Table 3 Interleukin-23 receptor (IL23R) rs11209026G/A (Arg381Gln) transmission disequilibrium testing in trios with childhood onset IBD

Arg381Gln IL23R	Informative families (n)	Transmissions observed	Transmissions expected	p Value
IBD	34	59	50.5	0.004
CD	23	39	34	0.04
UC	9	16	13.5	0.09

Assessed using FBAT software Version 1.7.3 available from <http://www.biostat.harvard.edu/~fbat/fbat.htm>.

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis.

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JAK V617F missense mutation is absent in pancreatic cancer

Aberrant constitutive activation of STAT3 (signal transducer and activator of transcription) leads to cellular transformation and aids tumorigenesis in pancreatic cancer and its inhibition can lead to growth arrest.¹⁻⁴ The exact mechanism of this constitutive activation

has not been elucidated, although downstream mediators may include ERK and p21 signalling.¹⁻⁴ Blocking JAK2 (Janus Kinase), a known upstream activator of STAT3, by AG490, a tryphostin inhibitor, reduced phosphorylation of STAT3 and produced comparable in vitro effects, suggesting a role for JAK2 in pancreatic carcinogenesis.³

JAK2 V617F missense mutation has recently been shown by several independent groups to play an important role in myeloproliferative disorders⁵ as well as prothrombotic states such as Budd-Chiari syndrome (which may be due to latent myeloproliferative disorders).^{5,6} We postulated that JAK2 V617F mutation may play a role in pancreatic cancer, in which the prothrombotic state is well recognised.

We analysed genomic DNA (all from unstained slides of representative surgical specimens) from 26 patients undergoing surgery for various pancreatic diseases (table 1) along with genomic DNA from 10 cell lines (Panc1, Pca3, MiaPaCa2, Capan1 and 2, Suit2, AsPc1, 818.4, Hpa2, H766T) for JAK2 V617F mutation using phenol-chloroform extraction with ethanol precipitation, using appropriate positive and negative controls as previously described.⁶ Briefly, all cells (>70% tumour tissue in cancer specimens, no microdissection) were scraped from unstained slides into high salt buffer and samples were made up to 200 µl with proteinase K, RNase A and sodium dodecyl sulfate, incubated at 37°C overnight before phenol extraction and ethanol precipitation. Genomic DNA from cell lines was extracted from 70% confluent million cells using Trizol (Invitrogen Ltd, Paisley, UK) reagent digestion followed by ethanol precipitation. A highly sensitive allele-specific PCR was used to detect the G to T mutation in exon 14 of JAK2 (corresponding to amino acid position 617) as previously described.⁶ Briefly, a three primer PCR was performed which, in the absence of a mutation, produces an internal amplification control band. Where a mutation is present, an additional band is also amplified and is specific to the mutant sequence. The sensitivity of the assay is 1 cell in 100, determined by mixing positive control genomic DNA (extracted from HEL cells) with non-mutated genomic DNA. We have previously validated this methodology by conventional Sanger sequencing and pyrosequencing.⁶ No such mutations were detected at the JAK2 617 codon for pancreatic cancer or cell samples.

We propose that STAT3 activation, as previously described in pancreatic cancer,¹⁻⁴ is by mechanisms other than constitutive activation of JAK2 by missense mutation at the V617F site. Similarly, while JAK2 mutation is absent in acute myeloid leukaemia, STAT3 activation is common and is being explored.⁷ In glioblastoma, for example, it has been suggested that STAT3 is activated by exogenous interleukin (IL)-4.⁸ IL-4 interacts with IL-13Rα2 receptor and, although IL-13Rα2 does not bind with STAT3 directly, it blocks STAT6 activation and excludes this downstream event. Thus, IL-4 can have an anti-apoptotic effect in glioblastoma cells via STAT3 signalling. Conversely, deletion of the SOCS3 (suppressor of cytokine signalling 3) gene in liver cancer⁹ and silencing of the SHP1 gene (by methylation) in lymphoma¹⁰ can activate STAT3 signalling. It has recently been suggested that there may be novel mutations in exon 12 which may account for a minority of patients with polycythemia vera and idiopathic erythrocytosis, who are

Table 1 Characteristics and treatment of patients analysed

Diagnosis	N (males)	Median (range) age (years)	Stage (n)	Adjuvant chemotherapy or chemoradiotherapy	DVT/PE
Pancreatic ductal adenocarcinoma	16 (9)	64 (39–80)	I (1), II (4), III (9)	6 chemotherapy, 5 chemoradiotherapy	1 PE 6 months after adjuvant treatment
Periapillary neoplasms	6 (2)	61 (43–71)	II (2), III (2)	2 chemotherapy	–
Normal pancreas	1 (1)	47	–	–	–
Chronic pancreatitis	3 (1)	58 (47–65)	–	–	–

DVT, deep vein thrombosis; PE, pulmonary embolism.

V617F-negative.¹¹ The exact nature of STAT3 activation in pancreatic cancer remains to be elucidated.

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BOOK REVIEWS

Sleisenger and Fordtran's Gastrointestinal and Liver Disease

Edited by Mark Feldman, Lawrence S Friedman, Lawrence J Brandt. Philadelphia: Saunders Elsevier, 2006, £180 (hardback), pp 1–1540 and 1541–2890. ISBN 1-4160-0245-6

The 8th edition of this famous textbook is the first not to be edited by either of the original editors and the 3rd edition to include hepatology as well as gastroenterology, with 38 of the 124 chapters focused on liver and biliary disease. This book thus provides a comprehensive reference for general gastroenterologists as well as more specialised practitioners in gastroenterology and hepatology. The two volumes are presented in a modern glossy style with clear figures and plenty of high-quality line drawings and tables which make the individual chapters easy to read.

The first section on basic biology is relatively brief, but this is supplemented by introductions to the subsequent sections that include anatomical, embryological and developmental aspects for each organ. The book is multi-authored with 177 contributors, and the editors have done well to maintain a high general standard and a relatively uniform style. The book is dominated by North American contributors (154 out of 177) and, although this is understandable given the origins of the book in the USA, it is perhaps a shame that a more international authorship was not used.

There are several new chapters covering, for instance, gastrointestinal stromal tumours and eosinophilic disorders, plus expanded information on obesity and nutrition and a new section on psychosocial aspects. This latter section is particularly welcome in a gastroenterology textbook, given that so many patients present with symptoms that may reflect underlying psychosocial problems rather than established disease processes. On the whole, this section is thought-provoking and useful in outlining some alternative approaches to deal with difficult patients including an excellent section on palliative care. However, it is important to maintain scientific rigour in assessing alternative therapies. In several places in chapter 25, papers giving results of homeopathy trials are referred to as either showing a trend to improvement or highlight individual small studies, the results of which were not borne out by larger studies or meta-analysis. Reporting weak or defective clinical

trials is rightly considered unacceptable in other areas of medicine and the same rigour should apply to alternative therapies, particularly in the case of homeopathy where there is no scientific rationale for its action. Homeopathy has some powerful advocates, especially celebrities who give it a veneer of respectability which its lack of scientific integrity does not warrant. We must be careful as scientists that we do not inadvertently add to this by making ambiguous or conciliatory statements about studies that lack scientific rigour. To the authors' credit, they have added a section at the end of the chapter stating the importance of proper safety monitoring and regulation of complementary and alternative medicines and emphasising the enormous amounts of money involved in this lucrative market.

Elsewhere in the book there are a few idiosyncrasies in layout; for instance, primary sclerosing cholangitis is in volume 1 under biliary tract whereas primary biliary cirrhosis and autoimmune hepatitis are in volume 2 under liver, but for the most part the layout is clear and easy to follow.

One of the problems with textbooks is keeping up to date. An example of this is the omission of any reference to chemokines from the index and the use of outdated terminology when referring to chemokines in the section on mucosal immunity and lymphocyte trafficking to the gut. This emphasises the fact that textbooks are best used to reference clinical information and the established basis for disease rather than as cutting edge reviews of current scientific thinking. This brings up the conundrum of whether textbooks are still required when instantly updated information is readily available via the internet and when even a general facility such as Wikipedia contains increasingly sophisticated and comprehensive entries under medical and scientific subjects. If you haven't used Wikipedia before, look up coeliac disease for an example of the excellent quality of information available (http://en.wikipedia.org/wiki/Coeliac_disease). However, even superficial dipping into this book reveals a wealth of information which is not readily accessible elsewhere, which shows that although very few of us read such books from cover to cover, there is still a place for the well-written comprehensive textbook that can be consulted on encountering a difficult clinical problem or—more frequently these days in my case—a lapse in memory.

The quality of the latest version of this famous textbook makes it an ideal choice for the clinician who needs a comprehensive reference book covering all the important areas in clinical gastroenterology and hepatology.

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