# In the news

## COLD–CANCER LINK

Common infections that affect mothers and babies might trigger certain types of childhood cancer, according to a report in the December issue of the *European Journal of Cancer*.

A team led by Richard McNally (University of Newcastle upon Tyne, UK) analysed more than 3,000 childhood cancer cases, in individuals of 0–14 years of age, that occurred over a 45-year period. They found unusual clusters of brain tumours and leukaemia that were typical of infection-related diseases (*BBC News*, 12 December 2005).

"We found that place of birth was particularly significant, which suggests that an infection in the mother while she is carrying her baby, or in a child's early years, could be a trigger factor in cancer … these could be minor common illnesses, such as a cold, mild flu or respiratory infection", said McNally (*Reuters*, 12 December 2005).

However, the researchers stressed that people could not 'catch cancer' from a cold, as only a small number of children that are already susceptible to the disease will be affected. "It is important to stress that it doesn't look as if it is any particular infection that is involved: rather it is the response of the body to a number of different infections", said Tim Eden, Cancer Research UK Professor of Paediatric Oncology at the University of Manchester (*Manchester Evening News*, 13 December 2005).

Analysis of patterns of childhood leukaemia and brain tumours suggested that 8% of cases were probably linked to the spread of infectious diseases. These findings support previous research that showed that young children who are socially active, such as those who attend nurseries, are less at risk than those who are more sheltered, because they develop stronger immune systems (*Telegraph*, 12 December 2005).

*Kris Novak*
*Senior Editor,* Nature Reviews Cancer

EVOLUTION

# Evidence stacks up for evolutionary link

Although the ability to distinguish between self and non-self (that is, histocompatibility) is common among metazoans, the genetic basis of this process has only been well described for vertebrates. In vertebrates, this process is mediated by molecules that are encoded by the highly polymorphic MHC locus and results in the rejection

ANTIBODIES

# IgG effector function: a question of balance

There are four subclasses of IgG antibodies, in both humans and mice, whose Fc regions differ in their ability to activate effector responses. Two theories have been proposed to explain these differences; first, that the differences are due to varying abilities to activate complement components in serum, and second, that the differences are due to differential binding to Fc receptors (FcRs). Now, in a study reported in *Science*, Falk Nimmerjahn and Jeffrey Ravetch show that the *in vivo* activity of IgG antibodies correlates with their interactions with FcRs and not with complement components.

FcRs can either activate or inhibit immune responses. A single inhibitory FcR, FcγRIIB, is present in both humans and mice, and the cellular response is determined by the balance between activating and inhibitory signals through FcRs on a cell. Each IgG subclass has a different affinity for different FcRs. In previous work, the authors developed the idea of an activating-to-inhibitory ratio (the A/I ratio, calculated by dividing the affinity of a specific IgG subclass for an activating receptor by the affinity for the inhibitory receptor) and found that these ratios varied between IgG subclasses. In the current study, an *in vivo* system was established to address whether A/I ratios correlated with the variation in subclass activity. The IgG2a subclass had the highest A/I ratio (~70) and the IgG1 subclass had the lowest ratio.

> "the differential biological activities of the IgG subclasses are dependent on their differential affinities for FcRs"

Two series of soluble IgG antibodies were generated, one specific for the melanoma antigen gp75 (TA99) and the other for the platelet integrin antigen 6A6, which allowed the authors to test whether A/I ratios correlated with the biological outcome. The antibodies were assessed for their ability to clear lung metastases in mice that were injected with tumour cells, or to clear integrin-expressing platelets. In both model systems, IgG2a, the IgG antibody subclass with the highest A/I ratio, displayed the best biological



© 2006 Nature Publishing Group

of transplants from donors who do not carry identical MHC alleles. Now, a report in *Nature* describes the isolation and characterization of the first known invertebrate histocompatibility gene.

When colonies of the sea squirt *Botryllus schlosseri* come into contact, they either fuse into a single colony or reject fusion. This was previously shown to be determined by histocompatibility reactions occurring at the periphery of each colony, the outcome of which depends on the alleles of the highly polymorphic locus FuHC (fusibility/histocompatibility) present in each colony. In this study, the authors mapped the FuHC locus and identified a candidate gene (*cFuHC*) that is highly polymorphic and encodes an immunoglobulin-superfamily member with no marked homology with MHC molecules. Polymorphisms in *cFuHC* were shown to segregate with histocompatibility, as determined by fusion or rejection of pairs of colonies. Protein expression was also shown at sites of histocompatibility reactions.

Histocompatibility in vertebrates is thought to be a by-product of MHC-gene polymorphism. For *B. schlosseri*, however, histocompatibility reactions might restrict DNA exchange, allowing these organisms to maintain a diverse gene pool. So, this form of interaction might have preserved the genetic fitness of our ancestors. The dual function of MHC molecules in histocompatibility and immunity has long indicated that these processes are evolutionarily linked, and FuHC is the first structural link between vertebrate adaptive immunity and invertebrate histocompatibility.

*Davina Dadley-Moore*

**ORIGINAL RESEARCH PAPER** De Tomaso, A. W. *et al.* Isolation and characterization of a protochordate histocompatibility locus. *Nature* **438**, 454–459 (2005)

outcome, and IgG3, the subclass with the lowest ratio, had the poorest outcome, showing that A/I ratios correlate with *in vivo* activity. When these experiments were repeated in complement-deficient mice, no differences in activity were observed. By contrast, the IgG subclasses showed enhanced activity in mice lacking the inhibitory receptor FcγRIIB, and IgG subclasses with low A/I ratios were most profoundly affected. The link between A/I ratios and biological activity was further explored by altering the glycosylation pattern of the IgG constant regions to alter the A/I ratios, and again a correlation between A/I ratios and biological activity was noted.

These results support the idea that the differential biological activities of the IgG subclasses are dependent on their differential affinities for FcRs. Although there is no direct correlation between the mouse and human IgG subclasses, the principle established with this study might be applicable to human situations and might lead to better predictability of antibody performance and selection of the most appropriate isotype for therapeutic situations.

*Elaine Bell*

**ORIGINAL RESEARCH PAPER** Nimmerjahn, F. & Ravetch, J. V. Divergent immunoglobulin G subclass activity through selective Fc receptor binding. *Science* **310**, 1510–1512 (2005)

# IN BRIEF

## DENDRITIC CELLS

### Siglec-H is an IPC-specific receptor that modulates type I IFN secretion through DAP12.

Blasius, A. L. *et al. Blood* 17 Nov 2005 (doi:10.1182/blood-2005-09-3746)

Marco Colonna and colleagues previously generated an antibody (denoted 440c) specific for interferon (IFN)-producing cells (IPCs; also known as plasmacytoid dendritic cells). They now show that 440c binds a new member of the sialic-acid-binding immunoglobulin-like lectin (SIGLEC) family, SIGLEC-H. SIGLEC-H is unique because it binds the adaptor protein DAP12 (DNAX activation protein 12). Stimulation with 440c has been shown to inhibit IPC production of IFNα that is induced by CpG-containing DNA (a Toll-like receptor 9 (TLR9) ligand), and low concentrations of CpG-containing DNA induce DAP12-deficient IPCs to produce more IFNα than wild-type cells. But high concentrations of CpG-containing DNA induce equivalent amounts of IFNα, leading the authors to suggest that low-level activation of DAP12 for example, by antibodies specific for associated receptors, sequesters signalling molecules and interferes with TLR signalling.

## PHAGOCYTOSIS

### A role for mammalian Diaphanous-related formins in complement receptor (CR3)-mediated phagocytosis in macrophages.

Colucci-Guyon, E. *et al. Curr. Biol.* **15**, 2007–2012 (2005)

Phagocytosis is mediated by receptors such as Fc receptors (FcRs) and complement receptor 3 (CR3). Colucci-Guyon *et al.* show that Diaphanous homologue 1 (DIA1), which regulates actin remodelling in fibroblasts, colocalizes with polymerized actin at the site of CR3-mediated phagocytosis in the macrophage cell line RAW264.7. In RAW264.7 cells, mutated DIA2 proteins that can inhibit endogenous DIA1 and DIA2, as well as knockdown of *Dia1* expression by small interfering RNA, decreased CR3-mediated phagocytosis, but had no effect on FcR-mediated phagocytosis. In addition, both the DIA2 mutants and knockdown of *Dia1* expression decreased actin recruitment to the site of CR3-mediated phagocytosis, providing a molecular distinction between CR3- and FcR-mediated phagocytosis.

## AUTOIMMUNITY

### Identification of autoantibody clusters that best predict lupus disease activity using glomerular proteome arrays.

Zhen, Q. L. *et al. J. Clin. Invest.* **115**, 3428–3439 (2005)

Systemic lupus erythematosus (SLE) is characterized by circulating autoantibodies, in particular autoantibodies specific for DNA or the glomerulus. Zhen *et al.* developed a 'glomerular-proteome array' to analyse the fine specificity of these autoantibodies and screened numerous glomerular, glomerular basement membrane and DNA antigens using this approach. IgG in the sera of patients with SLE fell into five clusters of antigen reactivity, two of which were associated with higher disease activity. By contrast, the specificity of IgM autoantibodies fell into two clusters of antigen reactivity (DNA-reactive or seemingly polyreactive). Individuals with IgM in the DNA-reactive cluster had more severe disease, leading the authors to suggest that analysing autoantibody specificity on a glomerular-proteome array might provide a new means of screening patients with SLE.



© 2006 Nature Publishing Group