MILESTONE 16

Phosphorylate and conquer

The mystery of the cell-transformation process and the seemingly simple principles that are involved in cancerous growth began to be unravelled with the study of retroviruses. Research into the function of the protein products that are encoded by oncogenes followed closely on the heels of the discovery of the oncogenes themselves (see [Milestones 15 and 17](#)).

In 1978, in an effort to understand the function of the *src* oncogene from the avian Rous sarcoma virus (RSV), Michael Bishop and colleagues prepared anti-sera from rabbits that were infected with RSV-induced tumours, to isolate and further characterize the putative product of *src*. They found that the anti-sera precipitated a 60-kDa

phosphorylated protein product, which they consequently designated as **pp60**. They showed that phosphorylation of this protein was essential for its function, and that it probably possessed a kinase activity. This study, along with similar findings from the group of Raymond Erikson, indicated that protein phosphorylation might be important in the transformation process.

In late 1979, Tony Hunter and colleagues identified a phosphotyrosine kinase activity in protein immunoprecipitates of the **polyoma virus middle T antigen**. Soon thereafter, studies of the Abelson murine leukaemia virus by David Baltimore and colleagues, and of RSV by Hunter and Bartholomew Sefton, identified tyrosine-specific protein kinase activities associated with the product of the Abelson leukaemia viral oncogene (Abl) and Src. Both groups showed that these enzymes were essential for the malignant transformation of cells by the oncogenic proteins. As viral Src was derived from an evolutionarily conserved *c-SRC* cellular proto-oncogene (see [Milestone 15](#)), logic dictated that all vertebrate cells must contain at least one protein kinase that phosphorylates tyrosine. Yet, the functional relationship between kinase activity and oncogenesis remained unclear.

Work published by the Stanley Cohen laboratory a few months later, using cell membranes isolated from epidermal growth factor (EGF)-responsive carcinoma cells, provided further insights. They found that activation of the EGF receptor (**EGFR**)–protein kinase complex resulted in protein phosphorylation, mainly on tyrosine residues. The association of both virus-induced and EGF-induced cell growth with the activation of protein kinases specific for tyrosine was certainly intriguing, and indicated a functional relationship between oncoprotein activity and receptor signalling.

Importantly, shortly thereafter in 1983, Mike Waterfield and colleagues, and Harry Antoniades and colleagues identified the

putative transforming protein of simian sarcoma virus as platelet-derived growth factor (**PDGF**). In addition, in 1984, Mike Waterfield, Yossi Schlessinger and colleagues reported that *v-erbB* from the avian erythroblastosis virus encodes a similar protein to EGFR. These three papers, along with those identifying the cellular Ras oncogenes (see [Milestone 17](#)), showed that the oncogenes found in retroviruses encode components of the normal growth-regulatory machinery of the cell.

Many other oncogenes were shown to encode proteins that bound to these kinases as upstream modulators or downstream signal transducers. Not only was it now apparent that tumours might arise owing to the de-regulation of these kinase-mediated signalling pathways, but the possibility of therapeutic intervention was also evident. The outcome of much of this early work has been the development of therapeutic agents (see [Milestone 24](#)) that target the mutated oncogenes.

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Nature Reviews Molecular Cell Biology

References and links

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URLs

src

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

pp60

<http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=protein&val=40796163>

polyoma virus middle T antigen

<http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=protein&val=555285>

EGFR

<http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=protein&val=8815559>

PDGF

<http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=protein&val=338209>