Natural selection under the go-or-grow dichotomy leads to the emergence of phenotypic and genetic heterogeneity

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Cancer is a significant global health issue, with treatment challenges arising from genetic and phenotypic heterogeneity in tumors. In this study, we examine the complex relationship between evolutionary processes and phenotypic plasticity, specifically focusing on the interplay between cell migration and proliferation. Our novel cellular automaton model takes into account the movement, growth, and death of cells, as well as a change between mobile and growing states controlled by inherited and mutation-driven genotypes and the cells' microenvironment, specifically the local cancer cell density. We observe that cells at the tumor edge evolve to favor migration over proliferation and vice-versa in the tumor bulk. However, we show that this phenotypic heterogeneity can be realized by completely distinct regulations of the phenotypic switch, and that parameters such as the apoptosis rate determine which go-or-grow strategy is most effective. We estimate the transition between the different evolutionary regimes using a mean-field approximation of the evolutionary dynamics. This new approach demonstrates that a specific pattern of phenotypic heterogeneity can result from different cell decision making processes that need to be distinguished in different microenvironments. It also indicates that equating phenotypic traits and genotype in theoretical models can hide the underlying complexity of the cell decision-making process required to produce any observed phenotypic heterogeneity. We expect that the explicit incorporation of decision-making processes in evolutionary models can shed light on various topics in the field of tumor ecology and evolution, such as the plasticity of metabolism, cell migration, and treatment resistance in the future.