506e Topology and Dynamics of Pro-Mitogenic B-Catenin Signaling in Mammary Epithelial Cells

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Quantitative engineering analysis is required to understand how an intricate network of intracellular signaling pathways regulates cell proliferation. Recently, we reported on a novel system in non-cancerous mammary epithelial cells where extracellular cues, including epidermal growth factor, stimulate proliferative signaling through β-catenin, an intracellular protein that participates in transcription of cell cycle genes when localized to the nucleus. Here, we report on the topology and dynamics of the signaling network through which these extracellular cues regulate β-catenin-mediated transcription in the nucleus. We first demonstrate that even in the presence of stimuli which trigger β-catenin signaling, the majority of cellular β-catenin is signaling incompetent by virtue of being sequestered at the plasma membrane. The small fraction of cellular β-catenin that is signaling-competent is affected by several factors, including de novo β-catenin synthesis, decreased flux through a degradation pathway, and decreased stability of the β-catenin degradation complex, all operating on dissimilar time scales ranging from minutes to hours. Using a suite of pharmacological inhibitors, we dissected which upstream signaling pathways control these biochemical phenomena, and uncovered synergistic crosstalk between divergent pathways on the β-catenin degradation pathway. Taken together, this data suggests a complex network of intracellular signaling pathways which regulate β-catenin signaling, and thus proliferation, in non-cancerous epithelial cells.