TUMOUR SUPPRESSORS

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URLs

Neuroblastoma
http://www.cancer.gov/cancertopics/types/neuroblastoma/

Chd5
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=26038

ARF
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1029

INK4a
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1029

In 1977 a deletion of chromosome 1p was described in human neuroblastoma. Since then deletions in 1p36 have been shown to be a common event in advanced tumours, and much evidence has suggested that a tumour-suppressor gene resides at this location. Now, Alea Mills and colleagues have identified the suppressor in residence.

Mills and colleagues made use of chromosome engineering to generate mice with deletions (*df*; decreased expression) or duplications (*dp*; increased expression) of the mouse chromosome region that corresponds with human 1p36. Heterozygous *df* mice developed normally, but *dp* heterozygous newborns were not obtained owing to severe developmental defects and increased levels of apoptosis that resulted in perinatal lethality. Indeed, *dp* heterozygous mouse embryonic fibroblasts (MEFs) had a reduced proliferative capacity and senesced *in vitro*. By contrast, *df* heterozygous MEFs had increased rates of proliferation and spontaneously underwent immortalization *in vitro*, and *df* heterozygous adult mice developed hyperplasia in a number of tissues and were prone to spontaneous tumours. *dp*;*df* embryos were viable with no obvious defects, indicating that a change in gene dosage is responsible for the heterozygous phenotypes.

The deregulation of proliferation, apoptosis and senescence indicated that the p53 pathway might be involved, and this was confirmed by the authors — the *dp* heterozygous phenotype was rescued by a p53-null background, and p53 function was compromised in *df* heterozygous MEFs and increased in *dp* heterozygous MEFs. With this information, the authors were able to assess which genes within 1p36 were most likely to affect cell proliferation. Knockdown of the expression of the most probable candidates using short hairpin RNAs was used to see if any could rescue the *dp* heterozygous phenotype. One gene was able to do this — chromodomain helicase DNA binding protein 5 (*CHD5*). They verified that CHD5 can regulate p53 and can also suppress transformation by oncogenic Ras. Increased Ras activity activates both the ARF (an activator of p53) and INK4a tumour-suppressor pathways, but the expression of these proteins was reduced in *df* heterozygous MEFs and in cells deficient for *Chd5* expression. Moreover, knockdown of *Arf* enabled the proliferation of *dp* heterozygous MEFs.

Is CHD5 a tumour suppressor? MEFs that do not express CHD5 formed tumours in immunocompromised animals much like the *df* heterozygous MEFs. Moreover, analysis of human brain tumours indicated that CHD5 expression is reduced in tumours that have a deletion of 1p36.32 and 1p36.22 (where *CHD5* maps to) compared with brain tumours that do not have this deletion or with normal brain tissue.

Regulation of the INK4a–ARF locus by proteins that remodel chromatin has been shown previously, however, CHD5 might be the first chromatin remodelling protein to be implicated in tumour suppression.

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ORIGINAL RESEARCH PAPER Bagchi, A. *et al.* *CHD5* is a tumour suppressor at human 1p36. *Cell* **128**, 459–475 (2007)