correlations in colorectal cancer (CRC). We have recently compared two mouse polyposis models (*Apc*^{Min} and *Apc*^{1322T} mice) to demonstrate that 'just-right' levels of wnt signalling underpin the severity and distribution of lesions in mouse intestinal neoplasia. We have also shown that human *APC* mutation spectra varies according to the anatomical distribution of colorectal lesions. We hypothesise that an intestinal gradient of wnt signalling and stem cell number may influence optimal mutation spectra selection.

Methods Wnt target gene activity in individual small intestinal and colonic whole mount crypts was assessed using qRT-PCR. Stem cell number was counted using in-situ hybridization for *Lgr5*. The regional intestinal effect of increased wnt signalling was examined in the mouse using a stabilized beta catenin transgenic model (*Villin-CreERT2; Catnb*$^{lox(ex3)/lox(ex3)}$) and the human by comparing upper gastrointestinal (UGI) and colonic *APC* mutation spectra in FAP and sporadic CRC patients.

Results Wnt target gene activity and stem cell number were greatest in the proximal small intestine (SI) decreasing steadily through to the colon. The *BMP2* gradient was inversely correlated. The stabilized beta catenin transgenic mice had a striking phenotype with lesion distribution mirroring this gradient. Human FAP associated UGI *APC* mutations retained more beta-catenin binding 20 amino-acid repeats (AAR) than the same patient's colonic lesions. Sporadic CRC lesion distribution tended to vary according to the number of 20AAR's retained with left sided lesions requiring fewer 20AAR's than right sided.

Conclusion The 'just right' hypothesis proposes a threshold of wnt signalling should be reached but not exceeded in order for polyp formation to occur. We have demonstrated a physiological SI to colonic gradient of wnt signal and stem cell number. Thus the wnt signal threshold gap varies throughout the intestinal tract. Beta-catenin stabilization in the mouse provides sufficient wnt signal perturbation to initiate tumour formation in the small intestine but is insufficient in the colon. The physiological wnt gradient determines the distribution of sporadic and polyposis-associated tumours by selecting for the optimal mutation spectra in each lesion – thus left sided lesions select for common mutations that provide a greater wnt perturbation than their more proximal counterparts.

Competing interests None.

Keywords carcinogenesis, 'just right' hypothesis, stem cells, wnt signalling.

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HUMAN AND MOUSE GASTROINTESTINAL TUMOUR DISTRIBUTION IS SELECTED ACCORDING TO A BASAL INTESTINAL WNT SIGNALLING GRADIENT

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Introduction It is established that *Adenomatous polyposis coli (APC)* mutations occur non-randomly with respect to each other, resulting in characteristic genotype-phenotype