

P026 Intestinal adenoma progression due to loss of imprinting of *Igf2* is suppressed by a soluble IGF2 receptor

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Insulin-like growth factor II (IGF-II) is a potent promoter of growth in embryos and tumours. Expression of *Igf2* is controlled by genomic imprinting, with the paternal allele expressed. The maternal allele is silenced because of the impact of differentially methylated regions (DMR) that modify enhancer promoter interactions. In humans, 10% of the population are bi-allelic expressers of *IGF2*, which has been correlated to increased colorectal cancer susceptibility (Feinberg). IGF2R sequesters IGF-II, binds several ligands including mannosylated proteins and latent TGF β 1, and mutations occur in HNPCC. The effects of gene dosage were evaluated in the *Apc^{Min/+}* mouse. Co-isogenic crosses between mice with differential allelic expression of *Igf2* (nullizygous, monoallelic paternal allele, and biallelic expression due to disruption of *H19* DMR) with *Apc^{Min/+}* were dissected at 120 days. Bi-allelic *Igf2* resulted in increased colonic adenoma ($p < 0.005$) with histological features of carcinoma, and increased size of adenoma in the small intestine with features increased dysplasia. Expression of a full length soluble IGF2R protein using a keratin 10 promoter driven transgene rescued this increase in adenoma progression. This data supports the human observational studies that correlate differential allelic supply of *Igf2* as a modifier of adenoma progression, and identifies soluble IGF2R as a potential targeted therapeutic.