Modelling wnt signaling and colon cancer

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MOST colon cancers are associated with the truncation of the tumor suppressor gene apc. Although the cell physiology and biochemistry associated with apc are still far from clear, initial measurements indicated that apc regulates the intracellular concentration of β-catenin and consequently, its sub-cellular distribution. Indeed the canonical wnt signaling involves receptor mediated inhibition of GSK3β, a reduction in phosphorylation of β-catenin, and so a reduction in apc/axin mediated proteosomal degradation of phospho-β-catenin, and a consequential increase in cytosolic and nuclear β-catenin. Many of the initial experimental reports have studied transfected proteins and cell lines not closely related to colonic cells. We have studied the concentrations and distribution of E-cadherin, β-catenin (and its phospho-isoforms), GSK3β, axin and apc in several epithelial and colonic cell lines. We are measuring the responses of these proteins to wnt signaling. Our initial data indicate wnt induced changes to the E-cadherin/β-catenin complex at the membrane and relocalization of a sub-population of β-catenin to cytosolic structures. In colonic epithelial cells we have not detected a significant wnt induced change in the cellular levels of β-catenin nor an increase in destruction of β-catenin in the absence of wnt signaling. Significant wnt induced increases in the nuclear localization of β-catenin only occur in the absence of cell surface cadherins and involve processes other than the truncation of apc. We are developing a quantitative model to simulate the time dependent effects of wnt signaling and apc truncation on the concentration and distribution of β-catenin isoforms in normal and neoplastic colonic cells.