Hunting the elusive oncogene: a stroke of good luck

Robert A. Weinberg

Through a succession of happenstances, in 1972 I ended up in the MIT Biology Department faculty, an institution from which I had previously received both my undergraduate and doctoral degrees. I was soon to become an MIT lifer — a proverbial stick-in-the-mud. But this has not involved an enormous sacrifice on my part. MIT was, and is, an exciting place to do science. My return to MIT occurred two years after David Baltimore and Howard Temin had discovered reverse transcriptase, and so I was drawn inexorably into retrovirology. I undertook, in effect, a third postdoctoral stay with Baltimore in the then recently formed MIT Center for Cancer Research, and after two years became a faculty member.

In the beginning, my interests were focused on the molecular biology of retrovirus replication, specifically what happens inside an infected cell soon after infection. By 1975, my group discovered that we could trigger a complete viral replication cycle by transfecting murine leukaemia proviral DNA prepared from recently infected cells into NIH3T3 mouse cells. Soon thereafter, this transfection technique, which we had adopted and fine-tuned several years earlier, offered us a unique opportunity to address another question: could we transfect the genomic DNA of cells that had acquired Harvey sarcoma virus (HaSV) proviral DNA in their genome and observe the subsequent transformation of the recipient cells to a neoplastic state? The read-out was, in this case, the formation of foci of transformed cells arising amid the monolayer of NIH3T3 cells that had been exposed to HaSV DNA.

The experiment actually worked. The take-home lesson was clear: the presence of a single viral genome, embedded in a million-fold larger host cell genome, could be detected through its ability to transform transfected cells. Hence, the transfection technique, together with the scoring of transformed cells, was extraordinarily sensitive.

At the time, Bruce Ames, at UC Berkeley, had published a provocative result: the carcinogenic potency of a chemical was directly related to its mutagenic potency. For me and others the corollary of this finding was clear: cells that had been transformed through exposure to a carcinogen were likely to harbour mutant, cancer-causing genes that were responsible for their neoplastic behaviour. While retrovirus-infected cells clearly acquired potent viral oncogenes, the genetic nature of the genes in chemically transformed cells was still a mystery. So, perhaps, we could apply the transfection/focus-forming technique to discover transforming oncogenes in the genomes of chemically transformed cells, possibly even in human tumour cells.

In fact, no one in my lab could be persuaded to undertake this experiment, as potentially important as it might be; it was too challenging technically. Instead, they were interested in what most students and postdocs focus on — publishing a paper and moving on to the next phase of their career.

It was then that the 'turning point' occurred. An MIT predoctoral biology student, Chia-Ho Shih, had begun his research in the laboratory of a colleague, but there was some fundamental chemical incompatibility in their personalities. Soon Shih was out roaming the hallways, looking for a new lab in which he could undertake his doctoral research. He came to me and, always flattered that anyone should be interested in the goings-on in my own lab, I agreed to take him in. Only weeks later did it occur to me that Shih represented a unique scientific resource. Unlike others in my group, he had not yet developed a healthy disrespect for the meanderings of my mind. On the contrary, he was most eager to please me in any way possible, as he could ill-afford another failed relationship with a doctoral mentor.

So, Chia-Ho Shih actually agreed to follow up on the idea that transfection of DNA from chemically transformed cells might yield transformed recipient cells. The stakes were high, as success would represent a direct proof that cancer cells with no history of tumour virus infection carried transforming genetic sequences in their DNA. After many months, his experiments actually worked! Most convincing were double-blind experiments in which he transfected various types of normal and transforming DNA into cultures of normal recipient NIH3T3 cells, which were then labelled by some randomly generated identifier number. Weeks later he would score the plates for the numbers of transformed foci and I would decode the identities of the transfected DNA, a procedure that I called the "the blind leading the blind". Indeed, these experiments yielded unequivocal evidence of transforming sequences in the DNA of chemically transformed cells and later in the DNA of a variety of human tumour cells — results that turned out to be most consequential in my own research career.

All this depended on an unlikely turning point — the ruptured relationship of a mentor with an aspiring doctoral student. Without that, I would never have been able to participate vicariously in this experiment, and others would have surely done so within a year or two. This was, in the end, not an example of "good luck favouring the prepared mind". Instead, it illustrated something quite different, that is, good luck favouring the lucky.

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