In the news

COLD–CANCER LINK

Common infections that affect mothers and babies might trigger certain types of childhood cancers, according to a report in the December issue of the *European Journal of Cancer* (http://www.intl.elsevierhealth.com/journals/ejca/).

A team led by Richard McNally (University of Newcastle, UK) analysed more than 3,000 childhood cancer cases in 0–14-year-olds that occurred over a 45 year period. They found unusual clusters of brain tumours and leukaemia that were typical of infection-related diseases, reported the BBC news (http://news.bbc.co.uk, 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 (http://today.reuters.com, 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 Manchester University's Tim Eden to the Manchester Evening News (http://www.manchesteronline.co.uk, 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. This supports previous research that showed that young children who are socially active are less at risk than those who are more sheltered, because they develop stronger immune systems (http://www.telegraph.co.uk, 12 December 2005).

Kristine Novak

CACHEXIA

Strong potential?

> "DGC deregulation is an underlying cause of cachexia in cancer…"

Skeletal muscle wasting — cachexia — is a common and debilitating syndrome that is estimated to contribute to a third of all cancer deaths. Anti-cachexia therapy is often ineffective, but a recent publication by Denis Guttridge and colleagues, which shows that tumour-induced changes in the dystrophin glycoprotein complex (DGC) are a key early event in cancer cachexia, has the potential to help improve these treatments.

Muscle-wasting disorders, such as Duchenne muscular dystrophy (DMD), are commonly associated with mutations in DGC components. The DGC provides a crucial mechanical link between the cytoskeleton and the extracellular matrix (ECM) in muscle cells, as well as being involved in signal transduction and membrane integrity.

Histological analysis of cachectic muscle tissue from a tumour-bearing mouse model of muscle wastage showed that membrane morphology was abnormal and membrane integrity was compromised in these tissues. Similar to the situation in DMD, levels of dystrophin were reduced in cachectic tissue, and levels of the related molecule, utrophin, were increased. The DGC-associated molecules α- and β-dystroglycan were also hyperglycosylated. Moreover, the DGC dissociated from the cytoskeleton–ECM axis in the cachectic tissues, which is probably due to these molecular changes. Similar changes were found in the DGC from a different cachectic tumour-bearing mouse model, which shows that changes in the DGC are characteristic of tumour-induced muscle wastage.

Induced loss of DGC also exacerbates tumour-related muscle wasting — a severe atrophic effect was seen in tumour-bearing mice but not in otherwise normal mice. Furthermore, muscle-specific dystrophin expression in cachectic tumour-bearing mice rescued the cachexia phenotype,

IMMUNOLOGY

Suppressing T-lymphocyte cytotoxicity

One way in which tumour cells avoid the host tumour-specific T-cell response is by producing, or inducing host cells to produce, transforming growth factor-β (TGFβ). TGFβ has a broad range of immunosuppressive effects but the specific mechanism by which it inhibits T-cell-mediated clearance of tumours is not known. Now, in a report published in *Cancer Cell*, it is shown that TGFβ inhibits the expression of effectors of cytotoxic T-lymphocyte (CTL)-mediated cytotoxicity.

Although TGFβ can inhibit the growth of tumour cells, as tumours progress they often become resistant to these growth-inhibitory effects, enabling the tumour to take advantage of the immunosuppressive properties of this cytokine. The importance of this was shown by the authors, as

which provides further evidence for the crucial role of the DGC in this syndrome.

The muscle-specific E3 ubiquitin ligase, MuRF1, is involved in proteasome-mediated proteolysis in cachexia, and MuRF1 was found to be induced at around the same time that changes in the DGC are first detected. MuRF1 expression was also reduced in muscles in which the cachexia phenotype had been rescued by DGC expression, which together indicate that DGC dysfunction might regulate the ubiquitin–proteasome system.

Finally, DGC was found to be deregulated in cachectic cancer patients: 59% of 27 gastro-oesphageal adenocarcinoma patients had deregulated DGC, and 91% of patients with cachexia, who were selected using stringent parameters, had prominent DGC deregulation. Strikingly, 100% of the 10 non-surviving cases had DGC deregulation.

So, DGC deregulation is an underlying cause of cachexia in cancer as well as in muscular dystrophy, and restoration of this complex should be explored as a possible anti-cachexia treatment.

Lesley Cunliffe, Copy Editor, Nature Reviews Molecular Cell Biology

ORIGINAL RESEARCH PAPER Acharyya, S. *et al.* Dystrophin glycoprotein complex dysfunction: a regulatory link between muscular dystrophy and cancer cachexia. *Cancer Cell* **8**, 421–432 (2005)

they found that (consistent with previous studies), in a mouse tumour model, systemic neutralization of TGFβ *in vivo* results in tumour clearance. Tumour clearance was associated with an increase in $CD8^+$ T-cell-mediated tumour-cell-specific cytotoxicity. Consistent with this, the gene-expression profiles of T cells activated *in vitro*, in the presence or absence of TGFβ, showed that the genes encoding perforin, granzyme A, granzyme B, interferon-γ (IFNγ) and CD95 ligand (CD95L, also known as FASL) — which are the effectors of CTL-mediated cytotoxicity — were downregulated in the presence of TGFβ. Further analysis showed that the intracellular level of each of these proteins was also decreased after *in vitro* activation of $CD8^+$ T cells in the presence of TGFβ, as was the ability of the CTLs to mediate target-cell lysis. Most importantly, in the mouse tumour model, in which systemic neutralization of TGFβ *in vivo* results in tumour clearance, tumour-specific $CD8^+$ T cells were shown to recover expression of perforin, granzyme A, granzyme B and IFNγ, but not CD95L, if TGFβ was neutralized *in vivo*.

This study indicates that TGFβ not only inhibits the clonal expansion of tumour-specific $CD8^+$ T cells, but also suppresses the ability of these cells to mediate cytotoxicity. These data led the authors to suggest that further understanding of the mechanisms by which TGFβ mediates these effects might provide new impetus to the development of therapies that inhibit TGFβ because such therapies would not only target the immunosuppressive effects of TGFβ, but also target the pro-metastatic effects of this cytokine on tumour cells.

Karen Honey, Senior Editor, Nature Reviews Immunology

ORIGINAL RESEARCH PAPER Thomas, D. A. & Massagué, J. TGF-β directly targets cytotoxic T cell functions during tumor evasion of immune surveillance. *Cancer Cell* **8**, 369–380 (2005)
FURTHER READING Trapani, J. A. The dual adverse effects of TGF-β secretion on tumor progression. *Cancer Cell* **8**, 349–350 (2005)

IN BRIEF

ANTICANCER DRUGS

Activated B-RAF is an HSP90 client protein that is targeted by the anticancer drug 17-allylamino-17-demethoxygeldanamycin.

Da Rocha Dias, S. *et al. Cancer Res.* **65**, 10686–10691 (2005)

Heat-shock protein 90 (HSP90) is a chaperone protein that is essential for the proper folding and activity of many proteins that are involved in cancer, making it an ideal, broad-range anticancer target. A drug that targets HSP90, 17-allylamino-17-demethoxygeldanamycin (17-AAG), is currently in clinical trials. This paper shows that activated BRAF is a HSP90 client protein. The oncogenic forms of BRAF are degraded in the presence of 17-AAG and seem more sensitive than wild-type BRAF, making 17-AAG a potential treatment for tumours with mutated BRAF.

CANCER STEM CELLS

Hematopoietic stem cells express multiple myeloid markers: implications for the origin and targeted therapy of acute myeloid leukemia.

Taussig, D. C. *et al. Blood* **106**, 4086–4092 (2005)

Stem cells are generally thought not to express lineage-specific differentiation markers. But evidence from mouse haematopoietic stem cells (HSCs) contradicts this. Now, David Taussig and colleagues show that human HSCs express a set of myeloid markers and that leukaemic stem cells from patients with acute myeloid leukaemia (AML) are restricted to the $CD33^+$ (a myeloid marker) fraction. These findings indicate that our current models of HSC differentiation might need to be re-assessed, and that the use of myeloid-based therapies for AML might also target healthy HSCs.

IMMUNOLOGY

TWEAK attenuates the transition from innate to adaptive immunity.

Maecker, H. *et al. Cell* **123**, 931–944 (2005)

Innate immunity is the first line of defence against infection and protects the host during the development of the adaptive immune response. This paper demonstrates that the tumour-necrosis-factor-α-related protein, TWEAK, functions to control the transition from an innate to an adaptive response. Importantly, TWEAK-null mice demonstrate a more robust response than controls when challenged with melanoma cell lines. These findings indicate that the inhibition of TWEAK might increase the anti-tumour immune response.

SENESCENCE

Involvement of MINK, a Ste20 family kinase, in Ras oncogene-induced growth arrest in human ovarian surface epithelial cells.

Nicke, B. *et al. Mol. Cell* **20**, 673–685 (2005)

Activated mutant RAS can induce senescence when expressed in some untransformed cell types. David Hancock and colleagues have employed RNA interference to identify proteins downstream of RAS that induce this response. They have isolated a mitogen-activated protein kinase kinase kinase kinase, MINK, which has not previously been implicated in Ras signalling. Activation of MINK in response to RAS mutation might act to suppress cellular transformation.