

PostScript

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The number of intraepithelial T cells decreases from ascending colon to rectum

The $\alpha^E\beta_7$ -integrin (CD103) is expressed almost uniquely by T cells of the mucosal immune system, where it is upregulated on activated cells by the action of transforming growth factor β . The only known ligand for this integrin is E-cadherin,¹ which is expressed by all epithelial cells, where it constitutes a homotypic adhesion system necessary for tight junction formation. A role for interaction between the $\alpha^E\beta_7$ -integrin and E-cadherin in the localisation of intraepithelial T cells is supported by the reduction in numbers of mucosal T cells seen in CD103 deficient mice.²

The role of CD103+ T cells remains unclear. However, the potential of these cells to bind specifically to the epithelium is consistent with a capacity to mediate damage localised to this tissue. Indeed, CD8+CD103+ T cells have been shown to kill epithelial targets *in vitro*,³ and have been implicated in disease processes such as tubular destruction during renal allograft rejection.⁴ The potential for modulation of experimental colitis by the administration of antibodies directed at CD103 provides evidence that these cells might also act as effectors during this disease.⁵ Given the increasing severity of

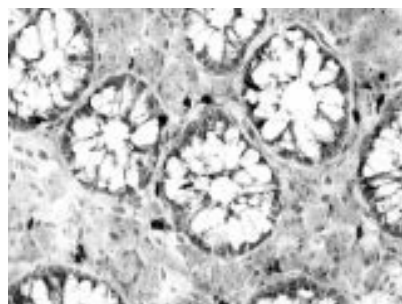


Figure 1 Immunocytochemical localisation of CD103+ cells (stained black) within the normal human colon.

ulcerative colitis from the proximal to distal colon, it is perhaps reasonable to propose the existence of a similar gradient in the number of potential T cell effectors within the epithelium of the normal colon.

In our study we performed a survey of the linear distribution of cells expressing the CD3, CD8, and CD103 phenotypic markers within the normal human colon. Pinch biopsies were collected from the ascending, transverse, descending, and sigmoid colon and the rectum of patients attending clinic for routine diagnosis. Frozen sections were analysed from eight patients who were considered normal after routine histological evaluation. Endogenous peroxidase was blocked and the sections were stained with appropriate monoclonal antibodies (CD3, clone T3-4B5; CD8, clone CD8/144B; and CD103, clone BerAct8). In each case an isotype matched control antibody was also applied to demonstrate the specificity of the staining process. The labelled sections were visualised using a streptavidin-biotin-peroxidase kit. After counterstaining with Mayer's haematoxylin, the number of CD3, CD8, and CD103 positive cells was counted in each crypt cross section, and the mean number of each cell type in each crypt was calculated. Image analysis was used to demonstrate that the crypt cross sectional area did not vary between different sites within the colon.

Figure 1 shows the typical distribution of CD103+ T cells within the normal colon; it is apparent that many, but not all, of these cells are present within the epithelium. Figure 2 presents a summary of the numerical data derived from each of the eight normal patients. In the case of each phenotypic marker, the data are reproducible between individuals and show a significant decrease in the number of cells in

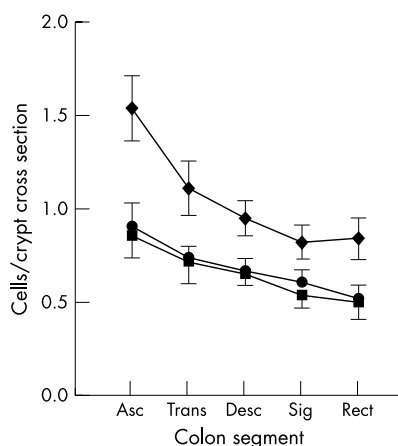


Figure 2 Summary cell count data showing the number of cells positive for CD3 (closed diamonds), CD8 (closed circles), and CD103 (closed squares) in each crypt within sections from the ascending (asc), transverse (trans), descending (desc), and sigmoid (sig) colon and the rectum (rect) from eight normal patients. Data points show the mean value; the error bars represent the SEM.

each crypt from ascending colon to the rectum (CD3, $p < 0.005$; CD8, $p < 0.02$; CD103, $p < 0.03$).

Our data show clearly and for the first time a linear decrease from the normal ascending colon to the rectum in the number of cells expressing the CD3, CD8, and CD103 phenotypic markers. Although it appears paradoxical that this gradient runs contrary to that which may be expected if CD103+ T cells are, indeed, the effectors responsible for tissue damage in ulcerative colitis, it is tempting to speculate that this gradient of T cell distribution has some impact on the potential for immune reactivity within the gut.

Acknowledgement

This work was supported by the National Association for Colitis and Crohn's Disease.

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Food for thought

We read the poem by Dr Tirumalae with interest.¹ Our particular interest stems from the work we did some years ago on the understanding, use, and potential modernisation of food terms in pathology. Having moved south from Lancashire and Cheshire, respectively, we found our missionary zeal to maintain the position of "sago spleen" as core knowledge in the medical curriculum was thwarted. The students of the South did not find reference to a Lancashire pudding tree bark to be of value in their education at all. In an attempt to rectify this we tried to update archaic food terms to ones more fitting to the 21st century. However, we stayed in the South and continued to modernise a small part of pathology, some years ahead of the "Pathology Modernisation

Programme". We hope the following references²⁻⁴ may be of some interest to Dr Tirumalae and the readers of this journal.

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How do we define Hodgkin's disease? The authors' reply

We have read with interest the eletter by Dr Naresh dated 26 March¹ in response to our earlier review.² This letter dealt with the problem of the borders between classic Hodgkin's lymphoma (cHL) and anaplastic large cell lymphoma (ALCL) and suggested that the proponents of the World Health Organisation (WHO) classification had a more flexible attitude towards cHL than ALCL.³ We believe that the WHO classification simply reflects the philosophy of the revised European-American (REAL) classification of lymphoid neoplasms, by drawing up a list of entities that can be readily recognised with the techniques available at the moment, which are defined by the amalgamation of cell morphology, phenotype, cytogenetics, molecular data, and clinical findings.⁴ This list can be easily updated, whenever new validated information becomes available in the literature.

We believe that the present scenario of cHL is much more homogeneous than the one depicted for ALCL. In fact, most if not all examples of cHL have a germinal centre cell derivation, as shown by molecular data and B cell specific activator protein (BSAP) expression,⁵ with cases of T cell origin being exceptional and still a matter of speculation.² In addition, a reasonable explanation has been found for the lack of immunoglobulin (Ig) expression by Hodgkin and Reed-Sternberg cells (HRSC), being related to either crippling Ig gene mutations or deregulation of the transcription factors Oct-2, BOB.1, and PU.1.^{2,6} These mechanisms differ—for instance—from the ones at work in primary mediastinal large B cell lymphoma (PMBL), which also lacks Ig expression and can at times be confused with cHL in needle biopsies. In fact, PMBL shows functional IgV_H gene mutations and intact expression of the above mentioned transcription factors, findings that—along with CD45 expression, regular B cell marker positivity, and the absence of CD15—allow the easy distinction between the two processes.⁷ Further information on the pathobiology of cHL (including the problem of the cytokinesis of HRSC)² is expected from the studies using the recently developed gene expression profiling and tissue microarray techniques.⁸⁻¹¹ The application of gene expression profiling may be more complex than in non-Hodgkin's lymphomas because of the need to isolate single neoplastic elements from the reactive

cellular background, but is certainly not impossible.⁸⁻¹⁰ Tissue microarray methods have already found a preliminary use, by showing in 330 examples of cHL that cyclin E plays a central role in the cell cycle deregulation of HRSC.¹²

On the other hand, the issue of anaplastic large cell lymphoma still sounds like the Pirandello's drama "Six characters in search of their author". The decision of considering anaplastic B cell tumours as a morphological variant of diffuse large B cell lymphoma (DLBCL)—adopted by the REAL classification⁴ and maintained in the WHO scheme³—is supported by the following arguments: (1) the consistent lack of ALK protein expression; (2) the evidence for possible transformation from a follicular lymphoma; (3) the occurrence of IgV_H gene somatic mutations; and (4) the clinical behaviour, which is quite similar to that of the remaining forms of DLBCL.^{13,14} Focusing on what is currently diagnosed as ALCL of T/null cell derivation,^{13,14} a basic distinction should be made, based on ALK protein expression.^{13,14} ALK positive ALCL, which comprises about 60% of all ALCL cases, corresponds to a distinct clinicopathological entity, characterised by: (1) ALK protein expression as a result of the t(2;5)(p23;q35) or a variant translocation involving the ALK gene (at 2p23); (2) a wide morphological spectrum (ranging from the common type to the small cell variant); (3) male predominance; (4) prevalence in the first two decades of life; and (5) a very good response to conventional chemotherapy in most instances (about 80% of patients are cured).^{13,14} This form of ALCL has nothing to do with cHL, which always lacks t(2;5) or variant translocations.³ The combined application of antibodies against the ALK protein and BSAP has allowed the critical revision of the so called Hodgkin's-like ALCL: at state of the art, there is evidence that most tumours diagnosed as such in the past are really histologically aggressive forms of cHL (ALK⁺ and BSAP⁺), whereas ALK⁺/BSAP⁻ ALCLs provided with some nodularity and sclerosis (thus mimicking nodular sclerosing cHL) are exceedingly rare.^{13,14} ALK protein expression, which leads to homodimer formation and constitutional activation of the ALK catalytic domain, is probably involved in the process of lymphomagenesis and seems to act on signalling proteins, such as phospholipase C γ and phosphoinositide 3-kinase, with a direct influence on the transduction of mitogenic signals and activation of the antiapoptotic Akt pathway, respectively.¹⁴ None of these events is known to occur in cHL. With regard to ALK negative ALCL, when excluding the primary cutaneous forms, which behave quite characteristically (with possible spontaneous regression in 25% of cases) and are related to lymphomatoid papulosis,¹⁴ the remaining tumours are controversial. In contrast to ALK⁺ tumours, they mostly occur in old patients and run a very aggressive clinical course, with a poor response to conventional regimens (only 30% of patients survive at five years). Thus, it is unclear whether ALK negative ALCL of the T/null cell type represents a separate entity or the end of the spectrum of peripheral T cell lymphomas. Within this context, a further intriguing problem is the recent observation that some cases phenotypically belonging to the null cell group express BSAP and carry IgV_H gene clonal rearrangements, the genes encoding T cell receptor β and γ being in germ line configuration.¹⁵ This finding highlights the need for the systematic evaluation of ALK

negative ALCLs using all of the tools available to collect histogenetically homogeneous tumours and to assess whether there is some common event among these that leads to neoplastic transformation.

Acknowledgements

Supported by AIRC grants to SAP and BF.

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BOOK REVIEWS



Cytopathology of Bone and Soft Tissue Tumours

Layfield LJ. (£115.00.) Oxford University Press, 2002. ISBN 0 19 513236 X.

"Fine needle aspiration (FNA) is only now gaining acceptance as a primary modality for the study of musculoskeletal lesions." So opens the preface to this book, and immediately the reader needs to choose how they are going to receive this statement. If you are sceptical then read the rest of the preface for its outline of the justification of FNA in this context, prepared to stay on the ship if persuaded; if you instantly agree then dive straight into the first chapter. It is an introduction, but with more than just technical aspects and analysis of rates of success or failure; the cost aware can read how many dollars are saved by FNA compared with open biopsies. Of more value are the tables and diagrams summarising cellular features in benign and malignant lesions, and algorithms for diagnosis. If you are going to use FNA for this purpose then get a copy of these tables on to the wall in front of you.

Most of the book works systematically through soft tissue and then bone tumours, using a standard pattern giving a description or overview, histological findings, cytological findings, problems in diagnosis, and a summary of key features. The text is clearly written, with good descriptions of the cellular features, and numerous illustrations: bullet points give added clarity where appropriate.

So what are you hoping to achieve by reading this book?

Are you part of a soft tissue/bone MDT actively involved in diagnosis, with appropriate discussion and information? This book will get you started.

Are you active in cytopathology and liable to receive incidental soft tissue pathology? This book should help prevent some errors, and will provoke clinical liaison.

Are you a histopathologist who is an occasional cytopathologist? All the illustrations will look the same, and you should not expect to make a useful comment most of the time.

In summary, this is a well written text on a difficult subject, with clearly presented information. Should you show this book to your clinical colleagues to encourage them to use FNA more often? It depends on whether you are an enthusiast.

J Goepel

The Hospital Autopsy, 2nd ed.

Burton J, Ruddy R, eds. (£55.00.) Arnold, 2001. ISBN 0 340 76420 1.

Didactic information in a textbook cannot substitute for practical experience in gaining skill and dexterity in the performance of autopsies. However, the editors have produced a commendable syllabus, making the most of the potential of a textbook in this area. This text is almost unique in this respect; it should be of major interest to trainees, but also presents useful reference material for established practitioners.

The first five chapters cover essential preparatory information for the autopsy, starting with the history and comments on the future of where autopsies are going. Autopsies and the law are then covered, in up to date and comprehensive detail (although the detail is likely to be UK specific). The ethical and religious aspects of autopsies are adequately covered. There then follows a valuable chapter on biological safety, which links through to a following chapter on autopsy suite design and construction.

The group of chapters that follow (5–8) cover the practical conduct of routine autopsies, which are well described and illustrated.

The next group of chapters (9–12) cover specialist dissection and circumstances, such as examination of the nervous system, and fetal, perinatal, infant, and maternal autopsies.

There then follows a group of chapters (13–15) that are a very valuable source of information on ancillary investigations such as toxicology, microbiology, and even immunological analyses.

The final group of chapters (16–18) round off the syllabus by discussing clinical demonstration, autopsy report formulation and teaching, reconstruction of the body, and the role of the autopsy in clinical audit. It might have been slightly more logical if reconstruction of the body had been included with the routine autopsy techniques.

Allowing for the limitations that a textbook cannot teach practical technique, that chapters on autopsy and the law are jurisdiction

specific, and that information on autopsy consent procedures is liable to become out of date as the regulatory environment moves on, it is difficult to conceive of a better syllabus within a textbook of this size. I warmly commend it as a bench book in all histopathology departments, whether trainees are present or not. Even for experienced practitioners, there is useful information on ancillary investigations, and advice on autopsy suite design of the calibre presented here is difficult to find elsewhere in any single source.

T Stephenson

Handbook of Toxicologic Pathology, 2nd ed

Haschek WM, Rousseaux CG, Wallig MA, eds. (£330.00.) Academic Press, 2001 ISBN 0 12 330215 3.

My first impression on being asked to review this "hand book" was that I would need big hands to hold it for long! I found this a most impressive text consisting of two volumes each of about 800 pages. The handbook is a multiauthor text and has now appeared in second edition.

Volume one describes various principles of toxicology whereas the second volume looks at organ specific toxicology. I found that some chapters were particularly good, such as those describing heavy metal toxicology and radiation damage. The handbook gives a wealth of information written by experts in their field. Colour photographs may have assisted the text but presumably at the expense of production costs.

In summary, I believe this to be a most comprehensive reference book covering the topic of toxicological pathology thoroughly. Although specialised, it may well find a place in the general histopathology or chemical pathology laboratory. More likely, it would be used in a specialist toxicology department or larger library.

M Crook

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How do we define Hodgkin's disease? The authors' reply

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J Clin Pathol 2003 56: 159
doi: 10.1136/jcp.56.2.159

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