Abstract

Collective invasion is a key mechanism by which tumors disseminate and metastasize, involving coordinated migration of heterogeneous cell populations. Experimental studies in spheroid-based assays have identified specialized leader and follower cells that work together during this process, but the biophysical rules governing their interaction remain unclear. We present a mechanistic, cell-based computational model using the Cellular Potts framework to investigate how heterotypic adhesion, leader motility, and follower proliferation jointly shape invasion. Leader–follower tumors were simulated across **13310** parameter sets, and invasion was quantified by invasive and infiltrative areas, finger-like protrusions, solitary defectors, and detached clusters. From these simulations, we identified four distinct invasion phenotypes: non-invasive, bulk collective, single-cell, and multimodal. Multimodal invasion—the coexistence of cohesive strands, solitary cells, and small clusters—emerged as the most prevalent phenotype, particularly under moderate adhesion, high motility, and intermediate proliferation. Proliferation exhibited nonlinear effects: moderate division reinforced cohesive invasion, whereas excessive growth destabilized tumor architecture. Mapping outcomes across the parameter space revealed sharp transitions between invasion modes, underscoring trade-offs between adhesion and motility in shaping invasion complexity. Our results show that hybrid invasion behaviors, previously considered rare, arise robustly from simple mechanical rules and are favored in a broad region of the parameter space. This framework reconciles binary models of invasion with experimental observations of heterogeneity, providing predictive insights into how modulating adhesion, motility, or proliferation can restrict metastatic spread.