 in breast cancer) or on the deletion of EMT inducers (for example, *SNAI1* or *TWIST1* in pancreatic cancer) that are not necessarily key drivers in the tumor type under study. Further studies and more complex lineage-tracing approaches have clarified these discrepancies and confirmed the role of EMT in cancer progression toward the metastatic state. For instance, tenascin- and N-cadherin-based lineage tracing in breast cancer in mice showed that both hybrid and more mesenchymal EMT states contribute to primary tumor growth and metastasis[95], and deletion of *Zeb1* in a pancreatic cancer model resulted in a notable reduction of metastatic burden[96].

EMT and metastasis

Once cancer cells activate EMT and acquire invasive properties, they can intravasate into the bloodstream, where they are classified as circulating tumor cells (CTCs). CTCs can be found either as single cells or in clusters, the latter showing a higher metastatic potential[97,98]. The presence of E-cadherin in CTC clusters, and the observation that E-cadherin depletion impairs CTC survival and metastatic seeding[99], led to the proposal that EMT was not important for cancer cell dissemination. However, CTCs have been shown to reside in hybrid EMT states, coexpressing epithelial and mesenchymal markers across various tumor types[100–103], and they are associated with enhanced tumor-initiating capacity, plasticity and therapy resistance[103–105].

Although EMT$^+$ cells can be found in established metastases, most metastatic cells are EMT$^-$, reflecting the limitations of using only two markers to interpret the full EMT spectrum, the MET or the epithelioid state required for metastatic colonization[32,33]. Recent integrative approaches combining single-cell RNA sequencing with CRISPR-based lineage tracing in pancreatic cancer have confirmed that metastases predominantly arise from clones that activate EMT in the primary tumor and especially from those in late hybrid EMT states[106] (Fig. 3a).

It is now clear that EMT is a major driver of invasion and can also confer cell plasticity and tumor-initiating capacity. However, the correlation between EMT activation and metastasis is not completely linear. Full mesenchymal states, identified by cell surface markers in squamous carcinoma and breast tumors, display higher invasive capacities than epithelial/mesenchymal hybrids but also harbor less metastatic potential in experimental metastasis assays[32,81] (Fig. 3). By contrast, hybrid EMT phenotypes show increased metastatic potential[107,108] (Fig. 3), and the cells identified as responsible for metastatic relapse, marked by EMP1 expression, also appear to be in a partial EMT state in colorectal cancer[109]. Consistently, low expression or downregulation of EMT-TFs has been identified as a necessary step for metastasis in certain models. For example, PRRX1 downregulation is required for metastatic outgrowth in the lung after tail vein injection with human breast cancer and melanoma cell lines[32,110], and the same applies to TWIST in a spontaneous squamous cell carcinoma mouse model[33]. These findings support the idea that MET, or at least a partial reversal of EMT, is required for effective metastatic outgrowth (Fig. 3a). Nonetheless, reversion might not be required for cells in a hybrid EMT phenotype, already bearing the highest tumor-initiating properties in breast cancer cells compared to epithelial, mesenchymal or mixed populations[80]. Recent lineage-tracing studies show that very few metastases arise from highly mesenchymal clones following MET in mouse models; rather, metastatic clones originate from small populations with intermediate EMT activation.[32,95,106]. Compatible with this, single-cell DNA sequencing in human tumors used to infer clonal lineages suggests that metastases tend to originate from highly proliferative clones in the primary tumor[111], unlikely to be mesenchymal, which are generally associated with proliferation arrest[60,112] (Fig. 3a). However, mesenchymal cells contribute notably to metastatic outgrowth after treatment[93,95] (Fig. 3b). This difference may result from two nonmutually exclusive mechanisms: either therapy increases the usually small number of fully mesenchymal cells leaving the primary tumor (if still present) or it induces a MET-like process in already-seeded mesenchymal cells that previously lacked outgrowth potential. A detailed analysis of EMT status in metastases arising from mesenchymal cells after therapy will shed light on why and how these cells can metastasize only after treatment.

In parallel with changes in EMT status at the metastatic niche, disseminated cells can also engage in a nonproliferative state, commonly termed dormancy[113] (Fig. 3a). Determining where, when and how this dormancy program is established and, more critically, how dormant

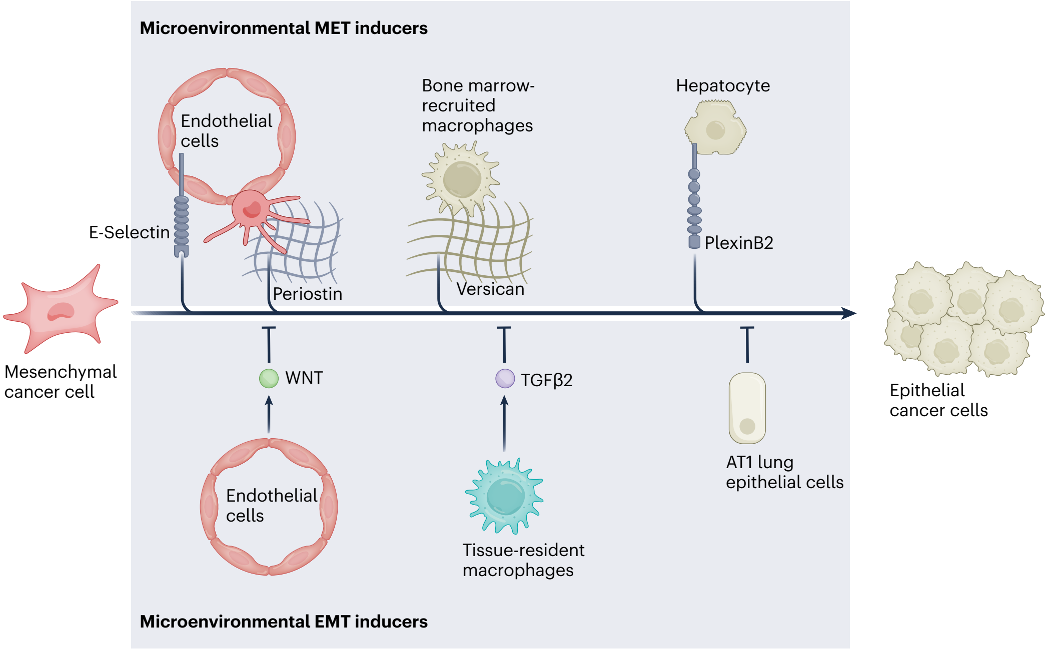


Fig. 4 | EMT–tumor microenvironment interactions at the metastatic niche. Full mesenchymal cells cannot metastasize and need to at least partially revert to an epithelioid phenotype. E-selectin on the surface of endothelial cells[123] or the secretion of periostin by tip cells promotes EMT reversion (MET) and metastatic growth, which is prevented by the secretion of WNT and other molecules[118,124]. Bone marrow-recruited macrophages secrete ECM molecules such as versican[126], which can also promote MET and, therefore, metastasis. Simultaneously, lung-resident macrophages can prevent metastatic outgrowth via TGFβ2–TGFβR3 signaling[125]. Nontransformed epithelial cells in the metastatic niche could either favor MET and macrometastasis or retain disseminated cells in an indolent EMT dormant state. Examples are respectively found in hepatocytes expressing PlexinB2 during liver colonization or through the action of AT1 cells after cancer cell dissemination to the lung[129].

cells awaken remains one of the most challenging aspects in metastasis research. Recent advances in tracing dormant cells reveal that, under naive conditions, proliferative metastases can arise from cells that never entered dormancy[114], indicating that dormancy is not a required step in the metastatic cascade and that some cells already possess high metastatic potential before reaching the metastatic niche. Once again, this scenario changes after chemotherapy, when a greater proportion of metastases originate from reawakened dormant cells[114]. Importantly, dormant cancer cells often display a mesenchymal state[115,116], consistent with the previously discussed findings that highly mesenchymal cancer cells have low metastatic potential[32,33,81,106] (Fig. 3a). Several studies support a link between EMT and cellular dormancy, including evidence that early dissemination in breast cancer is associated with dormant states driven by ZPF281 (refs. 116–118). More recent findings further suggest that EMT activation and dormancy programs are already coordinated within the primary tumor. Specifically, elevated expression of the EMT-TF PRRX1 in breast cancer cells confers invasive capacity while simultaneously inducing cell cycle arrest and dormancy-associated gene expression, thereby restricting metastatic outgrowth. Notably, intermediate PRRX1 levels appear to maximize metastatic potential, as they maintain invasive traits without imposing the proliferative limitations observed at higher expression levels. These findings indicate that EMT and dormancy are not independent programs but are co-regulated through shared transcriptional networks before dissemination, underscoring the potential of targeting dormant tumor cells by modulating EMT-TFs[119].

Finally, EMT does not only promote invasion or tumor initiation capacity, as it can be considered a driver of somatic cellular plasticity, inducing dedifferentiation, as observed during cancer progression and organ fibrosis[3,26,120,121]. Recent studies in colorectal cancer also highlight how EMT activation is part of a progressive cell plasticity process involving dedifferentiation and the acquisition of noncanonical transcriptional states necessary for metastasis[35,36].

Role of EMT in cancer cell metastatic niche interactions

As previously discussed, successful metastatic colonization by mesenchymal cancer cells requires at least a partial reacquisition of epithelial traits, enabling proliferative outgrowth and integration within the host tissue. In addition, microenvironmental signals in the new niche may induce strong EMT activation in arriving hybrid epithelial/mesenchymal cells, thereby diminishing their enhanced metastatic potential. Despite extensive characterization of microenvironmental EMT-inducing signals at the primary tumor, the mechanisms and cellular interactions governing EMT maintenance or reversion at metastatic sites remain poorly understood[122].

Microenvironmental modulators of EMT at the metastatic site

The perivascular niche represents the first microenvironment encountered by disseminated cancer cells at secondary sites and serves as a critical hub of interactions. For instance, E-selectin expressed by endothelial cells promotes bone metastatic colonization by inducing MET in breast cancer cells after binding to surface glycoproteins[123] (Fig. 4). Interestingly, this interaction is specific to bone metastases, suggesting that the mechanisms that favor MET vary across tissues and may partially explain the well-known cancer-specific organ tropism. In a separate study, responsiveness to WNT signals from lung endothelial cells was found as a key determinant of dormancy in disseminated cancer cells, associated with concurrent WNT and EMT activation (Fig. 4). Notably, sensitivity to environmental WNT was dependent on the pre-established epigenetic and EMT cell state[118]. Importantly, the extent of angiogenic activity seems to be critical in this context, as although endothelial cells promote dormancy via thrombospondin-1 secretion, tip cells secrete TGFβ1 and periostin that promote tumor growth[124] (Fig. 4).

Interactions with myeloid cells at metastatic sites also appear to regulate epithelial/mesenchymal plasticity. Tissue-resident

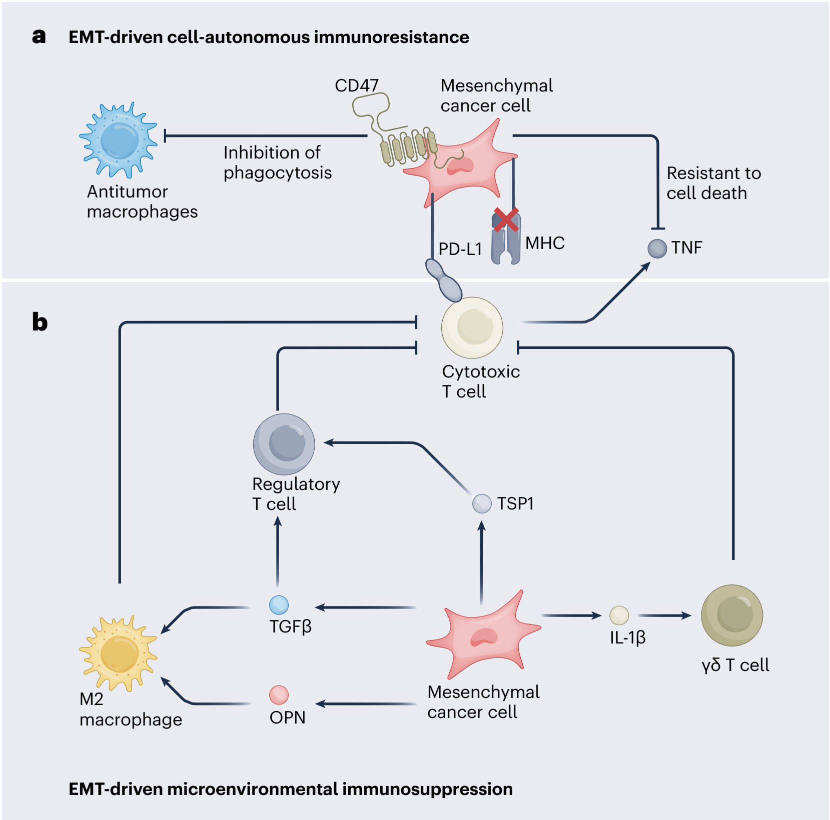


Fig. 5 | Cell-autonomous and cell-nonautonomous roles of EMT in immunosuppression. EMT activation in cancer cells is associated with immunosuppression, affecting immune cells through both intrinsic and extrinsic mechanisms. **a**, Examples of the former include inhibition of phagocytic activity via CD47 expression[135], reduced T cell-mediated killing through expression of PD-L1 (refs. 136,137), downregulation of antigen-presenting capacities[138] or resistance to the cell death induced by TNF and other cytotoxic signals[60]. **b**, In addition, cancer cells undergoing EMT create an immunosuppressive niche through the secretion of multiple factors such as TGFβ, OPN and IL-1β that recruit and expand immunosuppressive cell populations including M2-like macrophages and regulatory T cells[138,143].

macrophages secreting TGFβ2 can maintain disseminated cancer cells in a dormant state via TGFβR3 signaling, likely through sustained EMT activation. As such, conditioned medium from resident macrophages led to a upregulation of the EMT-TFs ZEB1 and TWIST1 (ref. 125; Fig. 4). The interaction depends on the timing of dissemination, as cells that disseminate late can escape dormancy by downregulating TGFβR3. A systematic analysis of TGFβ family members and their receptors in primary tumors during tumor progression may help explain the distinct metastatic behaviors of early versus late disseminated cells. Macrophages also modulate ECM composition altering the cues perceived by cancer cells after extravasation. In a breast cancer model, versican deposited by recruited macrophages promoted MET in the lungs through downregulation of phospho-SMAD2, thereby enhancing metastatic outgrowth without affecting initial seeding[126] (Fig. 4).

Cancer cells can also promote ECM remodeling via type 3 collagen secretion, thereby sustaining cell dormancy through discoidin domain receptor 1–STAT1 signaling in an autocrine manner[127]. Early disseminated cancer cells primed to enter dormancy express high levels of *COL3A1* (ref. 116), which has also been implicated in EMT activation in glioma cell lines[128]. These results reinforce the association between dormancy and EMT and suggest that dormancy-inducing signals can be derived from the cancer cells themselves.

Finally, interactions between disseminated cancer cells and nontransformed epithelial cells at the metastatic site also have an important role. Their interaction with AT1$^+$ lung epithelial cells induces SFRP2 expression in the dormant D2.OR breast cancer line, activating a prosurvival, nonproliferative partial EMT-like program[129] (Fig. 4). Notably, cancer cells also trigger stemness-like programs with EMT features in neighboring epithelial cells, resulting in a supportive niche for metastatic growth, a phenomenon known as 'reflected stemness'[130].

The emergence of new technologies, together with advanced experimental models, is key to identifying the diverse mechanisms that induce EMT reversion in different cancer types and organs. A recent in vivo CRISPR screen targeting ligand–receptor pairs revealed that PlexinB2 in hepatocytes, after binding to class 4 semaphorins expressed by colorectal and pancreatic cancer cells, induces MET through KLF4 activation and drives metastatic colonization[131] (Fig. 4). Similar screens, combined with spatial transcriptomics, could systematically identify tissue-specific MET drivers while simultaneously profiling microenvironmental changes[132].

EMT and immune surveillance

The EMT status of cancer cells has a critical effect on immune surveillance and, consequently, the response to immunotherapy. EMT signatures have been consistently associated with immunosuppression in human datasets[133,134], and several mechanisms have been proposed to explain this connection. For instance, the EMT-TFs SNAIL1 and ZEB1 directly activate the expression of CD47, a 'don't eat me' signal that inhibits macrophage-mediated phagocytosis[135] (Fig. 5a). These transcription factors also induce the expression of immune checkpoint ligands such as PD-L1, thereby directly impairing T cell function[136,137] (Fig. 5a). As already mentioned, the loss of PRRX1, a master regulator of the mesenchymal program in breast cancer cells, not only reduces invasion and metastasis but also increases the infiltration by MHC class II$^+$ antitumor macrophages[26].

Another key mechanism of EMT-driven immune evasion involves the suppression of antigen presentation. This can occur through downregulation of MHC[138] or through alterations in the immunoproteasome, the protein complex responsible for generating peptides for MHC presentation[139] (Fig. 5a). Recently, TCF4 has been shown to repress the expression of the antigen presentation machinery while simultaneously inducing EMT, which leads to dedifferentiation and mesenchymal transition in melanoma, exemplifying how EMT inducers can coordinate multiple functional axes[140]. Intrinsic features of the mesenchymal state can also render cancer cells more resistant to immune-mediated killing, as EMT confers resistance to prodeath signals such as TNF[60] (Fig. 5a), and the concomitant loss of E-cadherin may impair the formation of effective immune synapses with T cells[141]. In addition, EMT-induced autophagy protects cancer cells from lysis mediated by T cells[142].

EMT not only confers immunoresistance to cancer cells but also promotes the establishment of an immunosuppressive tumor microenvironment. SNAIL1 activation enhances the recruitment of regulatory T cells via TSP1 secretion, leading to the inhibition of cytotoxic CD8$^+$ T cell activity within the tumor[143] (Fig. 5b). Similarly, mesenchymal cancer cells with high SNAIL1 expression secrete immunomodulatory factors such as TGFβ1, OPN and macrophage colony-stimulating factor, generating a suppressive niche enriched in M2 macrophages and regulatory T cells and depleted in cytotoxic CD8$^+$ T cells[138] (Fig. 5b). Notably, a small fraction of mesenchymal cells is sufficient to establish this immunosuppressive environment, which also protects neighboring non-EMT cancer cells from immune attack[138]. This EMT-driven immunosuppressive niche is also present during early metastatic colonization, as EMT metastasis-initiating cells secrete interleukin-1β, which recruits immunosuppressive γδ T cells and reduces CD8$^+$ T cell infiltration (Fig. 5b), together facilitating the progression to macrometastasis[144]. Recent evidence shows that TGFβ-induced EMT in lung adenocarcinoma progenitors triggers gelsolin-mediated actin remodeling, leading to a softer, atypical mesenchymal state that reduces susceptibility to cytotoxic T cell killing and supports metastatic dormancy[145]. These data indicate that a link between EMT-associated dormancy at the metastatic niche could be partially explained by immune evasion mechanisms. When exactly these immune evasion mechanisms are activated during EMT, or whether different EMT states display distinct immune evasion trajectories, remain open questions in the field.

These immune-related roles of EMT need to be considered in experimental designs, as studies based on immunodeficient mice bypass immune surveillance at early stages and can overestimate the metastatic capacity of epithelial cells. It is still not clear where along the EMT spectrum immunosuppressive capabilities are acquired or whether different hybrid epithelial/mesenchymal states or EMT trajectories have specific immune-related mechanisms. The use of immunocompetent mouse models capable of recapitulating the full metastatic cascade, from the primary tumor to colonization in distant organs, combined with lineage-tracing tools, particularly single-cell DNA barcoding, is essential to understand the dynamics and contributions of distinct EMT states during cancer progression.

Emerging therapeutic approaches as potential anti-EMT strategies

A great effort has been made in finding antimetastatic agents, because advanced metastatic disease remains an unmet clinical need[146]. As EMT is a core step in the metastatic cascade, many groups have tried to inhibit or modulate it in the hope of preventing or curing metastasis, and a compilation of finished and ongoing clinical trials involving EMT has been recently published[46]. EMT confers resistance to standard chemotherapy[93–95,147], radiotherapy[20] and immunotherapy[138,140,144]. Thus, besides reducing metastasis, effective EMT targeting could boost the efficacy of current drugs.

Most efforts have focused on blocking EMT-activating pathways downstream of mesenchymal markers like vimentin or N-cadherin or inducing EMT reversal by targeting upstream pathways as discussed in a recent comprehensive review on clinical and therapeutic landscapes of EMT[46]. An additional point of intervention is to inhibit the microenvironmental interactions that drive EMT, also recently reviewed by Zhang et al.[122]. The clinical success of these approaches has been modest, as no anti-EMT drugs have been approved so far. A promising candidate is an antibody to netrin-1, which inhibits the late steps of EMT[148,149] and has shown clinical benefit in endometrial cancer. In this section, we discuss novel therapeutic paradigms that have not yet been explored in anti-EMT strategies but may hold considerable promise. We outline how they could be exploited to do so and rationally designed either to target the fundamental drivers or to selectively eliminate cells undergoing EMT.

Directly targeting the master regulators of EMT

As EMT-TFs have long been considered ‘undruggable’, most anti-EMT strategies used to date do not include rationally designed molecules to specifically hit these factors. Transcription factors are often intrinsically disordered[150], lack well-defined binding pockets for small molecules and have no obvious catalytic site to block. Blocking their DNA binding sites would be an attractive approach, but their structure and high positive charge make them difficult targets for small molecules. In addition, owing to their nuclear localization, they are harder to reach than cell surface targets[151,152]. Nevertheless, several therapeutic strategies that target transcription factors have emerged in recent years, and we anticipate their application to EMT master regulators.

Targeted protein degraders

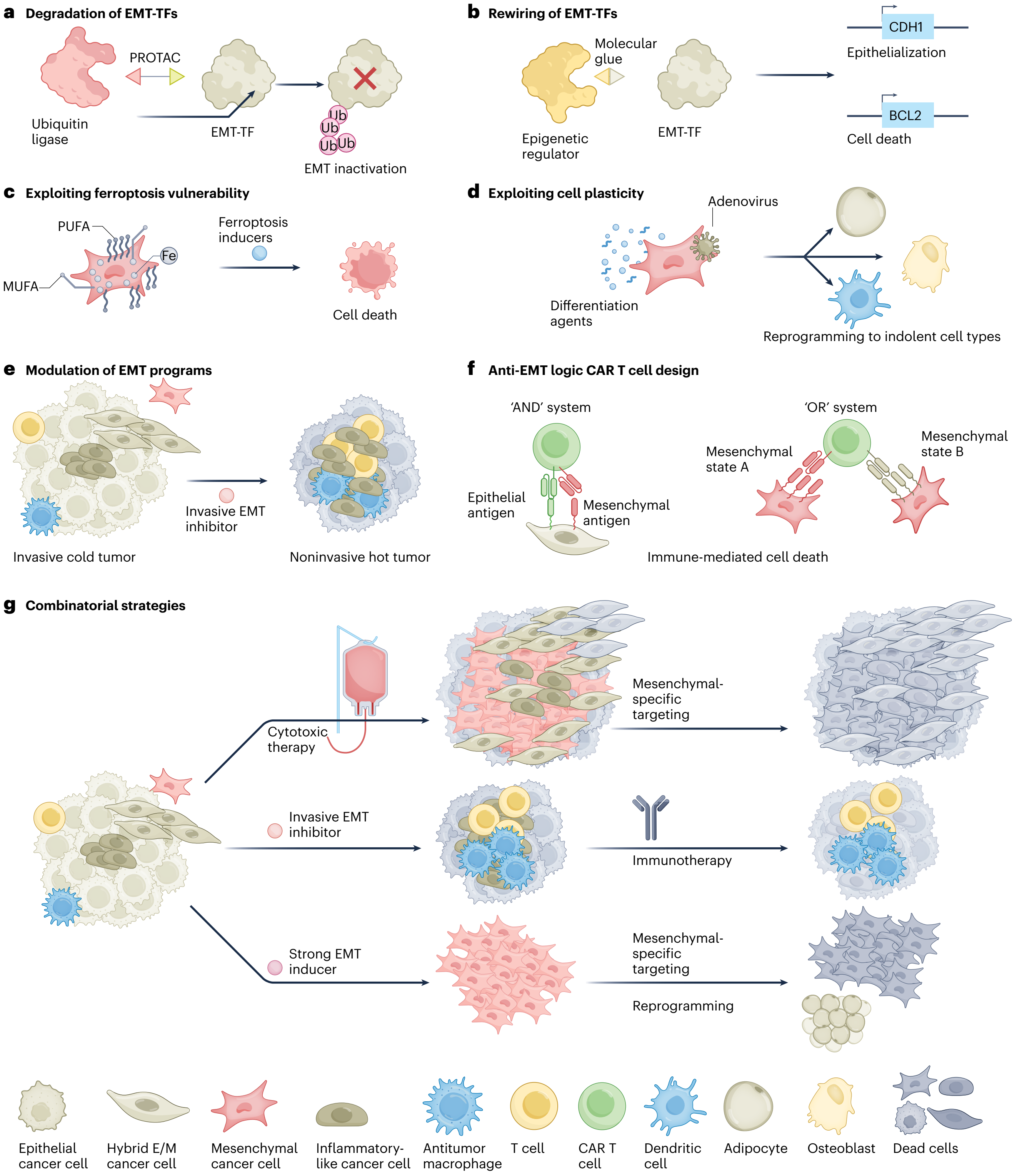
Protein degraders, including molecular glues[153] and proteolysis targeting chimeras (PROTACs)[154], bring the protein into close proximity with an E3 ubiquitin ligase, inducing its ubiquitination and degradation. These reagents may offer an effective approach for targeting EMT-TFs

Fig. 6 | Emerging approaches as potential anti-EMT therapeutic strategies. **a**, PROTACs could degrade specific EMT-TFs, preventing or attenuating EMT. **b**, Molecular glues inducing interactions between EMT-TFs and epigenetic regulators could rewire their activity, converting them to activators inducing the expression of epithelial genes or even activating apoptotic genes and inducing cell death. **c**, EMT activation confers ferroptosis vulnerability owing to the increase in intracellular iron and changes in fatty acid composition in mesenchymal cells, increasing the PUFA:MUFA ratio. This vulnerability can be enhanced using ferroptosis inducers such as GPX4 inhibitors, erastin or the recently developed fentomycin-1 to selectively eliminate cells undergoing EMT[167,171,173]. **d**, EMT activation is accompanied by an increase in cell plasticity properties, making cells more susceptible to reprogramming and generating inert cell types such as adipocytes or osteoblasts[181] or even cells with an antitumor activity like dendritic cells[182]. **e**, Tumor cells activate invasive and inflammatory-like EMT programs, which are plastic and interdependent. As such, inhibition of EMT-TFs in the invasive trajectory like PRRX1 could not only repress the invasive EMT program but also favor the inflammatory-like EMT, promoting an antitumor microenvironment[26]. **f**, Logic-gated CAR T cells could provide selective targeting of EMT$^+$ cells. ‘AND’ gates requiring coexpression of epithelial and mesenchymal antigens would enable precise killing of the highly metastatic hybrid epithelial/mesenchymal cells while sparing nontransformed epithelial or mesenchymal cells. ‘OR’ gate designs allow CAR T cells to recognize several antigens independently, making them ideal to tackle EMT heterogeneity. **g**, EMT-targeted therapies would likely synergize with other agents, particularly those to which EMT activation confers resistance such as chemotherapy, radiotherapy or targeted therapies such as EGFR inhibitors[200,201]. Strategies that exploit EMT heterogeneity, such as promoting inflammatory EMT or inducing homogeneous mesenchymal states, can synergize with immunotherapy that leverages greater immune infiltration or specific mesenchymal ablation (through ferroptosis inducers or CAR T cells) and reprogramming, respectively. Optimal sequencing and timing of interventions are critical to overcome resistance and maximize therapeutic effectiveness.

(Fig. 6a), as they have shown promise in preclinical studies against targets such as SMAD3 or MDM2 in blood cancers[155,156]. Degraders entered into clinical trials in 2019 (ref. 157), and vepdegestrant (ARV-471), an oral PROTAC for breast cancer now in phase 3, may become the first rationally designed degrader to reach the clinic[158]. Exploiting ubiquitin ligases with tissue or cell-type specificity could further minimize off-target effects. Examples include the skeletal muscle ligases KLHL40 and KLHL41 (ref. 159) or the central nervous system-restricted ligases RNF182 (ref. 160) and TRIM9 (ref. 161). Other ligases, such as members of the MAGE family, are usually confined to the male germ line but become overexpressed in many cancers[162,163]. Although EMT-specific protein degraders have not yet been developed, the possibility of directly targeting the master regulators is promising, although it would require deciphering the EMT code of each tumor type to ensure effectiveness and specificity (Fig. 6a).

Transcriptional rewiring

An advanced application of proximity-based chemistry is the use of transcription factor chemical inducers of proximity (TCIPs). TCIPs function by redirecting oncogenic transcription factors to epigenetic



regulators with opposing activity through an enforced proximity approach. In a notable example, a TCIP links BCL6, a repressor of proapoptotic genes, to the transcriptional activator BRD4, rewiring BCL6 to activate apoptotic pathways in diffuse large B cell lymphoma[164]. With respect to EMT, a similar logic could operate for SNAIL1 or other EMT-TFs, which would be converted into activators of epithelial genes (Fig. 6b). Importantly, the challenge of the dual repressor/activator nature of many EMTs should be considered during target selection. Nevertheless, the possibility of generating cells with an undesired hybrid epithelial/mesenchymal phenotype bearing increased metastatic potential should be taken into consideration. Informed choice of epigenetic modulators could add an extra layer of specificity to avoid unwanted effects. A more straightforward approach may involve inducing cell death following the expression of selected EMT-TFs. In this regard, the recent development of RIPTACs[165,166], bifunctional molecules that create a proximity-induced synthetic lethality, holds promise for specifically eliminating EMT-TF-expressing cells (Fig. 6b).

Exploiting acquired vulnerabilities of the mesenchymal state

The EMT program not only endows cells with motility and resistance to cell death but also imposes new liabilities that could be therapeutically exploited. Targeting the consequences of EMT activation may prove more effective than attempting to suppress the process itself.

Ferroptosis

Ferroptosis is a nonapoptotic cell death program dependent on intracellular iron, resulting from the accumulation of lipid peroxidation initiated in lysosomes[167] and with critical negative regulators (GPX4 (ref. 168) and FSP1 (ref. 169)) that can be targeted to enhance the process[170]. Interestingly, several studies have described an increased susceptibility to ferroptosis in mesenchymal cells[167,171–173] due to their higher concentrations of intracellular iron than epithelial cells[171] (Fig. 6c). EMT activation has also been linked to metabolic reprogramming, including lipid composition of the cell. The EMT-TF ZEB1 activates the expression of enzymes that synthesize polyunsaturated fatty acids (PUFAs; for example, ELOVL5 and ACSL4) and downregulates the expression of enzymes that synthesize monounsaturated fatty acids (MUFAs; for example, SCD and FASN)[174], increasing the sensitivity to ferroptosis, as PUFAs are the main substrate of lipid peroxidation[175] (Fig. 6c). Increased vulnerability to ferroptosis is specifically mediated by ZEB1 but not by SNAIL1 or TWIST, providing a clear example of nonredundant functions of EMT-TFs. Importantly, the incorporation of PUFAs to the lipid membrane increases fluidity, which is fundamental for the acquisition of migratory properties[176]. Thus, high intracellular iron and high content of PUFAs in the membrane may explain the vulnerability of mesenchymal cells to ferroptosis, which could be further enhanced by GPX4/FSP1 inhibitors, erastin or fentomycin-1 (refs. 167,170,171; Fig. 6c). Despite some initial doubts on the efficacy of ferroptosis activation in vivo[177], recent works confirm that its induction impairs tumor progression and metastasis in preclinical models of breast cancer, lung cancer and melanoma[167,178,179].

Cancer cell reprogramming

Mesenchymal cancer cells resulting from an EMT process are plastic and can, as mesenchymal stem cells, give rise to different cell lineages, including osteoclasts, adipocytes and chondrocytes, a strategy that has been used as a proof of concept in breast cancer models[180,181]. As such, the conversion of cancer cells to nondividing adipocytes resulted in reduced invasion and metastasis[181] (Fig. 6d). Building on this concept, recent advances have shifted the focus from converting cancer cells into inert lineages to actively reprogramming them into antitumorigenic cell types. Notably, tumor cells have been reprogrammed in vivo into dendritic-like cells after adenoviral delivery of key dendritic transcription factors[182] (Fig. 6d). Understanding which cancer cell subsets are most amenable to such reprogramming will be crucial for developing effective therapies. Although technically challenging, these strategies hold great promise, especially if cancer cells could be converted into antitumor effector cells.

Exploiting the plasticity and interdependence of EMT programs

As discussed in the previous sections, tumors deploy at least two general and distinct, yet interdependent, EMT programs that mirror those seen during embryonic development or those occurring in response to damage in the adult[26] (Fig. 2b). Recognizing this duality may open new therapeutic possibilities beyond a general EMT inhibition. As the cancer adult-like EMT is linked to proinflammatory responses and the recruitment of antitumor myeloid cells[26], promoting this EMT type may yield higher therapeutic benefit than complete suppression of EMT. Therefore, identifying inducers of the inflammatory EMT program could be relevant. In addition, as suppressing the invasive EMT, for instance via *Prrx1* genetic deletion, enhances the inflammatory program[26], inhibitors of the invasive arm could offer a double advantage, less dissemination and more antitumor immune infiltration (Fig. 6e). Such strategies require a detailed map of the EMT code that drives heterogeneity across tumor types, along with a clearer view of the epigenetic steps that control each transition. Integration of this knowledge with in silico perturbation simulations, such as the predictions obtained with CellOracle[183], have the potential to enhance target prioritization.

Immunotherapy approaches

Immunotherapy, particularly immune checkpoint blockade (ICB), has transformed the treatment of hematological malignancies and several solid tumors, including lung cancer, melanoma and triple-negative breast cancer[184]. However, even in the most responsive cases, an important proportion of individuals experience limited or no benefit[184]. Across tumor types, nonresponders are consistently enriched for mesenchymal markers[133,134], compatible with EMT dampening antitumor immunity through PD-L1 upregulation, increased TGFβ1 secretion, reduced antigen presentation and recruitment of immunosuppressive cells[136,138,143] (Fig. 5). Importantly, EMT heterogeneity greatly influences response to immunotherapy. In cutaneous squamous cell carcinoma, cells at different stages along the EMT spectrum activate distinct T cell checkpoints. Epithelial-like cells predominantly engage into the PD-1–PD-L1 axis, whereas hybrid and mesenchymal cells activate CTLA-4–CD80 and TIGIT–CD155. Consequently, EMT status assessment in the clinic could guide treatment selection, and the use of dual PD-L1 and TIGIT blockade may effectively target both cell populations[185]. Several combination strategies involving ICB and targeting EMT using inhibitors of TGFβ[186], EGFR[187] or integrin $\alpha_v\beta_6$ (ref. 188), which enhance ICB efficacy in preclinical models, have entered early trials. However, the extent to which this benefit derives from direct modulation of EMT remains unclear, as these pathways are pleiotropic, and EMT can be driven by multiple mechanisms, some of which may become dispensable once the mesenchymal state is fully established. Moreover, even a small mesenchymal clone (around 10%) can notably impair ICB response[136], suggesting that strategies aimed at eliminating all EMT$^+$ cells may be required.

CAR T cells, logic gates and EMT

The efficacy of chimeric antigen receptor (CAR) T cell therapy can be limited by immunosuppressive microenvironments and antigen heterogeneity, and EMT activation helps build that hostile niche. Hence, removing those cells could boost immunotherapy response (Fig. 6f). Single-antigen CAR T cells are unlikely to eliminate all malignant clones without also affecting healthy tissues, but logic-gated CARs hold promise. ‘AND’ gates require two antigens on the same cell for

CAR to trigger cytotoxicity[189,190]. A tumor-type-specific marker could be paired with a robust EMT antigen, sparing epithelial tumor cells and stromal mesenchyme while targeting EMT$^+$ cancer cells that still display tissue-specific lineage markers. Designing CARs that would specifically target cells simultaneously expressing an epithelial and a mesenchymal marker could destroy hybrid epithelial/mesenchymal cells (Fig. 6f). 'OR' gate CAR designs, which enable the same cells to recognize multiple antigens independently, are already being tested in trials in a different context[191,192]. This strategy could reduce the risk of antigen escape, either by targeting cells that have lost lineage-specific antigens or by addressing antigen heterogeneity within the tumor population. A panel of EMT-specific antigens tailored to each tumor type could serve as the foundation for next-generation CAR designs (Fig. 6f). The development of novel in vivo CAR T cell reprogramming holds the promise of reducing the manufacturing and delivery costs of current CAR T cell products[193] and will allow further development of tailored CAR T cell therapies. The combination of ICB or CAR T cell therapies with anti-EMT interventions also represents a promising therapeutic strategy.

Rational design of combination therapies

Targeting EMT alone, either by blocking the program or by eliminating EMT$^+$ cells, is likely to yield limited clinical benefit. However, EMT interventions combined with therapies to which EMT confers resistance hold greater therapeutic promise[194]. The rational design of combinatorial strategies, including their timing and sequencing, will be critical.

EMT activation endows cells with resistance to several cytotoxic agents, and EMT inhibition enhances chemotherapy efficacy in multiple tumor types[93–95,148,195]. EMT also promotes radiotherapy resistance, as mesenchymal cells repair DNA damage more efficiently through a ZEB1–USP7–CHK1 axis[20]. Therefore, combining anti-EMT drugs with chemotherapy or radiotherapy could increase tumor control while enabling dose reductions, an important consideration given the systemic toxicity associated with these treatments (Fig. 6g). The need for lowering doses is further emphasized by recent findings showing that high-dose radiotherapy, despite effectively targeting the primary lesion, can promote distant metastasis via amphiregulin release and remodeling of the immune microenvironment[196]. Notably, amphiregulin itself is an inducer of EMT[197,198].

The coexistence of embryonic-like (invasive) and adult-like (inflammatory) EMT programs within the same tumor provides novel opportunities for combination therapies. Boosting the adult-like, pro-inflammatory arm might amplify immunotherapy responses (Fig. 6g). Alternatively, driving tumors toward a homogeneous and stable mesenchymal state (for example, using small-molecule-based rewiring of the EMT-TFs) would make them less metastatic and vulnerable to more specific mesenchymal targeting, including ferroptosis or CAR T cells engineered to target mesenchymal antigens (Fig. 6g).

As already mentioned, the timing and order of drug administration may be critical because cell plasticity can evolve during treatments (Fig. 6g). Should an EMT-targeted therapy be administered first to prevent resistance or be reserved for later to eliminate the mesenchymal 'persister' cells that survive initial treatment? One strategy is to use standard therapy to eliminate sensitive clones followed by EMT-directed drugs to eradicate the resistant mesenchymal subpopulations (Fig. 6g). However, persister cells are heterogeneous and arise from multiple lineages[199], making a detailed profiling of their EMT status essential. Alternatively, initiating the treatment with EMT suppression might not only prevent resistance but also mitigate the microenvironmental alterations induced by EMT (Fig. 6g). Ultimately, the optimal strategy depends on the tumor's specific EMT landscape. The potential of these therapeutic strategies will depend on the development of dynamic biomarkers that can longitudinally track tumor plasticity.

Conclusions

EMT is a key driver of tumor plasticity, enabling reversible shifts that regulate invasion, immune evasion, therapy resistance and metastatic competence. Rather than a binary process, EMT spans a continuum where hybrid states often dominate metastatic colonization, whereas full mesenchymal states favor dormancy and increase survival. These dynamics are tightly linked to the tumor microenvironment, which can induce EMT or govern its reversion at metastatic sites. EMT heterogeneity complicates biomarker interpretation and influences responses to standard and immune-based therapies, highlighting the need for EMT-informed clinical strategies. Therapeutic efforts are moving from global EMT inhibition toward exploiting mesenchymal vulnerabilities such as ferroptosis or leveraging plasticity for reprogramming, combined with rational therapy sequencing. Critical questions remain, including a better understanding of the role of EMT in cancer initiation, the functional impact of EMT heterogeneity in naive versus treated tumors, its relationship with dormancy and how to integrate this complexity into clinical decision-making. Addressing these challenges will require spatial lineage tracing, multiomics and functional perturbations in silico and in animal models and tumoroids to decode EMT programs and guide adaptive interventions.

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