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From intravital microscopy to systems view: Tumor cell motility in microenvironment context.

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During the metastasis, tumor cells move through the primary tumor and enter blood vessels (1). Tumor cell motility has been previously investigated in details in vitro and the signaling pathways which control locomotion in 2D or invadopodia formation, which results in extracellular matrix degradation and penetration, have been dissected (2,3). However, the conditions for the onset of such movements in vivo are not yet fully understood. Using multiphoton-based intravital microscopy we previously reported that the vicinity of macrophages (4) or blood vessels (5) is essential for tumor cell locomotion to occur in primary breast tumors. Yet other studies have demonstrated that the changes in stiffness (6) and architecture (7) of extracellular matrix may lead to increased motility and subsequently, metastasis. However, each of these factors has been studied separately and no attention was given to their combinatorial effect. Here we show that multiparametric, systems-level analysis is vital to predict tumor cell motility-related behaviors in vivo. Our analysis reveals the context in which invadopodia or tumor cell locomotion appear in vivo. Direct link was found between invadopodia number and lung metastasis. To predict invadopodium formation, which leads to intravasation, we conclude, microenvironmental conditions must be studied in concert rather than in isolation. Furthermore, future development of diagnostic markers for early metastasis will most likely necessitate such multiparametric analyses.

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