LATENCY, IMMUNE EVASION, AND OUTBREAK OF METASTATIC STEM CELLS

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Metastasis typically occurs long after the removal of a primary tumor. It emerges from disseminated cancer cells that remain latent until conditions allow their outgrowth. Eradication of disseminated cancer cells would prevent metastasis in high-risk patients. We developed mouse models of latent metastasis using cancer cells from early-stage lung and breast tumors. These models allow us to define mechanisms that suppress the outgrowth, support the long-term survival, and enable the eventual outbreak of latent metastatic cells. These cells have stem cell-like properties imparted by SOX2 and SOX9 lineage-determining transcription factors. We refer to these cells as metastatic stem cells (MetSCs). MetSCs reside in perivascular niches. By avoiding WNT growth stimuli and responding to TGF-β in this context, MetSCs can self-impose a slow-cycling state that evades immune surveillance by NK (natural killer) cells. Latent MetSCs frequently enter the cell cycle, but are cleared by NK cells unless the proliferating MetSCs gain additional immune evasive capacities. Thus, metastatic latency can be a highly dynamic state, in which frequent attempts by disseminated MetSCs to reinitiate outgrowth are thwarted by immune surveillance. Outbreaks have additional organ-specific as well as general requirements. Spreading of MetSCs on capillaries via the cell adhesion molecule L1CAM is required for metastatic outgrowth in lung, bone, brain and liver. Organ-specific colonization traits include, among others, the expression of osteoclast mobilizing factors in bone metastasis, monocyte-binding receptors in lung metastasis, carcinoma-astrocyte gap junctions in brain metastasis, and choroid plexus disruption in leptomeningeal metastasis. An understanding of latent metastasis should is yielding therapeutic strategies for the prevention of overt metastasis.