Population dynamics of mutagenic phenotypes in the tumour microenvironment

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The role of the tumour microenvironment in the early stages of cancer initiation remains poorly understood. We investigate its potential role using a model inspired by an attractor landscape view of cellular phenotypes. Cell types are regarded as stable minima of a quasi-potential function that harbours additional spurious minima, some of which may be deleterious. The subset of spurious phenotypes with mutagenic potential is hypothesized to be a precursor to the emergence of cells with cancer driver mutations. Stochastic transitions between healthy and mutagenic minima leads to mutation accumulation in the population. Accordingly, the role of tumour microenvironment signalling is of particular interest, as evidence suggests tumour signals may amplify the transition rate from healthy to spurious cell types. We present a three-state ODE model which formalizes these hypotheses and allows us to investigate their roles in cancer initiation. Analysis of our model reveals that cell type-dysregulating tumour signals allow tumours to establish even if they grow much more slowly than healthy cells, and with mutation rates that are orders of magnitude lower than what is needed in the absence of signalling. This suggests that blocking pro-tumour microenvironment signals alone (i.e. without direct targeting of tumour cells) is a viable strategy to inhibit tumour development and progression.