URLs
Rb1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen
e&cmd=Retrieve&dopt=full_report&list_uids=19645
Trp53
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen
e&cmd=Retrieve&dopt=full_report&list_uids=22059

The road less travelled

Few would argue that the path to scientific discovery is short and simple. The realization that cancer could arise through the inactivation of recessive genes — tumour suppressors — is a case in point.

Throughout the 1970s and 1980s, oncogenes dominated the field of cancer research, and so the prevailing thought was that tumours were caused by activating mutations. The famous two-hit hypothesis was also finding increasing support (see **Milestone 9**), but lacked insights into the nature of the hits.

Perhaps the strongest impetus to pursue the unorthodox idea of tumour suppressor genes was provided by Henry Harris and colleagues, who observed that normal mouse cells were dominant to malignant cells when the two types were fused in the laboratory. This conceptually simple yet technically demanding work pierced the first hole in the theory that (dominant) oncogenes were the general rule.

While many scientists had previously presented support for a model of allelic loss (see Further Reading), it was David Comings who, in 1973, articulated a general framework for a role of tumour suppressor genes in all types of cancer: inherited tumours, he argued in a theoretical paper, were the result of a germline mutation in regulatory genes that suppressed tumorigenesis, followed by the somatic loss of the homologous allele. In non-heritable cancers, both alleles would be affected in somatic cells. However, the field had to wait 10 years to pin this hypothesis to a molecular locus.

Then, Webster Cavanee and colleagues localized the retinoblastoma gene (*RB*; also known as *RB1*) to a small region on chromosome 13; they showed that inherited and sporadic cancers had the same second hits, and that these cause homozygosity for mutations at the *RB* region, thereby confirming the allelic-hit hypothesis. By the end of the decade, the first two tumour suppressor genes — *RB* and *p53* (also known as *TP53*) — would be identified.

In 1986, Stephen Friend and colleagues isolated a human cDNA that mapped to the *RB* region and, importantly, was deleted at least partly in tumours. The next year, two groups — Wen-Hwa Lee and co-workers, followed by Yuen-Kai Fung and colleagues — cloned *RB* by chromosome walking their way to a cDNA fragment that hybridized to transcripts in normal tissue, but was aberrantly expressed or deleted in retinoblastomas. This pointed to the inactivation of *RB* as being causative for cancer, a conclusion that was confirmed by Huei-Jen Su Huang and colleagues, who rescued the neoplastic phenotype of *RB*-mutant retinoblastoma cells with wild-type *RB*.

The involvement of p53 in cancer was known for 10 years before its true role was identified. In 1989, Bert Vogelstein's group identified *p53* as the gene uncovered by the cancer-associated deletions on chromosome 17p, and showed that one copy was mutated and the other deleted in colorectal cancers. Similar to *RB*, the tumour suppressor function of p53 was confirmed by showing that it rescued the growth phenotype of p53-mutant carcinoma cells. If *p53* caused tumours only when both alleles were mutant, then it could not be the proto-oncogene it was widely regarded to be. Arnold Levine's group helped to dispel this misconception further, by showing that the *p53* mutations that arose in transformed cells *in vitro* were of the same type as that which occurs in human cancers — that is, they were inactivating mutations that probably acted in a dominant–negative manner.

Tumour suppressors and oncogenes started out at opposite poles; yet, in just 15 years, the field came full circle with the realization, as Comings had predicted years earlier, that tumour suppressors oppose the action of transforming genes — a mechanistic link that has provided the basis for all subsequent models of malignancy.

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Nature Reviews Genetics

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