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TUMOUR HETEROGENEITY

That's the theory

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A new model published as a Theory paper in *Cell* indicates that breast cancer cells with a stem cell phenotype can arise from differentiated luminal or basal cells to re-establish phenotypic equilibrium within a cell population.

Piyush Gupta, Eric Lander and colleagues investigated cell phenotype dynamics in two breast cancer cell lines, SUM149 and SUM159, using well-established cell surface markers and gene expression analyses for basal, luminal and stem cell populations. Having established that SUM159 cells are predominately basal (with some luminal and stem cells), and that SUM149 cells are mainly luminal with a minority of basal and stem cells, the first question they addressed was whether there is interconversion between the cell phenotypes. SUM149 and SUM159 cells were sorted (using fluorescence-activated cell sorting) into their different phenotypes to >96% purity, and each phenotypic subpopulation was cultured for 6 days. During this time the sorted cell subpopulations rapidly converged towards the phenotypic equilibriums that were seen in the parental cells. The proliferation rates between each cell phenotype did not markedly differ, and, as the cells that were in a minority would need to divide rapidly to re-establish equilibrium, it seems that interconversion between cell phenotypes is probable.

To examine this further the authors constructed a mathematical model of the possible cell transitions and included the assumption that the conversion probabilities of a cell depend on its current state and not its prior states. Use of such a 'Markov' model meant that the authors could use their *in vitro* data as defined outcomes for the model and then use the model to predict the conversions that were most likely to have occurred to achieve this outcome.

Perhaps of most interest was that the model indicated that both luminal and basal cells could give rise to stem cells in order for the sorted subpopulations to reinstate the parental phenotypic equilibrium. To test this, the authors injected the phenotypically sorted cell subpopulations into mice. As expected, only the stem cell fraction gave rise to tumours. However, the authors hypothesized that the predominately luminal and basal subpopulations did not survive long enough to re-establish population equilibrium and with it a stem cell population. To address this they injected the basal, luminal or stem cell subpopulations with irradiated carrier cells as a means to increase cell survival, and under these conditions all three subpopulations gave rise to tumours.

To examine the effect of cancer therapies on phenotypic equilibrium, the authors treated SUM149 and SUM159 cells with either paclitaxel or 5-fluorouracil *in vitro*. These drugs increased the number of stem cells in both cell lines and increased luminal cell numbers in SUM159 cells and basal cell numbers in SUM149 cells. Additional mathematical analyses that took into account the survival of each subpopulation and the phenotypic interconversion rates indicated that the SUM149 stem cell subpopulation is resistant to paclitaxel. Under these conditions the surviving stem cells will give rise to basal cells, which explains the fivefold increase *in vitro* of both the stem and basal cells, but which clearly shows that the basal cells are not resistant to this drug.

This model has many implications for tumour heterogeneity. First, the *de novo* generation of cancer stem cells implies that simply targeting a cancer stem cell population will not necessarily prevent tumour recurrence. Second, it indicates that we need to understand much more about how 'differentiated' cells can transition into a more primitive state. Last, it indicates that understanding the probable transitions between cell phenotypes in a given tumour population might help us to better understand drug resistance and tumour evolution.

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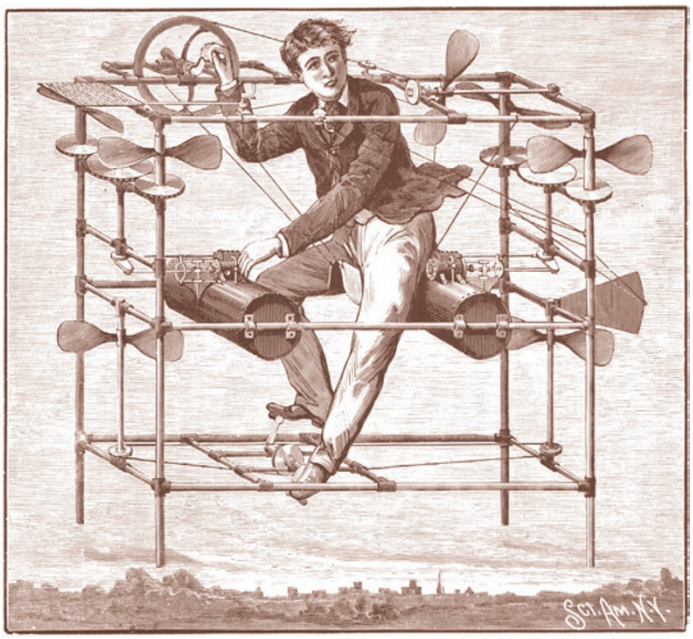

ORIGINAL RESEARCH PAPER Gupta, P. B. *et al.* Stochastic state transitions give rise to phenotypic equilibrium in populations of cancer cells. *Cell* **146**, 633–644 (2011)