317f Metabolic Flux Analysis of Tumor Evolved Breast Cells: Effect of Estrogen Stimulation and Comparison to Normal Cells

Adam L. Meadows, Douglas S. Clark, and Harvey W. Blanch

The metabolism of cancer is known to be aberrant with respect to non-cancerous tissue in several aspects. For example, cancer cells often exhibit high rates of aerobic glycolysis and show increased flux into the pentose phosphate pathway. One traditional explanation for these metabolic phenomena postulates that the faster growth rate of cancer cells requires this altered phenotype to supply of increased energy and growth associated metabolites. We explore this hypothesis by comparing the flux profiles of normal and cancerous breast epithelial cells growing at various rates. These profiles were determined by adapting the well-developed metabolic flux analysis methodology to anchorage dependent mammalian cell lines. Cell culture media containing 1-^{13}C glucose was supplied as the primary carbon source and subsequent ^{13}C detection in cellular metabolites was quantified by NMR and GC-MS. Our results indicate that when the breast cancer cells are manipulated to grow at half the rate of normal cells, they exhibit extracellular glucose and lactate fluxes approximately an order of magnitude smaller than the normal cells. When the growth rate of the cancer is stimulated with estrogen to equal that of the normal cells, the extracellular glucose and lactate fluxes are nearly identical on a per mass basis. Regardless of growth rate, breast cancer cells shunt a much higher fraction of glucose carbons into the pentose phosphate pathway. This implies that this metabolic decision may not be strictly growth related and is instead perhaps due to evolutionary adaptations made in response to the tumor microenvironment. A comprehensive flux network comparison will be presented and strategies for preferentially inhibiting cancer cell growth by enzyme inhibition and/or nutritional modifications will be addressed.