A hypermorphic epithelial \(\beta\)-catenin mutation facilitates intestinal tumorigenesis in mice in response to compounding WNT-pathway mutations.

Abstract:
Activation of the Wnt/\(\beta\)-catenin pathway occurs in the vast majority of colorectal cancers. However, the outcome of the disease varies markedly from individual to individual, even within the same tumor stage. This heterogeneity is governed to a great extent by the genetic make-up of individual tumors and the combination of oncogenic mutations. In order to express throughout the intestinal epithelium a degradation-resistant \(\beta\)-catenin (Ctnnb1), which lacks the first 131 amino acids, we inserted an epitope-tagged \(\beta(N^{1-131})\)-\(\beta\)-catenin-encoding cDNA as a knock-in transgene into the endogenous gpA33 gene locus in mice. The resulting gpA33(\(\beta\)-Bcat) mice showed an increase in the constitutive Wnt/\(\beta\)-catenin pathway activation that shifts the cell fate towards the Paneth cell lineage in pre-malignant intestinal epithelium. Furthermore, 19% of all heterozygous and 37% of all homozygous gpA33(\(\beta\)-Bcat) mice spontaneously developed aberrant crypt foci and adenomatous polyps, at frequencies and latencies akin to those observed in sporadic colon cancer in humans. Consistent with this, the Wnt target genes, MMP7 and Tenascin-C, which
are most highly expressed in benign human adenomas and early tumor stages, were upregulated in pre-malignant tissue of gpA33(?N-Bcat) mice, but those Wnt target genes associated with excessive proliferation (i.e. Cdh11, myc) were not. We also detected diminished expression of membrane-associated ?-catenin and increased intestinal permeability in gpA33(?N-Bcat) mice in challenge conditions, providing a potential explanation for the observed mild chronic intestinal inflammation and increased susceptibility to azoxymethane and mutant Apc-dependent tumorigenesis. Collectively, our data indicate that epithelial expression of ?N(1-131)-? catenin in the intestine creates an inflammatory microenvironment and co-operates with other mutations in the Wnt/?-catenin pathway to facilitate and promote tumorigenesis.