

MILESTONE 15

Bad seeds

The identification by G. S. (Steve) Martin of the Rous strain of avian sarcoma virus (RSV) that was temperature sensitive for transformation implied that RSV contained an ‘oncogene’ that conferred its tumorigenic properties in chickens. Work by Peter Duesberg and Peter Vogt soon showed that the genome of RSV contained RNA sequences that were missing from replication-competent but transformation-defective viral variants. Using elegant techniques developed in the laboratories of Michael Bishop and Harold Varmus, Dominique Stehelin used subtraction hybridization procedures to generate a cDNA probe that specifically hybridized to the putative oncogene (or *src* sequences) of RSV. In 1976, Stehelin and colleagues found that radiolabelled ‘cDNA_{src}’ hybridized to homologous sequences in the DNA of normal chicken cells, and to less-conserved sequences in the genomes of other avian species. So, RSV had acquired its transforming activity by recombining with, and transducing, the chicken cellular ‘*c-src*’ oncogene.

An analysis of the thermostability of the DNA duplexes formed between the RSV *v-src* probe and avian cellular DNAs provided an indication of the extent of relatedness, and showed that cellular *c-src* DNA sequences diverged in accordance with the phylogenetic distances between the different species. Using less-stringent hybridization conditions, Deborah Spector, Varmus and Bishop detected more distantly related *c-src* sequences in human and mouse DNA, but not in sea urchin, fruit fly or *Escherichia coli*.

Bishop, Varmus and colleagues went on to study the gene product of *v-src*, which

“These were very unexpected findings that launched the whole field of oncogenes.” *Julian Downward*

had first been identified by Joan Brugge and Raymond Erikson. Using the same experimental approach, the Oppermann, Bishop and Varmus team (followed a few months later by the Erikson laboratory) identified the cellular form by precipitating proteins from extracts of uninfected vertebrate cells with antisera derived from rabbits with RSV-induced tumours. This led to the isolation of a 60-kDa phosphoprotein in chicken cells, and subsequently in quail, rat and human fibroblasts. The 60-kDa proteins shared several antigenic determinants with the viral protein, and were chemically and structurally similar, although not identical. In addition, the cellular homologues seemed to function as protein kinases in a similar way to that previously shown for the viral protein (see [Milestone 16](#)).

Together, these papers provided the first evidence of the presence of genes related to viral oncogenes in the genomes of healthy vertebrates — this proved, as Bishop famously said, that ‘the seeds of cancer are within us’. Their function in the host organism remained unclear, together with the question of whether their function had been altered by the virus. These discoveries led to an explosion of oncogene research, which resulted in the identification of more than 40 different oncogenes, and provided a framework for understanding signal-transduction pathways that control normal cellular growth (see [Milestone 16](#)). Varmus and Bishop went on to win the Nobel Prize for their discovery.

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References and links

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URL

v-src

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1491925