IN THE NEWS

Younger sibs cut MS risk

Being joined by a baby brother or sister before the age of 6 years can reduce your risk of developing the autoimmune disease multiple sclerosis by up to 88%, according to a study in *The Journal of the American Medical Association*. Anne-Louise Ponsonby, of the Australian National University, and colleagues suggest that the effect results from "altering childhood infection patterns and related immune responses".

The study compared 136 adults with multiple sclerosis with 272 age- and sex-matched controls in Tasmania, Australia. Based on questionnaire results obtained between 1999 and 2001, the authors conclude that the longer people in the first 6 years of life were exposed to siblings younger than 2 years, the greater the reduction in their risk of developing multiple sclerosis. Exposure for 1–3 years reduced the risk by 43%; 3–5 years of exposure reduced the risk by 60%; and more than 5 years of exposure reduced the risk by 88%.

Blood samples from the study participants were analysed for the presence of IgG specific for Epstein–Barr virus (EBV), which is a common childhood infection. In individuals without multiple sclerosis, increased exposure to a sibling was associated with a decreased IgG response to EBV. This lends support to the hygiene hypothesis, which states that exposure to infections early in life can influence the types of immune response that are induced later in life — for example, to self-antigens in autoimmune disease.

Patricia O'Looney of the National Multiple Sclerosis Society (United States) welcomed further research in this area but was careful to point out that "you're not at a higher risk for multiple sclerosis just because you don't have a sibling" (*HealthDay*).

Kirsty Minton

AUTOIMMUNITY

Raising the bar against lupus

The balance between activating and inhibitory signals that are delivered to immune cells sets the threshold for determining whether a response is mounted against a particular antigen and therefore whether tolerance or immunity is the result. One example of an inhibitory receptor that is thought to raise the activation threshold and prevent autoimmune reactions is FcγRIIB, which recognizes the Fc component of IgG — for example, in immune complexes. Indeed, several autoimmune-prone mouse strains, such as BXSB, express reduced levels of FcγRIIB at the cell surface of B cells, owing to a promoter polymorphism. Two recent papers by Jeffrey Ravetch and colleagues have investigated how FcγRIIB maintains tolerance and have shown that increasing its expression can be used to restore tolerance in a mouse model of the autoimmune disease systemic lupus erythematosus (SLE).

The first paper, in *Nature Immunology*, used an immunoglobulin heavy-chain gene-insertion model to look at the mechanism of action of FcγRIIB. 56R V_H knock-in mice express a rearranged immunoglobulin heavy-chain variable region with a high affinity for double-stranded DNA. Such DNA-specific antibodies are commonly found in patients and mice with SLE. On the BALB/c background, the knock-in does not result in the production of DNA-specific antibodies because of pairing with 'silencing' light-chain variants that alter the specificity. However, this tolerance resulting from light-chain editing is less efficient in C57BL/6 mice, which do develop circulating DNA-specific IgM. When the C57BL/6.56R mice were crossed with *Fcγr2b*$^{-/-}$ mice, this non-pathogenic IgM was converted to high titres of IgG that caused renal pathology through immune-complex deposition. The increased frequency of IgG production in the

FcγRIIB-deficient C57BL/6.56R mice was shown to result from an increased number of IgG$^+$ cells with a plasma-cell phenotype. The authors suggest that FcγRIIB is therefore a modifier of autoimmunity by regulating plasma-cell generation, rather than a primary initiator of the loss of tolerance, which in this case was the result of strain-specific differences in light-chain editing.

HAEMATOPOIESIS

Notch balances self-renewal and differentiation

Haematopoietic homeostasis depends on a balance between haematopoietic stem cell (HSC) self-renewal and differentiation. Defining the signals that regulate these processes is an area of intense research, and a recent study published in *Nature Immunology* identifies Notch-mediated signalling as crucial for regulating one aspect of HSC self-renewal — the maintenance of an undifferentiated state.

Notch- and WNT-signalling pathways are both known to have a role in regulating HSC self-renewal. However, little is known about the distinct contributions of these two signalling pathways to discrete cellular requirements for self-renewal — inhibition of differentiation and induction of proliferation. To investigate the role of Notch signalling in HSC function, Duncan *et al.* generated a Notch-reporter-transgenic mouse, in which expression of green fluorescent protein (GFP) is induced by Notch signalling. Immunofluorescence staining showed that a substantial proportion of cells expressing the HSC marker KIT in the bone-marrow HSC niche were transducing Notch signals.

Further analysis indicated that Notch signalling was more prevalent among HSCs than among lineage-committed cells, both when cells were analysed *ex vivo* and when HSCs were differentiated *in vitro*. Consistent with the hypothesis that Notch signalling is a marker of the most primitive cells, a greater proportion of GFP$^+$ HSCs had multi-lineage potential when cultured *in vitro*. Inhibition of the Notch-signalling pathway accelerated differentiation of HSCs *in vitro* and markedly reduced long-term HSC reconstitution of lethally irradiated mice, providing evidence of a role for Notch signalling in maintaining HSCs in an undifferentiated state.

The role of Notch signalling relative to other signalling pathways was studied using mice expressing reporters of both Notch