Nature Reviews Cancer | AOP, published online 16 September 2010; doi:10.1038/nrc2938

TUMOUR PROGRESSION

Disease connections

There is increasing evidence to suggest that the Parkinson's disease susceptibility genes are also associated with cancer. Indeed, patients with Parkinson's disease seem to have an increased risk of developing melanoma. Mark Arends and colleagues now show that *PARK2*, the loss of which causes autosomal recessive juvenile Parkinson's disease, is a haploinsufficient suppressor of colorectal cancer (CRC).

Large amplifications and deletions on specific chromosomes are one characteristic of CRC. Arends and colleagues investigated whether smaller chromosomal alterations might also be associated with CRC and could be used to identify susceptibility genes. Analyses of more than 100 primary CRC samples and previously published data sets revealed that small copy number losses were common to chromosome 6q26, which encodes *PARK2*. They also found small deletions of the *PARK2* promoter as well as others that also covered the adjacent *PARK2* co-regulated (*PACRG*) gene. In total, 33 of 100 sporadic CRC samples had copy number losses affecting *PARK2*: most of these were heterozygous deletions, point mutations were rarely found and there was some evidence of hypermethylation of the *PARK2* promoter. Real-time quantitative PCR revealed that *PARK2* transcript levels were reduced in tumour samples with allelic losses at chromosome 6q26, and this correlated with reduced PARKIN (the protein product of *PARK2*) expression.

So, is *PARK2* loss important for CRC development? The authors analysed published transcriptional profiles from microdissected CRC samples and found that the reduced expression of adenomatous polyposis coli (*APC*) — a tumour suppressor commonly mutated in CRC — correlated with reduced *PARK2* expression, indicating that the expression of both genes is coordinately downregulated in CRC. The authors found that overexpression of PARKIN in CRC cell lines reduced proliferation and that this was significantly more pronounced in *APC*-deficient cell lines. Next, the authors studied $Park2^{+/-}$ mice and found that they did not develop intestinal adenomas; however, crossing with $Apc^{Min/+}$ mice (which do develop adenomas) increased the prevalence of adenomas fourfold compared with $Apc^{Min/+}$ mice. The remaining wild-type *Park2* allele was not lost in the adenomas that formed, suggesting that *Park2* is a haploinsufficient tumour suppressor.

CORBIS

PARK2 loss has also been observed in ovarian, breast and lung carcinomas, and glioblastoma, indicating that its role as a tumour suppressor might not be specific to colon epithelium. It will be intriguing to identify the underlying mechanisms that connect PARKIN, an E3 ubiquitin ligase, to tumour suppression.

Gemma K. Alderton

“There is increasing evidence to suggest that the Parkinson's disease susceptibility genes are also associated with cancer.”

ORIGINAL RESEARCH PAPER Poulogiannis, G. *et al.* *PARK2* deletions occur frequently in sporadic colorectal cancer and accelerate adenoma development in *Apc* mutant mice. *Proc. Natl Acad. Sci. USA* **107**, 15145–15150 (2010)