IN BRIEF

IMMUNOGENETICS

Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis

The International Multiple Sclerosis Genetics Consortium & The Wellcome Trust Case Control Consortium 2. *Nature* **476**, 214–219 (2011)

The results from the most extensive genome-wide association study to date of patients with multiple sclerosis have been published in *Nature*. Researchers from 23 groups based in 15 different countries analysed data from 9,772 patients of European descent and 17,365 controls. In addition to replicating previously identified multiple sclerosis risk loci, the data describe at least 19 new risk loci. Most of the risk alleles are found in regions of the genome associated with immune functions and, in particular, with helper T cell development. Indeed, although immune system genes (as defined in the gene ontology database) account for only 7% of human genes, the study found that in 30% of the regions linked to multiple sclerosis the nearest gene to the main single nucleotide polymorphism (SNP) is an immune system gene. Implicated genes include those encoding the cytokines interleukin-2 (IL-2), IL-7, IL-12, IL-22 and TNF, the co-stimulatory molecules CD40, CD80 and CD86 and several signalling molecules associated with T cell differentiation. Within the MHC loci, HLA-DRB1*15:01 was identified as the strongest risk allele and HLA-A*02:01 was confirmed as a protective MHC allele.

IMMUNOTHERAPY

T cells with chimeric antigen receptors have potent antitumour effects and can establish memory in patients with advanced leukemia

Kalos, M. *et al. Sci. Transl. Med.* **3**, 95ra73 (2011)

Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia

Porter, D. L. *et al. N. Engl. J. Med.* 10 Aug 2011 (doi:10.1056/NEJMoa1103849)

These two studies describe the positive findings of a pilot clinical trial that used engineered T cells (CART19 cells) to treat patients with chronic lymphocytic leukaemia (CLL). CART19 cells express a chimeric antigen receptor (CAR) that comprises the antigen-recognition domain of a CD19-specific antibody, a CD137 signalling domain and the CD3 ζ-chain. As the expression of CD19 is restricted to normal and malignant B cells, this antigen is regarded as a good target with which to test the safety of CARs. The CART19 cells were generated by transfecting autologous T cells isolated from each patient with a lentiviral vector that expressed the CAR construct. When a low dose of CART19 cells was transferred to the patients with CLL, these cells underwent population expansion, continued to express a functional CAR and persisted at high levels in the bone marrow and blood for at least 6 months. On average, each CART19 cell eradicated ~1,000 CLL cells and two out of the three patients who received the treatment showed complete remission. These results were particularly encouraging as two of the patients that were recruited for the study had p53-deficient CLL, which shows a poor response to conventional therapies and rapid progression. Toxic side-effects developed, including tumour lysis syndrome, lymphopenia and hypogammaglobulinaemia, but these were as expected. Overall, the studies highlight the potential of this new immunotherapy, but it may be challenging to develop this technique to treat cancers for which tumour-specific antigens are not well defined.