Braf mutation induces rapid neoplastic transformation in the aged and extensively hypermethylated intestinal epithelium

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Methods

We used an inducible model of Braf mutation to direct recombination of the oncogenic Braf V637E allele to the murine intestine. This induces morphological changes reminiscent of human serrated neoplasia (Figure 1)

Braf mutation was activated at wean and after periods of aging, and histological, DNA methylation, and gene expression analysis was performed thereafter.

Results

Aging and the Braf mutation induce DNA methylation alterations

- Braf was activated at wean and animals sacrificed at timepoints between 2 and 18 months thereafter
- DNA methylation profiling of > 2 million CpG sites revealed marked age associated alterations, some of which were accelerated by exposure to Braf

Braf mutation induces widespread hypermethylation (Figure 2).

DNA methylation targeted WNT signalling regulatory genes (P<0.0001).

Activating Braf in the aged intestine induces neoplastic transformation

- As DNA methylation is important for serrated neoplasia and DNA methylation occurs with aging (Figure 2), we hypothesised that aged animals may be prone to rapid neoplastic transformation.
- We activated Braf at wean (n=24) and after 9 months of aging (n=32) and sacrificed animals five months thereafter. We histologically assessed the entire lower GI tract.
- In the aged, but not the young intestine, Braf mutation induces rapid neoplastic transformation (Figure 3).

Conclusions

Braf mutation can induce rapid neoplastic transformation in the aged and extensively aberrantly methylated intestinal epithelium. This shifts the current paradigm, where risk is thought to correlate with the length of time since SSL initiation, to one depending on the age of the patient at onset. Age-associated DNA methylation occur in the intestinal epithelium, and these are potentiated by Braf mutation, and target pathways that are pertinent to colorectal neoplasia.