

Biological Noise and the Heterogeneity of Cancer Cell Traits

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HETEROGENEITY of cell phenotypic core traits within functionally homogenous cell populations (e.g., tissues, cell lines) poses an important challenge to modelers and experimentalists alike. Regardless of its source (genetics, epigenetics, signaling noise), this heterogeneity has implications for normal and pathologic tissue organization in at least two conflicting respects: i) correct function of a cell ensemble may be endangered by high levels of heterogeneity with respect to key cell traits; ii) on the other hand, adequate levels of cell-to-cell variability may be crucial for the response of cell ensembles to microenvironmental stress. The balance of these two opposite forces needs to be quantified and represented in mathematical models in order to extract realistic principles of multicellular tissue function and organization. Recently, High Content Automated Microscopy has begun to provide a powerful experimental tool for measuring trait heterogeneity at the single-cell level (Quaranta et al., *Methods in Enzymology*, vol. 467, 2009). As an example, we are evaluating cell-to-cell variability of motility within cancer cell lines by measuring motility in 500-2,000 cells/cell line in one experiment. Cell-to-cell variability of spontaneous, non-directed motility in cancer (AT1 and CA1d) versus non-cancer (MCF10A) breast epithelial cell lines was evaluated with respect to speed, step-length, motile cell fraction and a novel metric, Instantaneous Motion Fraction, under two culture conditions, full or serum/EGF-depleted media. Intrinsic speed fluctuation was greater in cancer cells, and increased in depleted media. The range of cell-to-cell speed variability was also greater in cancer cell lines, and likewise expanded in depleted media. Regardless of conditions, only a minority of cells was highly motile in any cell line. The motile cell fraction was highly variable across experiments in cancer cells. Changes in persistence time did not differ among cell lines, but a novel metric, Instantaneous Motion Fraction increased significantly in cancer cells in depleted media. In spite of this widespread variation, cell step-lengths appeared to be organized around a power-law distribution, suggesting the possibility of stabilizing mechanisms (perhaps both intrinsic and extrinsic to cells) that dampen variation and may be deregulated in cancer cells. Quantifying single-cell traits opens avenues to address the long suspected role of heterogeneity in cancer, especially in clonal selection and cell adaptation during cancer progression.