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Book Reviews

Cancer Cells 2/*Oncogenes and Viral Genes*. Edited by G. F. VANDE WOUDE, A. J. LEVINE, W. C. TOPP and J. D. WATSON. New York: Cold Spring Harbor Laboratory. 1984. 650 pages (approx.). $65 U.S.A. elsewhere $78 ISBN 0 87969 168 7.

'Oncogenes and Viral Genes' is a report of a Meeting held at the Cold Spring Harbor Laboratory in September 1983. Publication within one year of a meeting is something of a major achievement, especially considering the number of papers (68) submitted. The authors represent most of the important groups in this field and my general impression was that they all presented their up-to-date research. This makes the book suitable for the oncogene researcher who did not attend this meeting, as it brings together all the recent research on a wide variety of approaches to analyzing cancer genes, some of which is still not published. For any research worker entering the field this would certainly be an excellent way of catching up with research. Oncogene research covers so wide an area now, touching upon growth factors, protein kinases, lipid biochemistry, etc., that most biochemists and cell biologists should have a knowledge of the work presented here as it almost certainly has or will have some impact on their particular research. The book is of little use to scientists or clinicians in other disciplines, since these are essentially research articles with only a minimum of introduction to any given area.

The first 20% of the book is devoted to the *src* gene which is going through somewhat of a revival after the first flurry of papers almost 10 years ago when this, the very first oncogene, was characterized. The first three papers address the long outstanding question of the biological significance of the amino acid sequence differences between the cellular and viral *src* genes (c-*src* and v-*src*). Using recombinant DNA technology the three groups have been able to introduce c-*src*, v-*src* as well as recombinants between them, into cells and have investigated the effects of high level expression of these constructs on cell transformation. The conclusion reached is that the v-*src* and c-*src* proteins are qualitatively different. More functional aspects of the *src* protein ($pp60^{src}$) follow and three techniques are described for mapping the active site; mutagenesis of the gene, blocking of activities by monoclonal antibodies and protein chemical modification. Altogether this first chapter represents a very coherent description of the latest research on the *src* gene.

The next section deals with the role of the *src* protein in cells. This is necessarily a much less defined area of research, though one cellular protein (a 36 K membrane bound protein) has emerged as an important substrate for phosphorylation by the $pp60^{src}$.

The next section jumps to the DNA tumour virus, polyoma. This is turning out to be an interesting model system since the virus appears to code for three early proteins each of which contributes differently to the transformed phenotype. The first paper by Cuzin *et al.* summarises this beautifully, using vectors designed to express each of the three proteins (large, middle and small T) individually and analysing their effect on cells. According to Courtneidge *et al.* polyoma middle T associates with $pp60^{cellular\ src}$ indicating that both RNA and DNA tumour viruses probably interact with common biochemical pathways in the cell.

Myb and especially *myc* have turned out to be intriguing oncogenes, both of them coding for nuclear proteins. *Myb* expression appears to be restricted to haematopoietic cells and according to Lipsick *et al.* although the v-*myb* protein is nuclear, c-*myb* is cytoplasmic. This is an odd finding though more characterisation of the putative c-*myb* protein (a p110) is required. The *myc* protein binds to DNA and has some limited sequence

homology to the EIA nuclear protein of adenovirus and to *myb*. Wiman *et al.* present a very good summary of the mechanisms of activation of the c-*myc* gene, either by avian leukosis virus or by translocations. It appears that viral integration usually occurs between the 1st (non-coding) and 2nd (coding) exons. Similarly in many of the translocations in human Burkitt's lymphomas exon 1 is separated from 2 and 3. They propose that the 1st and 2nd exons contain complementary sequences that will form a stem and loop mRNA structure. This would result in inefficient translation under normal conditions but removal of the 1st exon would alleviate this block. Another example of proviral activation of cellular genes is provided by mouse mammary tumour virus (MMTV). This virus integrates at one of two sites (called int-1 and int-2, neither of which is related to any known oncogene). Dickson *et al.* present an analysis of the int-2 locus and its activation by MMTV while Nusse *et al.* describe the int-1 locus. Next follows a chapter by Diamond *et al.* on the *Blym*-1 transforming gene which appears to be a leukaemia specific oncogene. The final chapter in this section is a very nice summary of cellular oncogene amplification in tumours. In particular the newly discovered N-*myc* gene is amplified in many (though not all) neuroblastomas.

An introduction by Rowley opens up a section on chromosomal rearrangement in tumourigenesis. This section highlights the major controversy that still exists concerning the effects on *myc* expression of translocation to the immunoglobulin locus. Croce *et al.* show that high constitutive levels of c-*myc* are the consequence of translocation whereas Hayday *et al.* provide evidence to show that the effect of tissue specific enhancers and translational control are important. Groffen *et al.* then present data of the as yet only other example of a consistent translocation in a human cancer, namely c-*abl* in chronic myeloid leukaemias.

The next section deals with six oncogenes with three papers on *mos*, one on *fos*, *abl*, *rel*, *fes* and *fms*, and *erb*. Although (and maybe because) *mos* expression is undetectable in any normal cell, there is still a lot of interest in this gene. An interesting observation turns up in the paper by Wilhelmsen *et al.* who have inserted v-*src* into a high expression vector. This is not capable of morphologically transforming fibroblasts, leading to speculation that too much $pp60^{src}$ is toxic. This, together with the first three papers on the oncogenicity of c-*src* *versus* v-*src*, has shown that the original hypothesis, i.e. inappropriate high level expression of the cellular *src* gene (i.e. v-*src*) causes transformation, is probably wrong. It is more likely that v-*src* has a qualitatively different activity/specificity from the c-*src* product. In the next paper Sherr *et al.* point out that feline leukaemia virus has been particularly 'useful' in picking up and incorporating cellular oncogenes into its own genome. To date, *fes*, *fms*, *fgr*, *sis* and *abl* have all been found in independent isolates. This is especially interesting as these represent a variety of oncogene activities, e.g. protein tyrosine kinases (*fes*, *fgr*, *abl*), a growth factor (*sis*) and a glycoprotein (*fms*) with as yet unknown activity.

Several papers on SV40, p53 and Epstein Barr Virus nuclear antigen (EBNA) follow. The mechanism of transformation by SV40 and by retroviruses has different kinetics and consequences, though the final maintenance of the transformed phenotype may work through similar pathways. Pipas *et al.* look at the effects of SV40 transformation on growth factor requirements and Clark *et al.* analyse the intrinsic ATPase activity of the T antigen. According to Ellman *et al.* small t of SV40 is located in the cytoplasm and the nucleus, though this throws little light on what the function of this protein might be. The study of SV40 transformation led to the discovery of a cellular protein, p53, which is currently being intensively studied by a number of groups. The protein, which may play a role in the cell cycle, is very labile but is stabilized by binding to T antigen.

A section devoted to the *ras* genes follows. Altered forms of thes genes have been detected in human tumours using the 3T3 DNA transfection assay. Wigler *et al.* present a sequence comparison of the 3 active *ras* genes in human cells, i.e. Harvey (Ha)-, Kirsten (Ki)-, and N-*ras*. They have also isolated *ras* genes from yeast and the proteins have

remarkable sequence homology with the mammalian proteins. Finally, they show by *in vitro* mutagenesis that point mutations at amino acids 12, 13, 59 or 63 all lead to activation yielding a transforming *ras* gene. Two papers describe experimental models for generating *ras* mutations *in vivo*: Mammary carcinomas generated by MNU in rats (all these turn out to have activated Ha-*ras* genes) and carcinogen or radiation induced lymphomas of the mouse. Marshall *et al.* describe the isolation of the N-*ras* gene and its localization on chromosome 1 by *in situ* hybridization. They have also isolated morphologically-flat revertant cell lines of the human tumour cell line from which the active N-*ras* gene was isolated. These revertants will respond to the introduction of cloned N-*ras* and become retransformed. Some evidence that *ras* activation may be a late event in tumourigenesis is also presented. Bassin *et al.* have also isolated revertants from Kirsten Sarcoma Virus transformed cells. In this case the cells are resistant to retransformation by the Ki-*ras* gene.

The penultimate section introduces the fascinating story of transformation of primary cells. The first two papers show that oncogenes acting alone cannot transform primary fibroblast cells but that combinations can. Two complementation groups have been described. The first contains nuclear proteins, e.g. EIA and *myc*, whereas the second are cytoplasmic proteins, e.g. *ras*. The story is exciting since it addresses the multistep theory of the progression of cancer. However, in the final paper of this section a construct is described which produces very high levels of the *ras* proteins and this alone seems to transform primary cells, i.e. immortalize and morphologically transform. The significance of this result will have to await more experimentation.

The final section of the book is concerned with the adenovirus transforming proteins EIA and EIB. The EIA region of the virus initiates the transforming process and will immortalize primary cells whereas EIB produces the full transformed phenotype. Van der Eb *et al.* show that EIA also determines the oncogenicity of the transformed cells in nude mice, and that this depends on the serotype of the virus. EIA isolated from Ad12 results in a loss of MHC class 1 antigens on the cell surface, allowing the cells to grow better, at least in nude mice. Logan *et al.* show EIB is essential for efficient transformation but alone has no observable effect on cells. Another interesting aspect of this intriguing EIA gene is that the EIA protein can act as a transcriptional activator of either endogenous genes (e.g. heat shock protein) or contransfected genes. The latter transactivation phenomenon is also observed with a rearranged c-*myc* gene in place of EIA. The significance of any of this activation of other cellular genes in the development of the transformed phenotype is not known.

Overall 556 pages packed with the latest results on viral and cellular oncogenes. The only reason for a cancer-researcher not reading such a book would be if they either attended the meeting or if they already knew the latest from all these areas! The time is fast approaching when the extensive research in DNA tumour virology and RNA tumour virology will converge at the level of the biochemical pathways that lead to the transformed phenotype. Analysing the myriad ways in which transformation can be initiated and maintained will undoubtedly lead to a better understanding of the mechanism of carcinogenesis. This book represents an important first gathering of all this research information. We should look forward to the forthcoming meetings and the Cancer Cells books derived from them.

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