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Transforming growth factor-beta 1- and insulin-dependent regulation of carcinogenic transformation is in line with proteome profiling and identification of TGF beta and insulin as keynodes of carcinogenic transformation of MCF7 cells

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Glucose, insulin and transforming growth factor-beta (TGFb) are potent regulators of cell functions. We explored effects of glucose, insulin and TGFb1 on human conditionally tumorigenic breast epithelial cells MCF7. To identify the most affected carcinogenic transformation-related cellular function, we performed cell contact inhibition, proliferation, spheroid formation and migration assays. We have also performed a proteome profiling of MCF7 cells undergoing carcinogenic transformation. Systemic analysis of our proteomics data showed that TGFb and insulin signalling are among key regulatory pathways affected in transformation of MCF7 from conditionally tumorigenic into invasive cells. We observed that the high level of glucose and insulin promoted growth and loss of contact inhibition, as observed by overgrowth of cells. Treatment of the cells with TGFb1 led to inhibition of cellular growth and counteracting of the insulin effect. Migration and spheroid formation by MCF7 cells were also affected in the same way, notably, insulin enhanced and TGFb1 inhibited these activities. We observed that the mechanism of interaction between glucose- and TGFb1-dependent mechanisms on cells may include a Smad3/CAGA element-dependent transcriptional regulation, and transcriptional regulation and expression of PAI-1. Thus, we report that TGFb1 counteracted glucose- and insulin-dependent stimulatory effects on MCF7 cells proliferation, loss of contact inhibition, spheroid formation and migration. TGFb and insulin were identified as keynodes in the regulatory network which was built with proteins identified upon proteome profiling of transformation of MCF7 cells. We identified 150 proteins which change their expression upon acquisition of invasive phenotype by MCF7 cells (parental MCF7 vs invasive MCF7 clone c46). We also identified 302 proteins with different expression in invasive MCF7c46 and metastatic MDA-MB-231, and 279 proteins with different expression in non-invasive parental MCF7 and MDA-MB-231 cells. These combinations showed that the invasiveness signature may contain less than 100 proteins, with TGFb and insulin among the keynodes of the proteome-dependent network. Thus, the cell based assays, reporter assays and proteome profiling of MCF7 cells showed that TGFb and insulin signaling are indeed crucial regulators of carcinogenic transformation.

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