Title: Differentiation factors as tumor suppressors: Notch/Atoh1 pathway in colon cancer.

Abstract: Loss of cellular differentiation is one of the hallmarks of cancer; in colorectal cancer (CRC), a reduction in mucin producing goblet cells is frequently observed. We have previously identified the transcription factor ATOH1 as a critical gatekeeper for the program of Notch-directed intestinal epithelial differentiation. In this model, Notch and ATOH1 activities counterbalance to select absorptive (colonocyte) or secretory (goblet, enteroendocrine) cell fates. We found that ATOH1 is silenced in ~80% of human CRCs, by both CpG island methylation and genomic microdeletion. In several mouse CRC models, mutation of Atoh1 enhances CRC tumorigenesis. Other investigators found that Notch activity is high in human CRCs, where it promotes tumorigenesis. Inhibiting Notch activity with γ-secretase inhibitors (GSI) increased ATOH1 and goblet cell production and reduced proliferation. However, Atoh1-mutant tumors showed no response when treated with GSI. ATOH1-regulated genes include transcription factors such as SPDEF, which controls terminal differentiation of goblet cells. SPDEF is coordinately silenced with ATOH1 in CRC. Furthermore, SPDEF functions as a tumor suppressor in mouse models of CRC, where loss of SPDEF increases tumor burden, while its re-expression prevents tumor growth. Our results suggest that Notch exerts its effects on CRCs coordinately with ATOH1. In most human CRCs, silencing of ATOH1 promotes tumorigenesis and will prevent a chemotherapeutic response to Notch inhibitors. Therapeutic targeting of factors downstream of ATOH1 such as SPDEF may succeed in tumors that have silenced ATOH1. This work supports the concept of using differentiation factors as targets for cancer treatment.