

PostScript

CORRESPONDENCE

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Cancer stem cell theory: pathologists' considerations and ruminations about wasting time and wrong evaluations

The genomic revolution has changed the role of the pathologist. In daily practice, our work is no longer limited to reaching a correct diagnosis and we are asked to answer questions about the patient's prognosis and treatment options through the evaluation of selected molecular targets (such as erbB2 for breast cancer) in tumour specimens. Thus, we have acquired a major role in the translation of novel gene findings from experimental model systems to their clinical application.

There is overwhelming evidence that only a subset of cells within a tumour clone, referred to as cancer stem cells, are tumorigenic and possess the metastatic phenotype.¹ The recent identification of human breast cancer initiating cells by Al-Hajj and colleagues² provided a major step forward in this field. With this knowledge, the stem cell compartment should represent the selected target for tumour eradication.

As pathologists we would like to share some considerations and ruminations about this scenario.

Currently, tissue microarray analysis generates gene profiles capable of differentiating tumours with different biological behaviours.³ However, this screening method is conducted on heterogeneous tumour tissue samples containing a mixture of non-neoplastic cells, non-tumorigenic cancer cells, and cancer stem cells. Similarly, until now, we have evaluated the immunohistochemical expression of a molecular marker in the bulk of the tumour, considering it as relatively homogeneous.

What is the clinical relevance of these results? Although new therapeutic approaches based on these studies have modified the prognosis of some neoplasms,⁴ conflicting results are still seen with many other tumours.⁵ We should start to feel worried about the value of the information retrieved from this type of tumour analysis.

The few cancer stem cells and the large number of cells constituting the tumour are morphologically similar but functionally heterogeneous. It is likely that we are still evaluating the main population of tumour cells, which are not cancer stem cells, and are thus probably wasting time and losing essential treatment information. It is unlikely that gene expression profiles obtained using the currently available methods reflect those of the tumour stem cell population, which forms only 0.1-2% of the whole tissue sample.^{1,2,6}

The cancer stem cell hypothesis has started a new era in cancer research. Tumours contain functionally different subpopulations of cells. However, unique gene expression profiles are generated by current methods of evaluation. Probably, when the isolation and molecular characterisation of cancer stem cells from primary tissue becomes possible, the role of pathologists will change again. Collaboration between researchers and pathologists will be more widely practised and we will be able to rise to the next challenge; namely, assessing the prognosis of a patient from only one of 5000 tumour cells in a tissue sample.

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References

- 1 **Reya T, Morrison SJ, Clarke MF, et al.** Stem cells, cancer, and cancer stem cells. *Nature* 2001;**414**:105-11.
- 2 **Al-Hajj M, Wicha MS, Benito-Hernandez A, et al.** Prospective identification of tumorigenic breast cancer cells. *Proc Natl Acad Sci U S A* 2003;**100**:3983-8.
- 3 **Van de Vijver MJ, He YD, van't Veer LJ, et al.** A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med* 2002;**347**:1999-2009.
- 4 **Orr MS, Scherf U.** Large-scale gene expression analysis in molecular target discovery. *Leukemia* 2002;**16**:473-7.
- 5 **Carney DN.** Lung cancer—time to move on from chemotherapy. *N Engl J Med* 2002;**346**:126-8.
- 6 **Dick JH.** Breast cancer stem cells revealed. *Proc Natl Acad Sci U S A* 2003;**100**:3547-9.

Public opinion on the use of tissue samples

I read with interest and increasing concern the paper by Goodson and Vernon,¹ "A study of public opinion on the use of tissue samples from living subjects for clinical research". The paper demonstrates that the use of a vaguely worded and ambiguous questionnaire leads to misleading results. A few of the problems with the questions may be taken individually:

- (1) "Would you be happy for pieces of any of the following body tissues or organs to be used in clinical research? (Eyes, lung, heart, tissue from head and neck, embryo, brain, ovary, testes, bone, and breast.)"

The question could refer to postmortem tissue and the choice of organs is (as the authors confess) deliberately "emotional", with no insight into every day pathological services. Heart, brain, and eyes are not exactly common surgical specimens, whereas embryos are subject to special guidelines. Surely, this question is almost designed to make the patient believe it refers to post-mortem organs? The use of subjective words such as "happy" is extremely unhelpful. "Are you happy to vote Labour?" would not, for example, be acceptable in a comparable political survey!

- (2) "What kind of research would you be happy for your tissues to be used for? (Cancer research, testing medicines, genetic cloning, general knowledge of body tissues, genetic research for diagnosis or treatment of, for example, Down's syndrome.)"

Again scientific imprecision exists, because the writers of the questionnaire appear not to understand that these fields are interdependent. In particular, the lack of public understanding of cloning has caused them to reject this field, with no idea that this may include tissue culture or polymerase chain reaction.

- (3) "Would you want to be informed if your tissues were to be stored beyond the time required for diagnosis?"

This question seems to show no knowledge of the necessity for longterm storage of samples after diagnosis. Tissue retention for medicolegal, audit, clinical governance, and comparison with later samples has been ignored. No explanation has been given to the patients of why this is in their best interests.

- (4) "Would you be happy to give consent for a child's tissues to be used for scientific research?"

Apart from the obvious flaw that it has not been stated whose child is being talked about, again the question appears almost deliberately ambiguous and could be taken to refer to postmortem tissue. Apparently, the designers of the questionnaire are interested in "scientific research" on children's tissues, whereas in adults in question 1 it is only "clinical research".

- (5) "Would you be happy to give consent for your tissues to be used to teach medical students?"

The word happy is used again, in addition to a lack of explanation of how the tissues are "used", and the vital role of histology in teaching medical students and pathology trainees.

I suggest to the authors that their survey, in contrast to all other studies, shows that patients were unwilling to donate their tissues because they were presented with a poorly designed, misleading survey.

D M Berney

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Reference

- 1 Goodson ML, Vernon BG. A study of public opinion on the use of tissue samples from living subjects for clinical research. *J Clin Pathol* 2004;57:135–8.

Authors' response

We are grateful for the opportunity to respond to Dr Berney's letter. The questionnaire used in our study was piloted on a similar group of respondents. The patient information leaflet and consent form given and explained before completion of the questionnaire made it clear that we were only concerned with tissue donated by living subjects for research and did not refer to the use of postmortem specimens or tissue or organs for transplantation. In addition, all respondents were given the opportunity to ask questions before completing the questionnaire if they were unsure of the meaning of any questions.

We imagine that many of the research fields are interdependent, although the general public may not be aware of this. Our study did not attempt to explain why respondents answered questions in any particular way, but it shows that people may or may not be willing to donate different types of tissue for different types of research. This may be because of a lack of understanding of the clinical and laboratory techniques used in research, but we have not attempted to prove this in our study.

We agree that no explanation was given to respondents (who were not patients) about the benefits of retention of tissue samples; this would have biased the response.

Dr Berney says that our question surrounding consenting for donation of a child's tissue for research is flawed because it does not explain whose child we are discussing. Our pilot study demonstrated that the phrase "your child" eliminated responses from childless adults, adults with children over 16 years of age who were able to consent for themselves, and individuals who had children, but for various reasons were no longer the guardians of such children. The question merely attempted to identify whether or not there was some reluctance by adults to consent for children.

Our research showed a snap shot of public attitudes to tissue donation from living subjects for clinical research and offers no more than an indicator of public attitude, and like most research requires further qualification.

We are grateful to Dr Berney for his comments because they open up the debate on whether the public accepts tissue donation for research purposes. To restore public confidence in the medical profession and research in general, it is crucial for the profession to take account of public perceptions and to understand the nature of the explanations that are required.

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Limitations of the Wilcoxon matched pairs signed ranks test for comparison studies

We read the short report by Ellis *et al* with interest.¹ However, we are unsure whether

they have adequately proved that no significant difference was detected between the two outlined storage methods.

The hypothesis evaluated with the Wilcoxon matched pairs signed ranks test is whether or not the median of the difference scores equals zero. Let us consider the situation of x measurements tending to exceed y measurements in the low range and vice versa in the high range, with similar values in the mid range. Such results may have a median of the difference scores of approximately zero; that is, there might be no significant differences by the Wilcoxon matched pairs signed ranks test, although there would be differences by linear regression (Deming or Passing-Bablok) and/or difference plots.

However, this short report¹ lacks both a regression equation (proportional and constant error) and difference plots. Therefore, we believe that although the IgG anti-rubella activity in frozen serum stored in primary gel separation tubes may not be significantly different from that stored frozen in secondary tubes, this study did not sufficiently prove this. We recommend, in line with others,² that difference plots³ are used for such comparative studies and that such studies are put into a clinical context.^{3,4}

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References

- 1 Ellis V, Charlett A, Bendall R. A comparison of IgG anti-rubella activity in frozen serum stored in primary gel separation tubes or secondary tubes. *J Clin Pathol* 2004;57:104–6.
- 2 Hollis S. Analysis of method comparison studies. *Ann Clin Biochem* 1996;33:1–4.
- 3 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i:307–10.
- 4 Fraser CG, Kallner A, Kenny D, *et al*. Introduction: strategies to set global quality specifications in laboratory medicine. *Scand J Clin Lab Invest* 1999;59:477–8.

BOOK REVIEWS

Basic Pathology: An Introduction to the Mechanisms of Disease

Lakhani S R, Dilly S A, Finlayson C J, *et al*. (£22.99.) Arnold, 2003. ISBN 0340810017.

With the new "integrated" undergraduate medical curriculum being adopted by medical schools in many countries, there is an ever increasing need for an appropriate basic pathology textbook. The authors have produced a book which is based on the principles and objectives of the integrated curriculum. Consequently, it is an ideal basic pathology textbook for students in the integrated medical curriculum.

The book has a novel approach to basic pathology, which is different from the standard basic pathology textbooks. There are four parts: "Introduction—what is a

disease?", "Defence against disease", "Circulatory disorders", and "Disorders of cell growth". Each part consists of a variable number of chapters containing several unique learning aids.

The material is presented in a format that is easy to read and can be read at leisure. In accordance with the integrated curriculum, some material is presented by using clinical cases—for example, myocardial infarction, breast lump, and prostatic hyperplasia, among others. Innovative additions are the excellent cartoons, selected "key facts", "dictionary box", and "small print". The cartoons are well illustrated, extremely apt, and informative. There is also a selection of relevant tables that complement the text. The inclusion of appropriate colour diagrams, photomicrographs, and macroscopic pathology images aids the text. Clinicopathological case studies are used as a tool to facilitate the integration of pathology with clinical medicine. At the end of each part, there is a selection of questions covering core material with answers and cross references.

There are six colour coded theme maps that cover the four main pathology disciplines—histopathology, haematology, immunology, and microbiology—and two additional overview themes—science and disease and patient and disease.

The authors have produced a remarkable book, which deals with a difficult but important subject in a user friendly manner. The book ought to be prescribed reading for undergraduate students in the new integrated medical curriculum.

D Govender

The Cytology of Soft Tissue Tumours

Akerman M, Domanski H A. (€110.00.) Karger, 2003. ISBN 3 8055 759 7.

Åkerman's and Domanski's text *The Cytology of Soft Tissue Tumours* from the *Monographs in Clinical Cytology* series is a beautifully illustrated, well referenced and written treatise on the interpretation of fine needle aspirations (FNAs) of these lesions. The text starts with a brief overview of the FNA of soft tissue tumours including accuracy, pitfalls, complications, and a discussion of the aspiration technique itself, with application of ancillary studies. This is followed by a concise review of the specific entities following standard histogenetic organisation. With each major entity, the salient cytological features and differential diagnostic considerations are clearly listed, with comments on the potential pitfalls admixed with helpful hints, providing a practical approach to the diagnosis of the lesions. The final chapter summarises in tabular form the salient diagnostic features and results of ancillary studies of the various entities in groupings based on a pattern recognition approach. Illustrations abound and include air dried May-Grünwald-Giemsa, in addition to alcohol fixed haematoxylin and eosin or occasionally Papanicolaou stained cytological preparations. Little criticism of this text can be found and there is no question that this book should be in the library of those interpreting FNAs of soft tissue lesions.

S Boerner

CALENDAR OF EVENTS

Full details of events to be included should be sent to Maggie Butler, Technical Editor JCP, The Cedars, 36 Queen Street, Castle Hedingham, Essex CO9 3HA, UK; email: maggie.butler2@btopenworld.com

Practical Pulmonary Pathology

27–30 July, 2004, Brompton Hospital, London, UK

Further details: Professor B Corrin, Brompton Hospital, London SW3 6NP, UK. (Tel: +44 (0)20 7351 8420; Fax: +44 (0)20 7351 8293; Email: b.corrin@ic.ac.uk)

ACP Management Course for Pathologists, 2004

8–10 September 2004, Hardwick Hall Hotel, Sedgefield, County Durham, UK

Further details: V Wood, ACP Central Office, 189 Dyke Road, Hove, East Sussex BN3 1TL, UK. (Tel: +44 (0) 1273 775700; Fax: +44 (0) 1273 773303; Email: Jacqui@pathologists.org.uk)

Combined Adult and Congenital Cardiovascular Pathology Course

8–10 November 2004, Imperial School of Medicine, National Heart and Lung Institute, London, UK

Further details: Short Course Office, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, UK. (Tel: +44 (0)20 7351 8172; Fax: +44 (0)20 7351 8246; Email: shourtcourse.NHLI@IC.AC.UK)

Asian Pacific Association for Study of the Liver Biennial Conference

11–15 December 2004, New Delhi, India

Further details: Dr V Malhotra (General Secretary) or Dr P Sakhuja (Treasurer and Pathology Coordinator), Room 325, Academic Block, Department of Pathology, GB Pant Hospital, New Delhi 110002, India. (Tel: +91 11 23237455; Email: welcome@apasindia2004.com; Website: www.apasindia2004.com)

CORRECTIONS

MUC1 and MUC2 in pancreatic neoplasia. E Levi, D S Klimstra, N V Adsay, A Andrea, O Basturk. *J Clin Pathol* 2004; **57**:456–62. The order of the authors should be E Levi, D S Klimstra, A Andrea, O Basturk, N V Adsay.

Urinary catecholamines and metabolites in the immediate postoperative period following major surgery. Dr A A Syed, H A Wheatley, M N Badminton, *et al.* *J Clin Pathol* 2004;**57**:548–50. The first author's name should be A A Syed.

Focal nodular hyperplasia with concomitant hepatocellular carcinoma: a case report and clonal analysis. S-H Zhang, W-M Cong, M-C Wu. *J Clin Pathol* 2004; **57**:556–9. The image shown in fig 2 should have been fig 3 and vice versa.