IN THE NEWS

A powerful argument?

Living within 200 m or between 200–600 m of power lines increases the incidence of childhood leukaemia by 70% or 23%, respectively, according to a study by John Swanson and colleagues (Draper, G. *et al. BMJ* 330, 1290 (2005)). However, this headline-grabbing result needs to be interpreted with caution.

Electromagnetic fields, such as those produced by power lines, have, among other things, been proposed to influence some biological processes, affect free radicals and even deflect cosmic rays onto people in their vicinity. But evidence to support any of these theories is "at best thin and at worst non-existent," according to a commentary in the *BMJ* (Watts, G. *BMJ* 330 (2005)). So despite Gerald Draper from the study team referring to these findings as "statistically really strong" (http://www.washingtonpost.com/, 2 June 2005), whether actual proximity to power lines is the cause of this pattern of leukaemia incidence is debatable.

The authors accept that the epidemiological results could be due to unidentified factors. Indeed, as electromagnetic fields should not influence people living over 200 m away from the source, other aetiological factors might be responsible for the results. Moreover, according to the study, only 5 of the 400–420 childhood leukaemia cases reported annually could be associated with power lines.

David Grant of Leukaemia Research concludes "There is no reason why anyone should be advised to move house on the basis of these results" (http://www.bbc.co.uk, 3 June 2005.)

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in MYC-driven lymphomas. Given that these miRNAs are also expressed in embryonic stem cells, the authors propose that expression of these miRNAs might confer a stem-cell-like phenotype. This, combined with a reduction in apoptosis, implies that the *mir-17* miRNAs have oncogenic potential in this context.

As miRNAs affect the regulation of a range of mRNAs, many of which have yet to be characterized, no doubt the genetics and microenvironment of the cell, and other factors, will influence their effect in tumorigenesis. More work on the *mir-17* cluster will undoubtedly follow.

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References and links

ORIGINAL RESEARCH PAPERS O'Donnell, K. A. *et al.* c-Myc-regulated microRNAs modulate E2F1 expression. *Nature* **435**, 839–843 (2005) | He, L. *et al*. A microRNA polycistron as a potential human oncogene. *Nature* **435**, 828–833 (2005)

FURTHER READING Lu, J. *et al*. MicroRNA expression profiles classify human cancers. *Nature* **435**, 843–838 (2005)

IMMUNOTHERAPY

Don't peak too soon…

Adoptive cell-transfer therapy (ACT), in which tumour-reactive T cells are activated and expanded *in vitro* before being returned to the patient, is one of the few methods of cancer immunotherapy that has managed to successfully induce clinical responses against metastatic solid tumours. A particularly attractive aspect of ACT is that specific T cells can be selected for their functional properties before they are transferred into the patient. However, which stage of T-cell differentiation is associated with the successful treatment of tumours *in vivo* has not been fully investigated, and the current T-cell-selection criteria do not guarantee *in vivo* efficacy.

Gattinoni *et al*. analysed the function of $CD8^+$ T cells at different stages of differentiation (naive, early effector, intermediate effector and effector) to determine whether this affected the ability of T cells to mediate tumour regression in a mouse model. Surprisingly, the authors found that, despite having the most effective antitumour effects *in vitro*, the highly differentiated effector T cells were 100-fold less effective *in vivo* than T cells that were only at the early-effector stage. In fact, the characteristics that are currently used to select T cells for use in the clinic — interferon-γ release and *in vitro* cytotoxicity — are negatively correlated with *in vivo* antitumour efficacy.

Microarray analysis revealed that the more differentiated T cells expressed high levels of genes encoding pro-apoptotic molecules, such as BID, BAD and FAS ligand, as well as genes associated with replicative senenscence, indicating that these cells might be less 'fit' *in vivo*. And the proliferative capacity of the transferred T cells *in vivo* did, in fact, decrease with the progressive acquisition of *in vitro* antitumour function.

Analysis of the early-effector T cells identified a subpopulation that expressed high levels of the CD26L marker ($CD62L^{high}$) and showed superior antitumour efficacy after vaccination with antigen, despite seeming similar to their $CD62L^{low}$ counterparts. $CD62L^{high}$ cells preferentially home to lymph nodes and analysis showed that this marker targets the transferred T cells to professional antigen-presenting cells (APCs) that are expressing tumour antigen as a result of the vaccination. Loss of CD62L through T-cell differentiation impairs the interaction with APCs and compromises T-cell activation and proliferation *in vivo*, thereby inhibiting their antitumour activity.

So, early-effector T cells with high levels of lymphoid-homing molecules are the best T-cell populations to use for ACT. However, the necessary step of *in vitro* T-cell expansion to produce clinically therapeutic cell numbers inevitably causes differentiation and loss of these important cell markers. At present, interleukin-2 (IL-2) is used to induce T-cell proliferation, but this also induces differentiation. However, the authors show that IL-15 can uncouple differentiation from proliferation to produce a large T-cell population that is more likely to retain CD62L and is therefore significantly more effective when used in ACT.

These findings will be crucial for the further development of ACT as a clinical treatment, and the authors propose that the current T-cell-selection criteria should be modified to select for less differentiated, more effective T cells.

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References and links

ORIGINAL RESEARCH PAPER Gattinoni, L. *et al*. Acquisition of full effector function *in vitro* paradoxically impairs the *in vivo* antitumour efficacy of adoptively transferred $CD8^+$ T cells. *J. Clin. Invest.* **115**, 1616–1626 (2005)