

Correspondence

p53 gene mutations in multiple myeloma

We were interested in the article by Owen *et al* on p53 gene mutations in multiple myeloma.¹ They had studied the p53 exons 5-9 by PCR-SSCP and they found only one p53 mutation among 36 DNA samples from 31 patients with multiple myeloma. They concluded that p53 mutations are rare and confined to end stage leukaemic forms of the disease. We also studied p53 protein expression in myeloma cases determined by immunohistochemistry,² and our results and conclusions were different from Owen and colleagues's.

Our study group comprised 31 patients with multiple myeloma and four with isolated plasmacytoma. Twenty of the myeloma cases were newly diagnosed and the other 11 had relapsed or had resistant disease. All of the multiple myeloma patients were in stage III and 13 cases had also renal involvement. Fresh bone marrow aspiration samples from myeloma patients and paraffin wax embedded tissue sections from plasmacytoma cases were stained by the ABC method. To determine p53 protein expression, a monoclonal antibody against the p53 suppressor gene product (DO-7 Novacastra K-32; Novacastra, Newcastle upon Tyne, UK) recognising both normal and mutant forms of protein was used. Eight of the 35 cases showed p53 protein expression, none of the plasmacytomas showed p53 protein expression; therefore, p53 protein expression was found in 26% of cases of multiple myeloma. Four of the eight p53 positive cases were newly diagnosed and four of them were resistant and/or relapsed cases. Four of the 24 newly diagnosed, four of 11 relapsed cases, four of the 18 stage IIIA, and four of the 13 stage IIIB cases had p53 expression. There was no significant difference for p53 expression between newly diagnosed and relapsed cases, or between IIIA and IIIB cases ($p < 0.25$). None of our patients had features of leukaemic phase disease.

p53 gene alterations in plasma cell dyscrasias have not been as well studied as other haematopoietic neoplasms, and the results of p53 alterations in multiple myeloma are limited but interesting. For example, p53 mutations have been found in eight of 10 multiple myeloma cell lines. This point was mentioned by Owen *et al* who speculated on the possibility of acquired occurrence *in vitro*.³ In clinical samples the frequency is between 3% and 50% depending on the methods used for detection.⁴⁻⁸ Owen and colleagues did not give an account of the stage and status of the renal involvement for their patients.

It is well known that p53 gene has a complex structure and that functional inactivation can result from the loss of p53 gene function. Therefore, there is no ideal method for the detection of p53 gene alterations; however, by using more than one technique such as immunohistochemistry and PCR-SSCP, the results may be more informative. We believe that if immunocytochemistry could be used concurrently with PCR-SSCP analysis, Owen *et al*'s results and comments might be more useful.

We conclude that p53 mutations are not particularly rare in multiple myeloma. We

agree that p53 mutation is not an initial step in myelomagenesis. We need larger studies with more patients and methods to determine the pathogenetic role of p53 mutations in multiple myeloma.

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Dr Owen and colleagues comment:

Using PCR-SSCP we found only one patient with multiple myeloma from 31 cases who had a mutation of p53. We agree that the incidence of detectable p53 protein expression is higher. In a small group of cases (not the same as those described in the paper) we found four of 17 (23.5%) in which p53 was present in plasma cells using the polyclonal antibody 1801. In three of the cases, p53 was present in a small minority of the plasma cells. The presence of p53 in a minor proportion of tumour cells is seen commonly in other types of B lymphoproliferative disorders, and there is no evidence that this is due to stabilisation of the protein by mutation. In general, the association between p53 expression and mutation in lymphoproliferative disorders is much less firmly established than for epithelial tumours. The incidence of p53 immunoreactivity, therefore, cannot be assumed to be directly relevant to establishing the incidence of p53 mutations in myeloma. Equally, the occurrence of mutated p53 in myeloma derived cell lines cannot be considered as any indication of the incidence of p53 mutation in clinical samples.

We have not correlated the presence of renal impairment with the presence of p53 mutation or overexpression. Renal dysfunction in myeloma involves multiple factors including calcium, Bence-Jones protein, and the development of amyloid. It is difficult to postulate a role for p53 expression or mutation in this process other than as a broad correlate with advanced stage disease.

Within the limits of detection of the PCR-SSCP method the incidence of p53 mutation in myeloma appears to be low although clearly an accurate estimate would require a larger study. The reason for the expression of

p53 by some plasma cells is a separate and more complex question that does not directly affect the conclusions of our study

Book reviews

Molecular Endocrinology: Genetic Analysis of Hormones and their Receptors. Rumsby G, Farrow SM, eds. (£65.00.) Bios Scientific Publishers, 1997. ISBN 1 8599 6235 1.

This book is divided between what one needs to know to understand its main contents and its principal theme. Thus the first two chapters are devoted to the gene, any gene, and how the structure of DNA and genes are currently investigated. The next two chapters constitute a lead into the more specialist topic of endocrinology, dealing with the mechanisms of action of the two major classes of hormones. These are followed by chapters devoted to specific topics. All the chapters are authoritative, and despite the continuing rapid advances in the various fields, are reasonably up to date.

Although the chapters are written by different authors, the editors have achieved a unified style of language and presentation. All the figures are black and white; however, they are well drawn, clear and informative. The referencing is adequate without being excessive.

The subject matter adheres strictly to classical endocrinology, and it seems a pity that the discussion of nuclear receptors does not include helix-turn-helix receptors to any extent. Although the aryl hydrocarbon receptor probably does not come within the strict compass of endocrinology, it seems a pity that a chapter was not given to this. Nevertheless, even with these minor criticisms, this book is a useful investment for anyone in this field of research, and an excellent source book for teachers to dip into time and time again when preparing undergraduate lectures.

D B RAMSDEN

Leucocyte Antigen Facts Book. 2nd edn. Barclay, Brown, Law, McKnight, Tomlinson, van der Merwe. (£29.95.) Academic Press, 1997. ISBN 0 1207 8185 9.

This second edition of *Leucocyte Antigen Facts Book* provides an update on the ever increasing number of leucocyte antigens, both with and without a CD number. It includes all the changes from the International Workshop in 1996. An introduction is followed by two sections, the first three chapters giving details of how these molecules have been discovered and analysed, an overview of the various protein superfamilies, and how they interact with the various ligands. In the last chapter there is an update of the interaction between B and T lymphocytes and the ligands involved. I feel this could have been slightly expanded to include other cell-cell interactions such as neutrophil and endothelium, and antigen presenting cells. The second section lists all the relevant CD antigens along with many of them that are yet to be designated a CD number. The molecular weight, carbohydrate content, gene location, tissue distribution, structure, and function of each antigen is

described. Database numbers are given along with key references from the past few years, many of which are from 1996 or unpublished data from the authors themselves. This allows the reader rapid access to the world literature. Finally the amino acid sequence of each antigen is described if known.

The book is a timely update and essential reading for all people working in this particular aspect of biomedical science. The authors deserve great credit for the rapidity with which this has been produced.

Although extremely compact and full of data it is slightly too big to fit in the average Christmas stocking but, with a price that is not prohibitive, this is a logical place for it if you happen to be getting on with your laboratory colleagues this year. As a book reviewer, one often spends many tedious hours out of devotion to the editor but on this occasion he has done me proud and certainly saved me the purchase price.

C FEGAN

Immunoglobulin Genes. 2nd edn. Honjo T, Alt FW, eds. (Pp 443; £50.00.) Academic Press. 1995. ISBN 0 120 53640 4.

Our knowledge of the immunoglobulins has expanded greatly over the years and recently, as the three-dimensional structures became known, much greater emphasis has been placed on understanding the molecular processes involved in generating and regulating immunoglobulin expression. This book offers a comprehensive insight into these mechanisms, provided by leading researchers in the field.

The format of the book is not particularly user friendly, being so tightly packed with information, but the comprehensive referencing associated with each chapter is excellent. Indeed, it is a pity that the constant use of author and date reference citations breaks up otherwise eminently readable text.

The coverage of B cell development is extensive and detailed, encompassing in several chapters the complex roles of the B cell

receptor, cytokines, and stromal cell influences. The presentation is marred only in some instances by overcomplex diagrams that could have been more informative if presented better. The chapters on immunoglobulin repertoires in a variety of species provides a basis for solid comparisons of the molecular mechanisms used to generate diversity and the evolutionary development of the immunoglobulins. It is good to see a whole chapter devoted to the lower vertebrates, providing a certain perspective to the human and mouse systems so fully described elsewhere in the book. The unique contributions provided through studying immunoglobulin transgenic mice are discussed, as are B cell tolerance, and autoantibody V region use.

These topics, however, are not covered as extensively as the earlier chapters on developmental controls and organisation of immunoglobulin genes. I think this book is, on the whole, an excellent reference text for anyone wishing to know more about the immunoglobulins and I would certainly recommend it.

PADDY TIGME

Molecular Diagnosis of Cancer. Cotter FE, ed. (£49.00.) Humana Press, 1996. ISBN 0 8960 3341 4.

Molecular Diagnosis of Cancer is a book from the *Methods in Molecular Medicine* series. It is targeted at clinicians and scientists as an introduction to the application of molecular pathology in a diagnostic setting.

The book is split into three sections. Part 1 is dedicated to the use of PCR based techniques in the diagnosis of haematological malignancy. This section illustrates the application of specific methods to the detection of genetic abnormalities. Chapters include PCR for gene rearrangements in minimal residual disease in childhood ALL and for t(14;18) translocation in follicular lymphoma, reverse transcriptase PCR for detection of BCR-ABL in haematological malignancies, PML/

RAR- α in acute promyelocytic leukaemia, NPM-ALK for t(2;5) in non-Hodgkin's lymphoma, and 11.q23 breakpoints involving the MLL gene in acute leukaemia.

Part 2 gives examples of the application of molecular biological techniques to solid tumours. This covers identification of mutations of the tumour suppressor genes in retinoblastoma and Wilms's tumour (WT1).

Part 3 examines general techniques for cancer analysis. This section gives examples of molecular based techniques that can be applied to all areas of the molecular biology of tumours. Techniques covered in this section include single-strand conformation polymorphism mutation analysis, fluorescence in situ hybridisation, comparative genomic hybridisation, in situ hybridisation, and apoptosis detection by DNA analysis.

Each section of the book uses specific examples to illustrate the efficacy of the techniques employed by the authors. Each chapter gives full details of the background for the experimental work, the reagents required, and protocols for the methods. This form of presentation is attractive both to newcomers to the field and those with some experience in diagnostic molecular pathology. A notable absence is the use of in situ PCR based techniques, which are becoming of interest in many areas of pathology.

The use of specific diagnostic situations to demonstrate the use of a technique helps to provide a model for how each method can be applied, and gives an insight into how it may be applied to diagnosis and monitoring of malignant disease.

The book is well thought out and provides a suitable level of information to anyone interested in the use of molecular pathology in diagnosis. It is interesting both as a general text and as a guideline for setting up specific diagnostic tests. In general this book is very informative while still being easy to read. I would recommend it to anyone who has an interest in molecular diagnosis in pathology.

J OATES



Leucocyte Antigen Facts Book

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Mol Path 1997 50: 329-330

doi: 10.1136/mp.50.6.329-c

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