Cancer dormancy

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Cell stiffness regulates immune evasion during metastatic dormancy

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Dormant metastases can lead to tumor relapse after many years by successfully escaping immune surveillance. A new study identifies an atypical epithelial-to-mesenchymal transition state that presents low stiffness mediated by actin depolymerization, which prevents immune cell-mediated killing of dormant metastatic lung adenocarcinoma.

Metastasis is the leading cause of death in patients with cancer. Cancer cells that leave the primary tumor and circulate to distant organs can enter a dormant state that lasts for months or even decades before re-awakening, leading to cancer relapse after long-term remission[1].

Epithelial-to-mesenchymal transition (EMT) is a reversible process during which cells lose their epithelial characteristics and acquire mesenchymal traits, such as increased motility[2,3]. EMT controls different aspects of tumorigenesis and recent studies have shown that it is not a binary switch, but instead occurs through different intermediate states associated with distinct tumor functions[4–6]. Activation of EMT enables tumor cells to detach from each other, leave the primary tumor, migrate and intravasate into the blood and lymphatic circulation, where they can exhibit high plasticity and intermediate or hybrid EMT states characterized by co-expression of epithelial and mesenchymal markers. At the metastatic site, tumor cells extravasate and colonize distant organs. During this stage, tumor cells can revert to an epithelial phenotype by a process known as mesenchymal-to-epithelial transition (MET), which promotes tumor cell proliferation and metastatic outgrowth, or alternatively the cells can enter dormancy, which confers immune evasion and resistance to therapy[1,7–9].

The mechanisms by which tumor cells enter dormancy and the intrinsic and extrinsic stimuli that maintain tumor cells in this quiescent and clinically undetectable state remain largely unknown[9]. Identifying the mechanisms that stimulate the entrance and maintenance of tumor cells into a dormant state is key to the development of more efficient strategies to treat metastatic cancer. In this issue of *Nature Cancer*, Wang et al.[10] identify an atypical form of EMT mediated by TGFβ that sustains metastatic dormancy and promotes escape from immune surveillance.

TGFβ is an inducer of EMT and can also induce cellular quiescence and tumor dormancy[11]. Dormant metastatic cancer cells often reside within the perivascular niche, where different cells of the microenvironment secrete TGFβ to promote tumor dormancy. In addition, dormant tumor cells need to activate strategies to evade the immune system to survive during long periods of time. Dormant metastatic carcinoma cells can evade immunosurveillance by downregulating major histocompatibility complex (MHC) class I molecules, NK cell receptors and the activity of the interferon pathway[11,12]. Increased stiffness of tumor cells has been suggested to elicit stronger immune responses from cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells[13]. In this context, TGFβ might have seemingly opposing roles by promoting cellular quiescence and tumor dormancy while also promoting a mesenchymal stiff state that renders tumor cells more sensitive to CTL- and NK cell-mediated killing.

To study the mechanisms by which tumor cells enter and sustain a dormant metastatic state, Wang et al.[10] used a technique they had developed previously[14] that enables the in vivo selection of a latency competent cancer (LCC) cell population, as well as an established LCC cell line derived from a human *RAS*-mutant lung adenocarcinoma. In addition, they generated a mouse LCC cell line from a primary lung adenocarcinoma with mutated *Kras* and *Trp53* to perform in vivo studies by transplantation into syngeneic immunocompetent mice, enabling the study of tumor dormancy under physiologically relevant immune surveillance conditions[10]. Human and mouse LCC cell lines were inoculated into the circulation of immunodeficient and immunocompetent mice, respectively, to assess the behavior of dormant cells in vivo. At early time points, the disseminated tumor cells that colonized the brain were elongated and located around capillaries. Surprisingly, at later timepoints, dormant metastatic cells displayed a spheroidal shape, while maintaining mesenchymal characteristics (Fig. 1). The authors[10] then assessed the extent to which this tumor state switch was reliant on TGFβ signaling. Mouse and human LCC cell lines were engineered with a genetic construct the enabled active TGFβ signaling to be monitored via an mCherry fluorescent reporter[15], and dormant metastatic cells were shown to express high levels of the reporter, thus indicating that dormant metastatic cancer cells experience sustained TGFβ signaling (Fig. 1).

To determine the importance of this sustained activity of TGFβ signaling in tumor dormancy, the authors knocked out the TGFβ receptor subunit *Tgfbr2* to block TGFβ signaling in the mouse LCC cell line. In vivo inoculation of *Tgfbr2* knockout cells together with depletion of NK cells and CTLs led to metastatic outgrowth when the depletion was performed soon after inoculation. By contrast, depletion of immune cells at later stages only led to metastatic outgrowth in wild-type *Tgfbr2* cells but not in *Tgfbr2* knockout cells, which indicates that TGFβ signaling is not essential for early metastatic seeding but is crucial for tumor dormancy and escaping immune surveillance at later stages. To assess whether these dormant spheroidal cells with sustained TGFβ activity exhibited EMT features, Wang et al.[10] treated the LCC cell lines with TGFβ in vitro. Initially, LCC cells grew as epithelial cell clusters. However, in response to TGFβ treatment for 3 days, the LCC cells exhibited a full EMT phenotype with the presence of actin stress fibers. Cultured LCC cells treated with TGFβ for longer than 3 days started to exhibit a round morphology, a lack of actin stress fibers and reduced motility. After 7 days, cells also displayed subcortical actin filaments and cellular quiescence (Fig. 1).

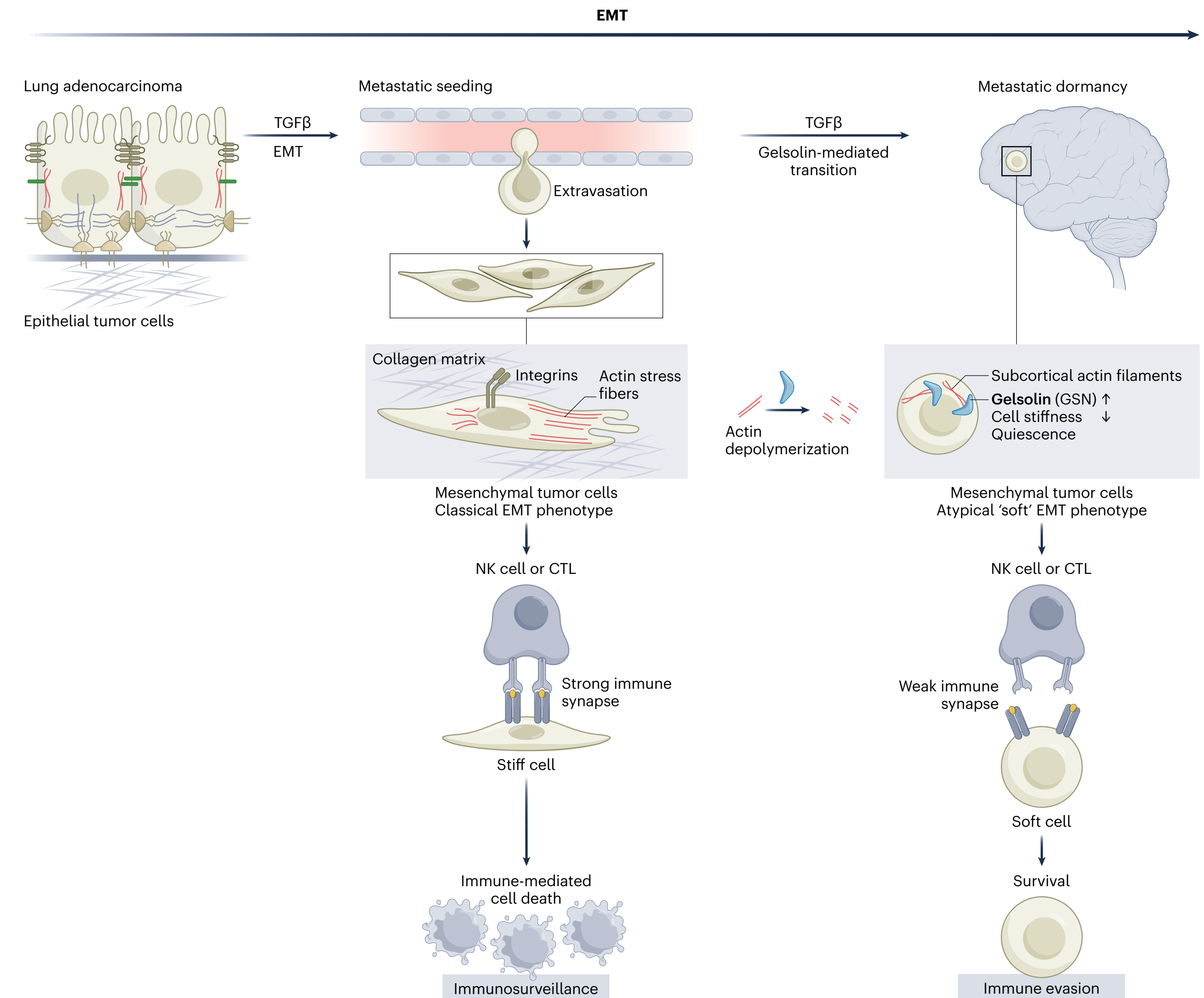

Fig. 1 | An atypical round and soft EMT state is crucial for survival and immune evasion of lung adenocarcinoma dormant metastatic cells. Upon EMT, metastatic lung adenocarcinoma cells (left) exhibit an elongated classical EMT phenotype (middle), in which tumor cells are stiff, rich in actin stress fibers and susceptible to NK-mediated and CTL-mediated cell death. After upregulation of gelsolin by sustained TGFβ signaling (right), tumor cells transition towards a round and soft quiescent atypical EMT state that enables immune evasion of dormant metastatic cells.

To understand the molecular mechanisms that underlie the progressive loss of actin stress fibers in TGFβ-treated LCC cells that occurs after 3 days of treatment, the authors performed RNA sequencing in TGFβ-treated LCC cells at 3 and 7 days. At the later timepoint, they found increased expression of *GSN*, which encodes gelsolin – an actin cytoskeleton regulator that binds and caps actin to induce actin depolymerization (Fig. 1). In addition, single-cell RNA sequencing of TGFβ-treated LCC cells at several timepoints showed that tumor cells have the highest *GSN* expression after 7 days of exposure to TGFβ, at which point the cells also had the highest EMT score and level of quiescence. These results suggest that TGFβ progressively induces this spheroidal, quiescent and gelsolin-high EMT state that may regulate the transition of actin stress fibers to subcortical actin filaments.

Wang et al.[10] knocked down gelsolin to investigate its potential role on the loss of actin fibers in TGFβ-treated LCC cells and found that it did not affect the initial induction of a spindle shape and actin stress fibers upon TGFβ treatment. However, gelsolin knockdown prevented the switch towards the spheroidal quiescent state. In vivo, gelsolin-deficient cells could extravasate and exhibited an elongated morphology after 7 days, whereas after 28 days, the switch to dormant spheroidal metastatic cells was reduced (Fig. 1). These results show that gelsolin has an essential role in the morphological switch from a spindle-elongated state towards a dormant round tumor state.

The authors assessed whether this spheroidal gelsolin-expressing EMT state led to a change in cell stiffness. Compared with epithelial LCC cells, spindle-shaped LCC cells treated with TGFβ for 3 days showed an increase in stiffness, whereas the transition towards a spheroidal shape was accompanied by a decrease in stiffness. To assess whether this change in stiffness was associated with a change in susceptibility to immune responses, TGFβ-treated LCC cells were co-cultured with activated NK cells or CTLs. Whereas NK cells were able to interact with both tumor states, they were more effective at killing elongated stiff cells compared with round LCC cells. Likewise, elongated cells showed a stronger CTL activation (Fig. 1).

Spheroidal quiescent cells exhibited an absence of actin stress fibers and the presence of subcortical actin filaments. To evaluate whether the depolymerization of the actin cytoskeleton that occurs in spheroidal cells was the direct cause of immune evasion, the authors transduced LCC cells with a fragment of a protein from *Salmonella enterica* that disassembles actin fibers. TGFβ treatment of tumor cells with depolymerized actin resulted in the absence of actin stress fibers, reduced stiffness and decreased susceptibility to immune responses by NK cells and CTLs. These findings show that the immune response is negatively regulated by depolymerization of actin fibers.

Lastly, to determine whether evasion to immunosurveillance through this transition towards a round EMT state was mediated by gelsolin, stiffness and immune response were assessed in gelsolin-deficient LCC cells. These cells sustained their stiffness after 7 days of TGFβ treatment and were rendered more sensitive to immune-mediated killing in vitro and in vivo, which indicates that upregulation of gelsolin after TGFβ signaling is required for immune evasion during metastatic dormancy.

Altogether, the elegant study by Wang et al.[10] contributes to deciphering how EMT plasticity sustains metastatic dormancy and promotes immune evasion. The authors demonstrated that gelsolin mediates a tumor state transition from a classical full EMT phenotype towards a spheroidal, soft and quiescent EMT state sustained by TGFβ signaling. This atypical EMT state protects tumor cells from CTL- and NK cell-mediated immune cell death, preventing effective immunosurveillance and enabling the survival of dormant metastatic cells (Fig. 1). In addition, the work shows that perturbations in TGFβ signaling, actin polymerization or cell stiffness lead to the depletion of dormant cells. These intriguing results provide a proof of concept for new opportunities to promote the eradication of dormant metastatic cells by promoting their elimination by immune cells. Collectively, the findings represent an important advancement in our understanding of dormant metastatic disease, providing promising perspectives for clinical interventions for metastatic disease.

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Competing interests

The authors declare no competing interests.