# Digest

Robin Spiller, Editor

#### Importance of underlying mesenchyme in the development of intestinal metaplasia and gastric cancer

The atrophy-intestinal metaplasia-gastric cancer sequence following H pylori infection is well recognised but the mechanisms are poorly understood. There has recently been great interest in the intestinal specific transcription factor Cdx2, which is expressed in human gastric mucosa with intestinal metaplasia. Over expression of Cdx2 in transgenic mice causes complete intestinal metaplasia of the gastric mucosa and subsequent development of gastric polyps and carcinoma. It is well known that the basement membrane derived from intestinal mesenchyme stimulates intestinal cell differentiation, but the role of mesenchyme in controlling intestinal metaplasia is uncertain. The present study examined the stomach of Cdx2 transgenic mice for the presence of the pericryptal fibroblasts (PCFs), which are normally only found in the intestine. Although there were no PCFs in the normal stomach, they were clearly detected when intestinal metaplasia had developed but disappeared as gastric cancer developed. Similar changes were noted in intestinal metaplasia and gastric cancer from humans. This highly novel finding will encourage further study of the role of the mesenchyme in controlling the atrophy metaplasia and carcinoma sequence.

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## Osteoprotegerin and inflammation associated osteoporosis

Bone loss associated with inflammatory bowel disease is an important as yet unsolved clinical problem. An important study describes a potential new approach. Osteoprotegerin (OPG) is a soluble decoy receptor that binds and neutralises RANKL, a signalling molecule which activates the transcription factor NFκB in osteoclasts. Mice lacking OPG developed osteopenia while OPG over expressing transgenic mice developed osteoporosis. Recent studies have shown that OPG can prevent bone loss in animal models of arthritis and oestrogen deficiency. The authors used a model of inflammatory bowel disease, which is induced when immune deficient SCID mice are injected with a specific subset of T cells, known as CD4+CD45RBHi. These react to the microbial flora in an uncontrolled way because the SCID mice lack regulatory T cells that would normally damp down the inflammatory response. The net effect is significant weight loss, bowel inflammation, and a decrease in the bone density associated with inflammation in the bone marrow. OPG, given as the fusion protein with Fc component of immunoglobulin, prevented osteoporosis and reduced the number of osteoplasts and osteoclasts. Whether or not this new treatment will be of benefit in clinical practice remains to be seen. The animals used were still undergoing bone growth and had significant inflammation in the bone marrow, which might be an important difference from the usual IBD adult patient. However, it does suggest important new avenues in the treatment of IBD associated bone loss. See p 78

### Relationship between intra-abdominal fat and hepatic steatosis

Previous studies have shown that MR spectroscopy can be used to non-invasively monitor intra-hepatic lipid (IHCL). The study reported by Thomas *et al* showed that MR assessed ICHL increased by 21%, 72%, and 104% for each 1% increase in total subcutaneous fat, subcutaneous abdominal fat, and intra-abdominal fat, respectively (all expressed as percentage body weight). The study supports the key role of intra-abdominal fat in determining hepatic lipid content, probably because of its higher lipolytic activity and its direct input into the portal vein. Interestingly there was a wide range of IHCL in healthy volunteers, some of whom had IHCL which overlapped with those in patients with biopsy proven hepatic steatosis, showing that NASH patients represent the tip of the iceberg.

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## Non-invasive assessment of severity of hepatitis C associated liver disease from hepatic transit times

Microbubble contrast agents enhance ultrasound imaging and are soon likely to be widely available. It is of interest, therefore, that the time of appearance of these bubbles in the hepatic vein after injection into an anti-cubital fossa vein can be used as a measure of severity of liver disease. The authors from the Hammersmith Hospital, London, examined 85 patients with biopsy proven hepatitis C liver disease ranging from mild hepatitis to cirrhosis. Transit times fell from a normal of 38 s to 15 s as the severity of liver disease increased. All cirrhotics had a transit time of <21 s while all but one of the patients with mild hepatitis had a transit time of >28 s. These thresholds need confirming in another cohort, but if reproducible, may provide a useful additional non-invasive assessment to monitor response to treatment, which avoids the sampling problems associated with a single needle biopsy

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