LETTERS TO THE EDITOR

Gastric cancer cell lines lack Fas ligand (FasL) expression but kill T cells via a FasL-independent pathway

EDITOR—Bennett et al (Gut 1999;44:156–162) reported that in each of 30 paraffin wax specimens of human gastric adenocarcinomas, FasL mRNA and protein co-localised to neoplastic epithelial cells. TUNEL staining revealed that a high number of tumour infiltrating lymphocytes (TIL) displayed apoptotic features. From these results and from their findings of FasL expression in human colon and oesophageal cancer, the authors propose that FasL might be a mediator of immune privilege in gastrointestinal cancers.

We studied intrinsic FasL expression in gastric cancer cell lines derived from primary (RF-1, SNU-1) or from metastatic sites (SNU-16, Kato-III, N-87, RF-48). We did not detect Fas mRNA or protein in any of the six cell lines analysed by RT-PCR and by flow cytometry (table 1).1 We then performed the JAM assay to rule out the presence of a functional FasL expression below the detection limit of our assays.2 Although we found that gastric cancer cells were able to induce DNA fragmentation in the Fas sensitive T-cell lymphocytic leukaemia cell line CEM-C7H2 (fig 1A), blocking FasL on the effector cell site did not reduce the extent of cytotoxicity. This result was confirmed by replacing the target cell line by a subclone stably expressing the viral protein crmA, which inhibits activation of caspases 1 and 8 and thereby mediates resistance to Fas triggering (fig 1B).3

Owing to the discrepancy between our results (all lines were FasL negative) and those of Bennett et al (all 30 primary neoplasms), we wondered whether tissue derived factors such as tumour necrosis factor (TNF) α and interferon (IFN) γ might upregulate FasL in vivo, thus explaining the differences observed. In our setting, neither of the cytokines was able to modify FasL expression on gastric cancer cell lines (table 1). In addition, killing of T cell lines was not mediated via secretion of TNF-α as blocking the cytokine using a monoclonal antibody did not influence the result of the JAM assay (fig 1A). How can the


Table 1 Expression of FasL and Fas in gastric cancer cell lines and their sensitivity toward Fas triggering by the CH11 monoclonal antibody

<table>
<thead>
<tr>
<th>Cell line</th>
<th>FasL mRNA</th>
<th>+TNF-α (100 ng/ml)</th>
<th>+IFN-γ (100 ng/ml)</th>
<th>Fas expression</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF-1</td>
<td>Negative</td>
<td>1.1/1.0</td>
<td>1.0</td>
<td>0.8</td>
<td>8.3</td>
</tr>
<tr>
<td>RF-48</td>
<td>Negative</td>
<td>1.3/1.0</td>
<td>0.9</td>
<td>0.9</td>
<td>6.1</td>
</tr>
<tr>
<td>Kato-III</td>
<td>0.9/1.2</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>1.4</td>
</tr>
<tr>
<td>SNU-1</td>
<td>1.1/1.0</td>
<td>0.9</td>
<td>0.9</td>
<td>4.9</td>
<td>8.9</td>
</tr>
<tr>
<td>SNU-16</td>
<td>1.0/1.2</td>
<td>0.9</td>
<td>0.9</td>
<td>4.9</td>
<td>8.9</td>
</tr>
<tr>
<td>N-87</td>
<td>Not done</td>
<td>1.0/1.2</td>
<td>Not done</td>
<td>Not done</td>
<td>1.1</td>
</tr>
</tbody>
</table>

1. RT-PCR analysis was done as follows: total RNA from about 1 x 10^6 cells was extracted by the acid guanidinium thiocyanate-phenol-chloroform protocol described by Chomczynski and Sacchi; 1 μg RNA together with 250 ng of oligo (dT)15, primer was diluted in a.d. to a final volume of 14 μl, denatured by heating up to 70°C for five minutes and immediately chilled on ice. To each reaction, 6 μl RT mixture containing 4 μl 5x buffer, 2 pmol each of dATP, dCTP, dGTP and dTTP, and 200 units Moloney-murine leukaemia virus reverse transcriptase, was added (all reagents from Promega, Wisconsin, USA). For cDNA synthesis all samples were incubated at 37°C for 60 minutes. The reaction was stopped by heating the sample to 80°C for two minutes; 100 ng cDNA obtained was amplified by 50 cycles with 1 μg of respective specific monoclonal antibody or a relevant isotype matched negative control antibody for 30 minutes at 4°C. In the case of staining with NO-1, cells were incubated for 20 minutes at 4°C with a secondary fluorescin isothiocyanate (FITC) labelled rabbit anti-mouse antibody (Dako, Vienna, Austria; dilution 1 in 10). Cells were washed and immediately analysed by flow cytometry for their specific fluorescence signals.

2. Constitutive expression of FasL protein was determined using two different monoclonal antibodies, NOK-1 (Pharmingen, San Diego, California, USA) and H11 (Alexis, Lüffelfingen, Switzerland). For detection of FasL expression, 0.5 x 10^6 cells were fixed with paraformaldehyde, permeabilised with a buffer containing 0.05% saponin and 1% boronate serum albumin and stained with 1 μg of the respective specific monoclonal antibody or a relevant isotype matched negative control antibody for 30 minutes at 4°C. In the case of staining with NO-1, cells were incubated for 20 minutes at 4°C with a secondary fluorescin isothiocyanate (FITC) labelled rabbit anti-mouse antibody (Dako, Vienna, Austria; dilution 1 in 10). Cells were washed and immediately analysed by flow cytometry for their specific fluorescence signals. Mean specific fluorescence intensities (MFI) were calculated as the ratio of mean fluorescence intensity achieved with the specific antibody/isotype matched negative control antibody. A ratio > 1.5 was considered positive.

3. Values are given for day 3. Tumour necrosis factor (TNF) α and interferon (IFN) γ were purchased from R&D Systems (Minneapolis, Minnesota, USA). Flow cytometric analysis was performed using the NOK-1 monoclonal antibody.

4. Cells were incubated with the CH11 monoclonal antibody (250 ng/ml) for 24 hours and the proportion of apoptotic cells was determined using the propidium iodide assay. Even after 72 hours' incubation, there was only a very small increase in the percentages of apoptotic cells (e.g. in the SNU-1 cell line the increase was from 3% (control) to 5% (CH11)).
differences between in situ and in vitro results be explained? Bennett et al mention that CD45+ TIL express FasL mRNA, but they did not analyse Fas expression and sensitivity, features that together characterize activation induced cell death. Although on a morphological examination of slides the authors excluded the possibility of lymphocytes being killed by infiltrating neutrophils potentially attracted by the expression of FasL on the tumour cells, it is possible that lymphocytes succumbed to apoptosis owing to extrinsic factors or suicide. This mechanism could well be under the (cytokine) control of the tumour as has been discussed for other diseases. 

Alternatively, lymphocytes could indeed be killed by the tumour cells but by a mechanism independent of the Fas system, a hypothesis supported by our data (fig 1).

Bennett et al did not use the standard Lauren classification system. It has been shown that gastric carcinoma cells of the intestinal and diffuse type (according to Lauren) differ in morphology, growth pattern and risk factors, and also in their expression of molecules involved in apoptosis such as Fas or p53. It is evidence that at least in some tumour models Fas and FasL expression are under transcriptional control of p53. Loss-of-function mutations or deletions of p53 have been reported to be involved in gastric carcinogenesis and the frequency of these events differs between intestinal and diffuse gastric cancers. Also, a correlation between p53 mutation, Fas expression and gastric carcinoma cell differentiation has been demonstrated. Further studies of the impact of differentiation and p53 functional status on FasL expression are therefore mandatory in gastric carcinoma cells.

In sensitiveness towards Fas is usually an early step in tumour development, allowing tumour cells to resist the attack of the immune system and to avoid suicide when FasL expression is acquired. Furthermore, a sequence of Fas resistance and FasL expression has been postulated for hepatocellular carcinoma. Secondary loss of the Fas gene or of its expression during continuous culture of gastric adenocarcinoma cells is unlikely for the following reasons: (I) All lines were resistant to Fas and thus loss of FasL expression does not seem to be a prerequisite for their survival, and (ii) to our knowledge, no data are available from other cell (line) systems that tumour cell lines lose FasL expression during long term culture.

In conclusion, we think that Bennett et al’s data suggest that CD45+ lymphocytes die in the immediate proximity of neoplastic cells. Although their data are compatible with Fas induced TIL cell death, our functional data from cell lines suggest that other tumour mediated mechanisms of killing immunocompetent cells might also exist in gastric cancer. Further work clarifying the sequence of Fas/FasL expression and function during the transformation and metastatic processes is needed.

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8 Tinhofer I, Marschitz I, Kos M, et al. Differen-
tional sensitivity of CD4+ and CD8+ T lymphocytes to FasL of FasL (CD95) ligand+ tumor cells in B chronic lymphocytic leukemia. Blood 1998;91:4273–81.


12 Shao VH, Paal B, Breyer GS, et al. Implica-

13 Ari H, Gordon D, Nabel GJ, et al. Gene trans-

14 Strand S, Hofmann WJ, Hus H, et al. Lymp-

Reply

Etzioni—We concur with the view expressed by Tinhofer et al that Fas ligand (FasL) mediated “counterattack” against antitumour lymphocytes is not the sole mechanism of immune evasion in gastric, or indeed any other form of cancer. Tumours evolve multiple immune evasive strategies. However, there is ample in vitro and in vivo evidence that constitutive expression of FasL enables cancers to promote apoptosis of antitumour immune effector cells. For example, FasL has been significantly associated with apoptosis and loss of tumour infiltrating lymphocytes in human esophageal cancer
depression of antitumour natural killer cells in a mouse model.

In stomach cancer, apart from our finding of FasL expression at the mRNA and protein level in vivo in all 30 gastric adenocarcinomas examined, Rudi and colleagues also showed FasL mRNA in all three gastric carcinoma cell lines examined—including one cell line, KATO III, in which Tinhofer et al failed to detect FasL mRNA. This poses serious questions regarding the sensitivity of the FasL RTPCR performed by Tinhofer et al. In fact, appropriate positive controls have not been shown to verify that their negative findings are not merely owing to the insensitivity of their assays for detecting FasL mRNA and protein in adherent cells.

Successful use of the JAM assay depends on using target cells that exhibit good sensitivity to FasL mediated apoptosis. Even different cultures of cell lines that are regarded as Fas sensitive, such as Jurkat E6 cells, can vary in their Fas sensitivity for reasons which are unclear, and Fas resistant target cells are commonly generated. Tinhofer et al need to demonstrate that their cultures of CEM-C7H2 target cells were indeed susceptible to apoptosis via Fas in order to validate their negative JAM results. 

Authentic FasL mediated killing of Fas sensitive target cells is normally detectable after eight hours of co-culture with FasL expressing effector cells. Tinhofer et al performed a prolonged co-culture of 72 hours. It is possible that the cell death detected in target cells at this late stage was from non-specific effects, such as exhaustion of nutrients or growth factors in the presence of proliferating effector cells, rather than a specific killing mechanism. Tinhofer et al should repeat their JAM assay for a shorter time of length with highly Fas sensitive target cell lines and include a proved FasL expressing effector cell line as a positive control.

Tinhofer et al’s findings that gastric carcinoma cell lines are relatively resistant to Fas mediated apoptosis is consistent with findings for several other types of cancer cell. Fas resistant cell lines are resistant to the expression of FasL. Colon adenocarcinoma cell lines, for example, are also Fas resistant, enabling most colon adenocarcinoma cell lines to coexpress Fas and FasL without undergoing Fas mediated suicide. We agree with Tinhofer et al that the sequence of Fas/FasL expression and function during gastric carcinogenesis merits further investigation. Their suggestion that these molecules should also be investigated in metastases of gastric cancer is also pertinent as recent evidence suggests that FasL contributes to the invasion of Fas sensitive organs, such as the liver, by colonic adenocarcinoma cells.

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4 Rudi J, Kuck D, Strand S, et al. Involvement of the CD95 (APO-1/Fas) receptor and ligand system in Helicobacter pylori-induced gastric
Vector manometry and LOS dynamics

Editor,—We read with interest the recent paper by Kahrlas et al on the effect of hiatus hernia on gastric-oesophageal junction pressure (Gut 1999;44:476–482). These authors used a novel technique that combined vector manometry, fluoroscopy, and endoscopic tagging of anatomical landmarks to map the differences in pressure profile between patients with and without hiatus hernia. Analysis of the vector profiles, taken at end expiration, revealed two distinct high pressure zones in each of the seven patients with hiatus hernia. These were thought to represent an axial separation of the internal and external components of the lower oesophageal sphincter (LOS). When these high pressure zones were repositioned to represent a simulated reduction of the hernia, the vector profile took on the appearance of a normal sphincter. This study drew some interesting conclusions regarding the effect of hiatal hernia on LOS pressure dynamics. We would like to raise some points with the authors on the method of analysis used and the reproducibility of vector manometry.

With regard to the methodology of this paper, the numerical vector pressure analysis used rapid pull-through vector manometry (8 channel catheter, 0.7 ml/s pull-back speed). They showed that mean LOS pressure varied from 20 to 80 mm Hg in 20 pull-throughs performed in one hour in the same patient.1 Kahrlas et al did not mention the number of pull-throughs for each patient or the reproducibility of vector profiling. It is therefore difficult to draw accurate conclusions on the size and position of high pressure zones, particularly when the study population is limited to seven patients.

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Mycophenolate mofetil for Crohn's disease

Editor,—On the basis of a study reported recently by Neurath et al (Gut 1999;44:625–628), commentators in Gut1 and the Lancet2 suggested that mycophenolate mofetil (MMF) should be used in patients with Crohn's disease who have either not responded to or are intolerant of azathioprine or 6-mercaptopurine. This advice is premature: firstly, because the study was flawed and, secondly, because it examined only management of acute inflammation, not the place of MMF in maintaining remission and in steroid sparing (a fact acknowledged in both commentaries).

The study by Neurath et al compared the effect of MMF 15 mg/kg daily with azathioprine 2.5 mg/kg daily, both with high dose steroids, in the treatment of active chronic Crohn's disease (six months' follow up). The main conclusions were that activity, as measured by the Crohn's disease activity index (CDAI), dropped further at one month in patients given MMF plus steroids, compared with those given azathioprine plus steroids, and that this was as a result of a faster effect in more severe disease. The major drawbacks of the study were as follows. As pointed out by the authors, neither patients nor investigators were blinded. Four (11%) of 35 patients in the MMF group were lost to follow up compared with none in the azathioprine group: thus, results may have looked different if analysed on an intention to treat basis. The MMF group had higher starting CDAIs: if the levels of CDAI reached at one month were compared between groups, rather than the fall of CDAI, the groups may not have been significantly different. The division of patients into those with moderate and severe activity was retrospective: thus conclusions based on this division should be regarded as hypothesis generating only. Finally, differences between the groups do not reach formal statistical significance if adjustments for multiple comparisons are made. Finally, steroid usage in the two groups is not recorded: one can imagine a scenario where a poor early response would lead to more steroids being given and so to a better overall result.

I agree with the authors and commentators that alternatives to azathioprine/6-mercaptopurine are needed. I also agree that the therapeutic effect of MMF in chronic active Crohn's disease should be assessed in properly performed trials, and provided it is shown importantly that its effect in maintaining remission and in steroid sparing should be assessed. However, until then, MMF should be considered to have no clear indications for use in Crohn's disease.

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Reply

Editor,—Mycophenolate mofetil (MMF) is an immunosuppressant drug that is often used in organ transplantation.1 It is an outer prodrug of mycophenolic acid that inhibits inosine monophosphate dehydrogenase and potently suppresses lymphocyte proliferation.2 Furthermore, various clinical trials have shown its efficacy in suppressing autoimmune and chronic inflammatory disorders, such as rheumatoid arthritis,3 pemphigus vulgaris,4 and psoriasis.5 There are several case reports6 7 and also our controlled study indicating that MMF can be successfully used in patients with Crohn's disease. In our study treatment of patients with moderately active Crohn's disease with MMF/cortisone led to a significant reduction in clinical activity scores compared with treatment with azathioprine/cortisone. These data suggested that treatment of chronic active Crohn's disease with MMF/cortisone would be effective in inducing remission. As corticosteroids were given to patients in addition to

The clear track record of success of Emergency Abdominal Surgery is proved by the publication of a third edition. The authors, who are all from Aberdeen, classify themselves as general surgeons and the book is dedicated to the general surgeons of the future. As we enter the millennium, general surgery is still vital to the management of unclassified surgical emergencies, and surgeons of all disciplines need to be trained in triage. Yet, ultimately, it is probable that few of the subjects in this book will remain the province of the general surgeon and many will be shared within the auspices of specialist service groups. However, although the days of the general surgeon being responsible for the gut in systemic disease, areas of interest to the more experienced reader. There are also sections on essential procedures for those involved in the preparation of patients, and a comprehensive chapter on gastroenterological emergencies which should prove invaluable in accident and emergency departments.

The breadth of coverage is impressive for such a small book although some parts lack depth. However, the authors live up to their promise to include recent advances in all areas and supply a comprehensive selection of further reading for those requiring more detailed information. The style is dogmatic and didactic and, in conjunction with clear algorithms, presents information in the clear, concise manner essential to a rapid reference text. There are few radiological indications but they are of good quality and are accompanied by line diagrams to aid their interpretation. The book aims to be a rapid and comprehensive reference tool for a wide audience of health professionals. This new edition easily achieves this and will undoubtedly continue to be useful in surgeries and wards for those who work in gastroenterology but have limited practical experience of the specialty.

R A HARRY


The first edition of this handbook was a valuable resource to both junior hospital staff and family doctors for its practical coverage of basic gastroenterology. In the seven years since it was first published, there have been many advances in gastroenterology and these have been included in the new edition, which is a rapid reference book in which the authors hope will be of interest to doctors and health professionals in clinics, accident and emergency departments.

Covering a wide range of topics, including the various aspects of hollow organ gastroenterology, liver, biliary, and pancreatic disease, the book would be a worth while addition for anyone who requires the integration of pathophysiology with psychology, and even sociology. FGIDs also suffer from having no objective measurable abnormalities, so that classifications must of necessity be symptomatic based. The Rome process is a valid attempt to make this area of study less confused, more consistent, and scientifically respectable. As such, it undoubtedly has had a major impact, and Rome criteria are now used for the creation into most clinical trials and studies in this area. The senior chairman claims that this book has “done for functional gastrointestinal disorders what the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) has done for psychiatry.” While this may appear grandiose, I think it just might be true.

This book provides an overview of many years’ work, which have contributed to the evolution of functional gastroenterological disease (FGIDs). This is due in no small part to the “Rome” process, which is described in detail in the book. The challenge was to create order out of chaos by agreeing criteria for the diagnosis of FGIDs. The major advantage of such a classification is that studies using agreed definitions become comparable and the next study can build on the results of the last. The major disadvantages, which the authors constantly remind the reader of, are that uncritical readers may accept these definitions as fixed in stone. This work of course simplifies individual patients. We need to be constantly reminded that the new Rome criteria (for example, for irritable bowel syndrome), in reality excludes as many as 60% of the patients diagnosed as having IBS in clinical practice. This has the advantage of producing closely comparable patients for studies, but the disadvantage of reduced generalisability to normal clinical practice.

The excellent introductory chapter outlines the ideas behind the Rome process and emphasises the importance of the “biopsychosocial model for IBS” for understanding how sufferers become patients. I much enjoyed the next chapter on the basic science for neurogastroenterology, which summarises much work and renders it in a form readily understandable to clinicians with only vague memories of neuroanatomy. There then follows a section on motility and sensation measurements, again comprehensive but suitably cautious. There are sections on psychological assessments, and a good account of the weaknesses and strengths of various psychological rating scales for the non-psychiatric. Specific functional disor-
ders are then dealt with by distinguished coauthors and, as would be expected, these chapters form a comprehensive, well referenced account of current understanding of these conditions. There is also a detailed account of how the new criteria differ from the old ones, and what evidence has been used to make these changes. One disappointment for me, was to see how sparse the new evidence was and what a long way there is to go before we understand the pathophysiology of most of these conditions.

One example of the dangers of classification, if it replaces true inquiry, is the lack of any mention in the definition of irritable bowel syndrome of the response to food. Exaggerated defecation after eating and remission of abdominal pain on fasting is a very common feature in IBS, and yet it is not part of the definition. The danger is that this will lead the response to food to be ignored and not subject to the same detailed study as it might otherwise justify.

Although reviews are meant to be critical, I do believe that this book is essential reading for gastroenterologists, particularly those entering research in the important field of functional gastrointestinal diseases. There is a useful chapter on the design of treatment trials and appendices including some sample questionnaire forms would be useful to examine before setting up a study. My main caveat is to ensure that readers do listen carefully to the words of wisdom of W G Thompson, who clearly states that this document “does not represent the end but rather the end of the beginning”. It is important to test these criteria and to alter them as new evidence accumulates on the underlying mechanisms. They are a vital staging post in the route to increased understanding, however the more we understand these symptom based definitions will become. Once understood mechanisms, the less important these definitions will become. Once understanding, however the more we understand these symptom based definitions will become. Once understood mechanisms, the less important these definitions will become.

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