IN THE NEWS

Gulf-war vaccination

'...classified 'secret' injections [given to soldiers before deployment in the 1991 Gulf War] ... have most probably led to the development of autoimmune-induced osteoporosis.'

This is the claim made in a leaked report for the war pensions agency by Lieutenant Colonel Graham Howe, clinical director of psychiatry with the British forces health service in Germany (*The Times*). This is the first official support for such a link.

The British Ministry of Defence (MoD) has rigorously denied the existence of a specific Gulf war syndrome — '...Gulf veterans do not present with a distinct and identifiable pattern of symptoms or signs.' (MoD website). For example, veterans have complained of a range of symptoms, from respiratory and digestive problems to memory and psychological problems (*Reuters*). Backed up by independent studies — such as a report by the Medical Research Council in May 2003 (*BBC News*) — the MoD also refutes any link between illness and vaccination.

However, Lt Col Howe describes the case of Lance-Corporal Alex Izett, who received vaccines against anthrax, botulism, plague and other unspecified biological agents in anticipation of war, but was not eventually required to fight. As the subject was not involved in fighting, the report states that the common factor linking the osteoporosis with which he suffers to the high incidence of osteoporosis in Gulf-war veterans is the vaccines he received.

Much of the press coverage has focused on the 'cocktail' of vaccines that soldiers are thought to have received, with some reports that 28 'jabs' were given. The coverage has been sufficient for this controversial issue to be raised in the House of Lords by Labour peer Lord Morris of Manchester (*The Guardian*).

Kirsty Minton

AUTOIMMUNITY

BCR and TLR9 cooperation in autoimmunity

The binding of haptenated CpG double-stranded (ds)DNA to hapten-specific B cells induces a suboptimal signal from a minimally crosslinked B-cell receptor (BCR). The BCR also functions to shuttle the CpG DNA antigen to an intracellular compartment containing Toll-like receptor 9 (TLR9). TLR9 signalling through a MyD88-dependent pathway, together with the signal from the BCR, leads to B-cell activation and proliferation.

Systemic lupus erythematosus (SLE) and other autoimmune diseases often involve a response to immune complexes containing DNA or chromatin-associated proteins. A new study published in *Immunity* has now set out to explain how the autoreactive B cells involved are activated and the exact nature of their specificity.

The AM14 autoimmune mouse strain produces B cells that recognize autologous IgG2a specific for DNA. In particular, the IgG2a antibodies that are recognized can complex with chromatin released from dying cells to form multivalent DNA-containing immune complexes (chromatin-ICs). Previous experiments have shown that in addition to B-cell receptor (BCR) recognition of IgG2a, the DNA portion of chromatin-ICs is involved in the activation of AM14 B cells through Toll-like receptor 9 (TLR9). TLR9 recognizes hypomethylated CpG-containing bacterial DNA, but such motifs are rare in mammalian DNA. The authors set out to investigate this system further using a series of defined haptenated double-stranded DNA fragments (such as NIP2-CG50-NIP) recognized by anti-hapten (NIP-specific) antibodies.

First, what are the relative roles of TLR9 and BCR signalling? Anti-NIP–NIP2-CG50-NIP immune

TUMOUR IMMUNOLOGY

STAT3 – a potential target for tumour immunotherapy

Inhibitors of signal transducer and activator of transcription 3 (STAT3) could be used to activate immune responses against tumours, according to a report now published in *Nature Medicine*.

Although tumour growth can activate inflammatory responses, the immune system generally ignores established cancers. As STAT3 is constitutively activated in many cancers, Wang *et al.* decided to investigate whether activity of this transcription factor could be involved in blocking the initiation of anti-tumour immune responses.

First, the authors observed that disruption of STAT3 signalling led to a selective increase in the production of pro-inflammatory mediators, including tumour-necrosis factor, interleukin-6 (IL-6) and the chemokine CCL5 by tumour-cell lines. By contrast, constitutive expression of STAT3 led to the inhibition of cytokine and chemokine production by tumour cells.

Next, they studied the effect of the pro-inflammatory mediators that are produced by STAT3-disrupted tumours on cells of the immune system. Cells of the innate immune

system, including macrophages and neutrophils, were activated to produce further pro-inflammatory mediators after exposure to the supernatant from tumour cells in which STAT3 was blocked. Furthermore, this supernatant also activated dendritic cells (DCs), which were then able to stimulate tumour-antigen-specific naive T cells to proliferate and produce IL-2 and interferon- γ . These results show that blocking STAT3 signalling in tumour cells results in the activation of both innate and adaptive anti-tumour immune responses.

Further experiments looked at the effects of constitutive expression of STAT3 by tumour cells. In addition to inhibiting the production of pro-inflammatory mediators by these cells, the authors showed that constitutive STAT3 activity induced tumour cells to