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Relating Single Cell Heterogeneity To Genotype During Cancer Progression

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Progression of normal cells towards cancer is driven by a series of genetic changes. Traditional population-averaged measurements have found that cell signalling activities are increasingly altered during this progression. Despite the fact that cancer cells are known to be highly heterogeneous, the response of individual pathways to specific genetic changes remains poorly characterized at a single cell level. Do signalling alterations in a pathway reflect a shift of the whole population, or changes to specific subpopulations? Are alterations to pathways independent, or are cells with alterations in one pathway more likely to be abnormal in another due to crosstalk? We are building a computational framework that analyzes immunofluorescence microscopy images of cells to identify alterations in individual pathways at a single-cell level. A primary novelty of our approach is a "change of basis" that allows us to understand signalling in cancer cells in terms of the much better understood patterns of signalling in normal cells. This allows us to model heterogeneous populations of cancer cells as a mixture of distinct subpopulations, each with a specific combination of signalling pathways altered beyond the normal baseline. We used this framework to analyze human bronchial epithelial cell lines containing a series of genetic modifications commonly seen in lung cancer. We confirmed expected trends (such as a population-wide epithelial mesenchymal transition following the last of our series of modifications) and are presently studying the relation between the mutational profiles of cancer cells and pathway crosstalk. Our framework will help establish a more natural basis for future investigations into the phenotype-genotype relationship in heterogeneous populations.