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ECM Organization and Cell-Cell Cooperation

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Single-cell or collective invasion results from coordination of cell shape, deformability and actin dynamics relative to the tissue environment. In monomorphic 3D invasion models in vitro, an obligate step of collective invasion is the degradation of extracellular matrix (ECM). Thereby, the density of the ECM determines the invasion mode of mesenchymal tumor cells. Whereas fibrillar, high porosity ECM enables single-cell dissemination, dense matrix induces cell-cell interaction, leader-follower cell behavior and collective migration as an obligate protease-dependent process. Conversely, in vivo monitored by intravital multiphoton second and third harmonic generation microscopy, tissue microniches provide invasion-promoting tracks that enable collective migration along tracks of least resistance. As main routes, non-destructive contact-guidance is mediated by preformed multi-interface perimuscular, vascular and –neural tracks of 1D, 2D and 3D topography. Consistently, spheroids of mesenchymal melanoma or sarcoma tumor cells switched from single-cell to collective invasion modes when confronted with 3D collagen matrices of increasing density, including gain of cell-to-cell junctions, supracellular polarization, suggesting cell jamming imposed by tissue confinement. Targeting of beta1/beta3 integrins induces unexpected plasticity of invasion, including collective and amoeboid single-cell dissemination, followed by enhanced micrometastasis, implicating a role of integrins in cell-cell cooperation and integrin-independent dissemination as effective route to metastasis. In conclusion, cancer invasion is maintained by physicochemical programs that balance cell-intrinsic adhesion and mechanocoupling with encountered physical space and molecular cues.