

P013 Truncating APC mutations have dominant effects on proliferation, spindle checkpoint control, survival and chromosome stability.

Tighe A, Johnson VL, Taylor SS.

Faculty of Life Sciences, University of Manchester, The Michael Smith Building, Oxford Road, Manchester, M13 9PT, UK

The majority of human tumour cells are aneuploid owing to an underlying chromosome instability phenotype (CIN). While the genetic lesions that cause CIN remain undefined, mouse ES cells harbouring homozygous adenomatous polyposis coli (APC) mutations are frequently tetraploid. In addition, colon cancer cells with APC mutations have weakened kinetochore-microtubule interactions. Furthermore, mitotic spindles assembled in APC-depleted *Xenopus* egg extracts are aberrant. Therefore, to determine whether APC mutations can initiate chromosome instability in human cells, we expressed N-terminal APC fragments in HCT-116 cells, a near diploid colon cancer cell line with two wild-type APC alleles. We show that cells expressing N-APC mutants exit mitosis prematurely in the presence of spindle toxins, consistent with a spindle checkpoint defect. In addition, N-APC cells show enhanced survival following prolonged spindle damage. In contrast to controls, the N-APC survivors frequently contain dicentric chromosomes and then go on to become highly aneuploid. These observations suggest that truncating APC mutations can exert dominant effects which in turn can initiate CIN. As such, APC mutation not only compromises tumour suppressor function but may also have oncogenic properties. We suggest therefore that the initial APC mutation acts as a 'double whammy', destabilising the genome and setting the stage for deregulated proliferation upon loss of the second APC allele.