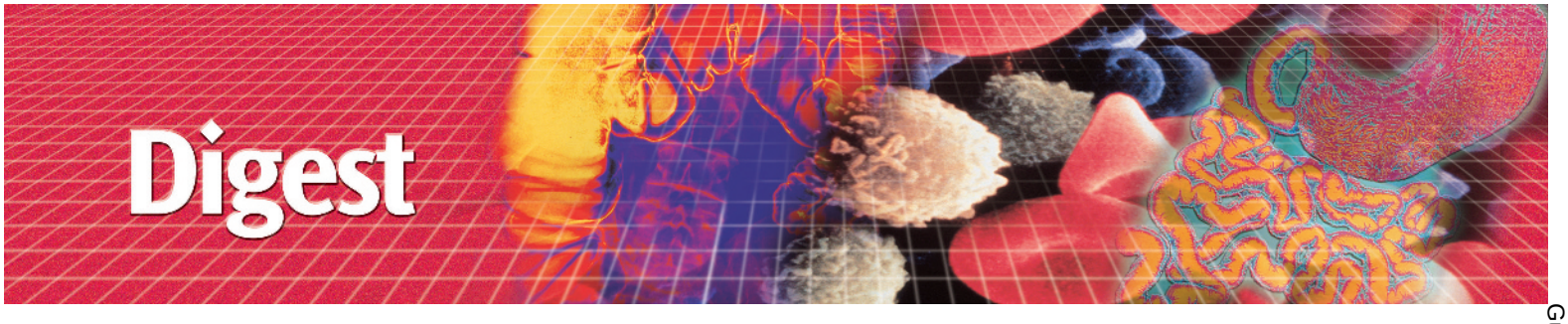

Robin Spiller and Alistair Watson, *Editor and Deputy Editor*

	IL-1B C−511T polymorphism		
	C/C	*C/T*	*T/T*
Case/control	26/36	60/34	26/8
OR	1	2.42	4.85
p Value	Referent	0.009	0.001
95% CI		1.25–4.68	1.86–12.6

GENETICALLY DETERMINED INCREASED SECRETION OF INTERLEUKIN-1β REDUCES THE RISK OF GASTRO-OESOPHAGEAL REFLUX DISEASE

Part of the confusion about the relationship between reflux symptoms and *Helicobacter pylori* infection arises because *H pylori* can be associated with both hyper- and hypo-acid secretion depending on whether antral gastritis or corpus gastritis predominate. The current study assessed symptoms of reflux, corpus atrophy, *H pylori* status, and the presence of the high producing interleukin 1β (IL-1β) polymorphism *IL-1β*−511 C/T. The key finding was that homozygotes for the *IL-1β*−511T polymorphism had a fivefold increased risk of atrophy (see table). They also found that homozygotes had a much reduced relative risk of reflux disease which was 0.14 (0.01–1.43) in *H pylori* negative and 0.14 (0.03-0.64) in *H pylori* positive patients. Thus genetically determined increased secretion of IL-1 β is likely to mediate both corpus atrophy and inhibition of acid secretion which may account for the reduced risk of reflux symptoms observed in these patients.

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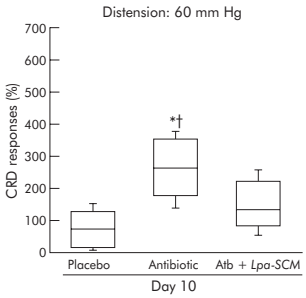

ANTIBIOTIC INDUCED VISCERAL HYPERSENSITIVITY CAN BE REVERSED WITH *LACTOBACILLI*

Use of broad spectrum antibiotics and gastrointestinal (GI) bacterial infection may both lead to the development of functional GI diseases. Subtle mucosal immune activation has been described in irritable bowel syndrome patients who often feature visceral hypersensitivity. This study examined how alteration of the mucosal flora impacts on these two features. The figure shows colorectal distension response (CRD) on day 10 expressed as a percentage of the day 0 response in placebo, antibiotic (Atb), and Atb+*Lactobacillus paracasei* (*Lpa*) treated mice. Broad spectrum antibiotics destroyed the normal lactobacilli found in the gut and were associated with visceral hypersensitivity, an effect which could be reversed with dexamethazone, implying an underlying inflammatory basis. Treatment with *L paracasei* also prevented the development of visceral hypersensitivity while decreasing tachykinin expression. These data provide some logic for probiotic therapy in patients suffering from visceral hypersensitivity and suggest that those with underlying inflammation might be particularly responsie.

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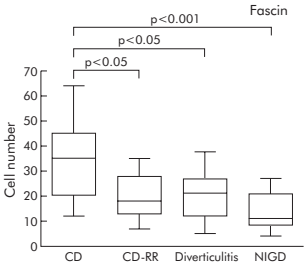

CD, Crohn's disease; CD-RR, non-inflamed colonic tissue affected by CD; NIGD, non-inflammatory gut disorder (normal controls).

THE ROLE OF MATURE DENDRITIC CELLS IN PERPETUATING INFLAMMATION IN CROHN'S DISEASE

The mechanisms initiating and maintaining an inflammatory reaction in Crohn's disease are poorly understood. Much attention has been devoted recently to an abnormality in the innate immune system of the gut, particularly the cytoplasmic immune receptor CARD15/NOD2, which is expressed in macrophages, epithelial cells, and Paneth cells, and recognises bacterial muramyl dipeptide. CARD15/NOD2 is mutant in 17% of patients with Crohn's disease and may result in failure of antibacterial immunity. The present paper focuses on acquired immunity and reports that there is an increase in mature dendritic cells in Crohn's inflammation leading to activation and proliferation of autoreactive T cells within the gut wall. There is also increased expression of the chemokine receptor CCR7 and its ligands CCL19 and 21 by reticular cells and lymphatics within the gut. The authors speculate that this abnormal chemokine environment traps dendritic cells at the sites of inflammation preventing its resolution.

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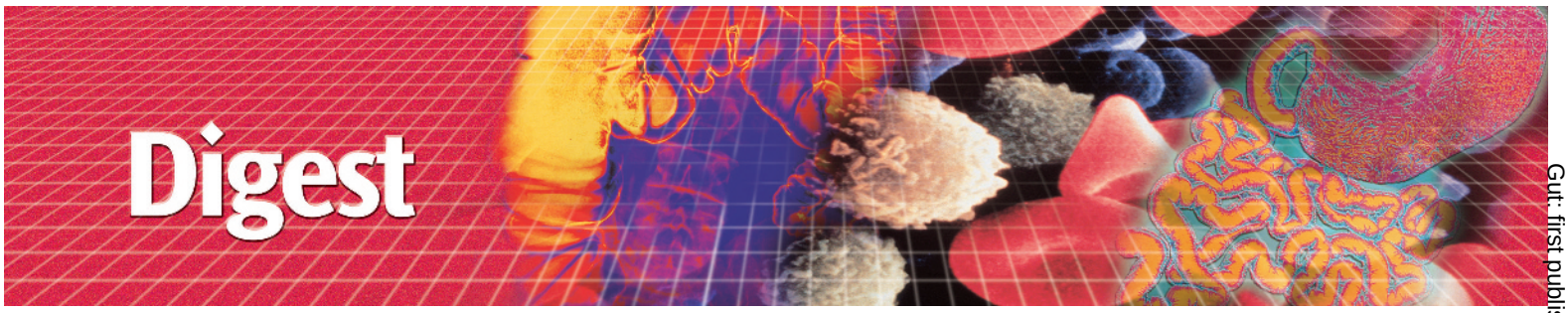

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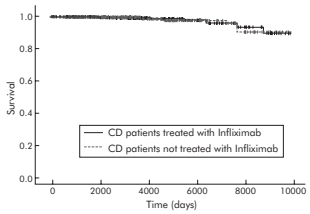

INFLIXIMAB AND CANCER RISK IN CROHN'S DISEASE

As Infliximab (IFX) use increases, concerns about the possible long term adverse effects of this potent immunosuppressant, especially the risk of cancer, also increase. This study used a case control design to compare the incidence of cancer in 404 Crohn's disease patients with no previous history of cancer who received IFX compared with 404 matched controls who never received IFX. As the figure shows, survival of these two groups from 1999 to 2004 was not significantly different. Nine of the Crohn's disease patients treated with IFX developed a neoplasm of whom three died while seven cases developed in those never treated with IFX and none died. While we can definitely say that over a five year period IFX does not significantly alter survival, it remains uncertain as to whether IFX impacts on survival of those who develop neoplasia while under treatment. A definitive answer to this question will require a much larger study.

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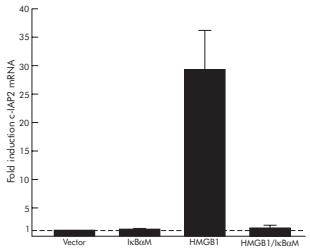

HMGB1 IS INCREASED IN COLON CANCER AND INHIBITS APOPTOSIS VIA NFκB AND IAP-2

It is widely appreciated that colon cancers are resistant to undergoing apoptosis. This promotes their growth and contributes to their resistance to therapy. In this article, the authors show that expression of high mobility group box 1 (HMGB1) is increased in human colorectal cancers. HMGB1 is a nuclear protein that contorts DNA and simultaneous binds to transcription factors, including nuclear factor κB (NFκB), thereby increasing its activity. The authors show that expression of HMBG1 inhibits apoptosis induced by a range of stimuli in cell lines. They hypothesise that the antiapoptotic effects of HMBG1 are mediated by induction of IAP-2 (inhibitor of apoptosis) expression via NFκB. Evidence for this is that inhibition of NFκB prevents induction of IAP-2 by HMGB1 and that in human cancers expression of HMBG1 correlates with IAP-2. The authors conclude that HMGB1 contributes to the development of colorectal cancer by inhibiting apoptosis via NFκB and IAP-2.

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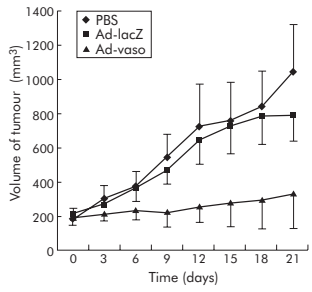

PBS, phosphate buffered saline; Ad-lacZ, Ad-vaso, adenovirus containing lacZ or vasostatin gene.

ANTIANGIOGENESIS THERAPY INHIBITS GROWTH OF PANCREATIC CANCER IN A MOUSE MODEL

Folkman's pioneering work demonstrating that new vessel formation is essential for the growth of cancers greater than 2 mm in diameter has stimulated research into cancer treatments based on inhibition of angiogenesis. Potent inhibitors have been developed, including endostatin, angiostatin, TNP-470 soluble flt-1, and NK4. In this issue, a study of the effects of the angiogenesis inhibitor vasostatin on pancreatic cancer is reported. The authors used a gene therapy strategy in which the vasostatin gene was engineered into an adenovirus. They were able to demonstrate that vasostatin reduced the growth of endothelial cells, but not pancreatic cancer cells, in vitro. The adenovirus containing vasostatin also prevented blood vessel formation in a cell culture model and chorioallantoic membranes in vivo. Crucially, the vasostatic substantially reduced the growth rate of pancreatic cancer cells in a mouse xenograft model. We now await the results of clinical trials of vasostatin in human disease.

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