European Journal of Cancer, Vol. 33, No. 10, pp. 1706–1707, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

Book Review

PII: S0959-8049(97)00259-1

Cancer Genes: Functional Aspects
Editors: Enrico Mihich and David Housman
Proceedings of the 7th Pezcoller Foundation Meeting, 1995
Publishers: Plenum Press (1996)
ISBN 0-306-45482-3

THIS BOOK is aimed at the specialist working in the field of cancer genetics who is trying to gain insight into the mechanisms of disease development by focusing on targeted cellular functions. There are several good chapters describing what is currently known about various aspects of cellular growth and control which, when taken together, provide a comprehensive introduction into this complex field. The reader must, however, have some understanding of cell biology as the contents of the book are not aimed at addressing clinical issues, more the control of gene expression which is often complex and sometimes confusing to the lay reader. The book consists of 17 chapters which present diverse aspects related to mechanisms believed to be aberrant in tumours. The first five chapters concentrate on the cell cycle followed by a section on transcription factors and finally a section devoted to how gene re-arrangement leads to the aberrant control of specific oncogenes.

The first chapter introduces the concept of an integrated control of cellular proliferation and viability using Rat-1 fibroblasts as the trial population. The effect of myc-induced apoptosis in these fibroblast cells appears to be dependent on not only the level of myc-expression but also on the serum concentration used to grow the cells. The authors go on to show that there is a dual signal molecule for c-myc action which may explain the coupling of cell suicide with cellular proliferation.

Chapter 2 goes further in the analysis of cell growth, and focuses on the control of invasive growth by the *MET* family of oncogenes. The *MET* family of oncogenes appears to be ligands that must bind to their respective receptors. The MET receptors show considerable homology to one another, and two of the ligands, hepatocyte stimulatory factor and macrophage stimulatory protein, have been identified. A third ligand which binds to the SEA receptor remains to be identified. The first indication that the MET receptor was oncogenic came from studies which showed that it was amplified in human gastric carcinoma. Thereafter, amplification has also been reported in colon carcinoma and ovarian cancer as well as some cell lines.

Chapter 3 continues the theme of cellular regulation by indicating where the *SRC* family of genes are likely to be implicated in the cell cycle, and indeed a model of interaction with other well-known oncogenes is proposed. The following chapter expands on this aspect of the cell cycle and introduces the feedback loop between the p16 family of proteins and the retinoblastoma gene *Rb* in relation to cell cycle control. The tumour suppressor gene *p53* is examined in terms of its involvement in apoptosis, which provides a good insight into where *p53* stands in relation to governing cell cycle progression after DNA damage has occurred.

The molecular genetics of Wilms' tumour starts the second section of the book and deals primarily with how the Wilms' tumour gene (*WT1*) interacts with specific sequences of DNA through a zinc finger motif that is similar to the early growth response gene *EGR-1*, but there are key differences which could account for the specificity of *WT1*. Interestingly, a common mutation for the Denys–Drash syndrome lies in the *WT1* zinc finger motif which goes some way to explaining this syndrome which has some symptoms that are not seen in Beckwith–Wiedemann syndrome or in familial Wilms' tumour. *WT1* is shown to be a transcription factor but, unfortunately, there is little discussion concerning which genes are affected.

The following chapters deal with a series of different genes all of which are intimately involved in transcriptional activation. An important aspect that is often neglected when discussing tumorigenesis is the role of viral proteins in the inactivation or activation of specific cellular genes which lead to changes in cell cycling. This aspect is presented in Chapter 7 using the *HTLV-1* and the *Tax* genes. The *Tax* gene is a transcriptional regulator and can modulate cellular growth by regulating the transcription factor Nf-κB. Thus, promiscuous activation of cellular and viral genes can be achieved by targeting their NF-κB promoter regions via *Tax*. Other transcription factors are discussed in four following chapters (CREM, MADS, Rb, E2F-1), which clearly illustrate their relative importance in cellular regulation.

Thereafter, one chapter is included which does not appear to immediately fit into any particular section, but its relative importance becomes immediately apparent. A cell has essentially four options: continued cell growth (leading to an expansion of numbers); apoptosis (leading to a reduction in numbers); cellular differentiation (static numbers and irreversible, i.e. cannot re-enter cell cycle); or entry into a quiescent phase (termed Go). Chapter 12 examines the growth-arrest specific (*GAS*) gene which is associated with entry into Go. The family of *GAS* genes (*Gas 1–6*) is presented and gives the reader a clear indication as to how these genes may regulate this key element in cell control and hence what to expect if things go wrong.

The last third of the book focuses on the activation of genes in several sorts of leukaemia. This section of the book is revealing in that several mechanisms are proposed that may account for some of the phenotypic differences seen in various leukaemias.

In summary, this book represents an attempt at portraying relatively recent knowledge of how oncogenes disrupt normal cellular function when aberrantly expressed. Relatively little is presented with respect to the role of tumour suppressor genes and genes associated with mutator phenotypes (such as the adenomatous polyposis coli (*APC*) gene, DNA mismatch repair and nucleotide excision repair genes) all of which can be termed 'cancer genes'. An editorial criticism that I feel

could be relatively easily addressed is the presentation of the discussion at the end of each chapter which requires improvement. The questions and comments presented by the audience are often insightful and relevant, not only to the chapter they deal with but also to the subject matter of the book in general. If they were edited it would make them an excellent addendum to each chapter.

Rodney J. Scott
Cyto and Molecular Genetics
Hunter Area Pathology Service
John Hunter Hospital
Locked Bag No. 1
Hunter Regional Mail Centre
New South Wales 2310
Australia

European Journal of Cancer, Vol. 33, No. 10, pp. 1707–1708, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

Letters

PII: S0959-8049(97)00112-3

Comments on *Inadequacy of Iridium Implant as Sole Radiation Treatment for Operable Breast Cancer,* Fentiman *et al., Eur J Cancer* 1996, 32A, pp. 608–611

R.G. Dale,[1] B. Jones[2] and P. Price[3]

[1]Departments of Radiation Physics and Radiobiology, Hammersmith Hospitals NHS Trust, London W6 8RF; [2]Clinical Oncology, Clatterbridge Centre for Oncology, Merseyside L63 4JY; and [3]Clinical Oncology, Hammersmith Hospitals NHS Trust, London W12 0NN

In a recent article published in the *European Journal of Cancer*, Fentiman and associates [1] compared the local tumour control achieved with two alternative treatments of the breast: (a) an existing, well-established treatment, consisting of an external beam regime of 46 Gy in 23 fractions over approximately 4.5 weeks, supplemented 1 week later by a continuous iridium application delivering 20 Gy over 2 days; and (b) a single continuous application of an iridium-192 implant delivering 55 Gy over 5–6 days.

After 6 years median follow-up, the local control rate with treatment (b) was found to be 20% lower than that achieved with treatment (a). The likelihood of such a finding is predictable using standard radiobiological calculations, the results of which are summarised below.

If tumour repopulation during treatment is ignored (probably a reasonable assumption in the case of breast carcinoma), the biologically effective doses (BEDs) may by calculated as follows:

For the teletherapy:

$$BED = nd\left[1 + \frac{d}{\alpha/\beta}\right] \quad (1)$$

where n is the number of fractions, d the dose per fraction (Gy) and α/β the tumour fractionation parameter (Gy) [2].

For the iridium implant:

$$BED = RT\left[1 + \frac{2R}{\mu(\alpha/\beta)}\right] \quad (2)$$

where R is the dose-rate (Gyh^{-1}), T the treatment time (h) and μ the recovery rate (h^{-1}) of sublethal DNA damage [3].

The BED for treatment (a) is found by summing the BEDs calculated from Equation (1); the BED for treatment (b) is found from application of Equation (2) alone.

The BEDs (in units of Gy) have been calculated for four assumed values for α/β and two for μ, and are summarised in Table 1. In all cases, the BEDs associated with treatment (b) are well below those achieved with treatment (a). Consequently, the multivariate analysis performed by Fentiman and associates [1] is essentially based on a comparison of two treatments which, in radiobiological terms, are disparate. It should, therefore, be concluded that this clinical study does not necessarily provide evidence that the use of an iridium implant alone is inferior to the well-established treatment, since the chosen dose was radiobiologically sub-optimal.

Although tumour recovery rates are not known with any absolute certainty, they are probably in the general range 0.5–1.5 per hour, with an increased likelihood of being towards the higher end of the range for tumours [4]. The tumour α/β values are generally greater than 5 Gy and, in individual cases, may be even higher than 20 Gy, the upper end of the range considered here [4]. The normal tissue responses are more likely to be characterised by α/β ratios of less that 5 Gy [5].

Thus, the standard linear-quadratic equations strongly indicate that the local tumour control associated with

Table 1.

α/β (Gy):	3 Gy		5 Gy		10 Gy		20 Gy	
μ (h^{-1}):	0.5	1.5	0.5	1.5	0.5	1.5	0.5	1.5
BEDs for group (a)	107.8	100.4	91.1	86.7	78.5	76.3	72.3	71.1
BEDs for group (b)	85.6	65.2	73.5	61.2	64.2	58.1	59.6	56.5
Difference:	−21%	−35%	−19%	−29%	−18%	−24%	−18%	−15%

Correspondence to R.G. Dale.
Received 13 Feb. 1997; accepted 24 Feb. 1997.