

treated individuals, and NADPH-oxidase activity was reconstituted in these cells. Although the amount of superoxide produced by genetically modified neutrophils from the patients was less than that produced by neutrophils from healthy individuals, it was sufficient to mediate bacterial killing. Furthermore, the two individuals who had received gene therapy showed no evidence of recurrence of the bacterial and fungal infections that they had suffered before treatment.

Although this trial resulted in the successful treatment of two individuals with X-linked CGD, monitoring of the individuals will continue for 3–5 years because of the possibility that the abnormal clonal expansion observed could eventually result in leukaemogenesis.

Karen Honey

ORIGINAL RESEARCH PAPER Ott, M. G. *et al.* Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of *MDS1-EV11*, *PRDM16* or *SETBP1*. *Nature Med.* 2 Apr 2006 (doi:10.1038/nm1393)

Mechanistically, it was shown that CRIg on the surface of Kupffer cells is constitutively being internalized and then recycled back to the cell surface. Consistent with this finding, internalized CRIg was observed to colocalize with transferrin, which is a marker of recycling endosomes, and not with lysosomal-associated membrane protein 1, which is a marker of lysosomes. Further analysis showed that during phagocytosis of C3-opsonized particles, CRIg is recruited to the forming phagosome but returns to the recycling endosomes before, or during, phagosome–lysosome fusion.

This study identifies CRIg as the main receptor expressed by Kupffer cells for pathogens opsonized with C3 fragments that induces phagocytosis, and thereby clearance, of these pathogens. As such, CRIg functions as a key mediator of the first line of host defence against systemic infections.

Karen Honey

ORIGINAL RESEARCH PAPER Helmey, K. Y. *et al.* CRIg: a macrophage complement receptor required for phagocytosis of circulating pathogens. *Cell* 124, 915–927 (2006)

IMMUNOTHERAPY

Right place, right time



The delivery of biological therapy to the right place at the right time is a key aim for the treatment of cancer. Such directed therapies will have an enormous advantage over non-specific chemotherapeutic approaches that do not differentiate between cancer cells and non-cancer cells. Reporting in *Science*, Thorne *et al.* have found a way of combining two candidate antitumour approaches to achieve specific targeting of tumours and to increase efficacy in mouse tumour models compared with either approach alone.

The authors isolated a population of cells — which they named cytokine-induced killer (CIK) cells — that are derived from human peripheral blood or mouse splenocytes after culturing in the presence of interferon- γ , interleukin-2 and CD3-specific antibody. The CIK cells express T-cell markers and the natural killer (NK)-cell receptor NKG2D (NK group 2, member D), through which they recognize and kill cells expressing the stress-associated ligands MHC-class-I-polypeptide-related sequence A (MICA) and MICB. Because MICA and MICB are expressed under conditions of cellular stress, such as in the tumour microenvironment and after viral infection, CIK cells can be used to specifically target tumour cells *in vivo* despite not knowing any tumour-specific antigens.

To further increase the cytolytic capabilities of CIK cells, the authors infected them with a modified vaccinia virus. The key advantage of this modified vaccinia virus is that it has been

engineered to preferentially replicate in and lyse transformed cells. This was achieved by deletion of the viral genes encoding thymidine kinase and viral growth factor. This modified virus, referred to as double-deleted vaccinia virus (vvDD), only replicated in dividing cells in which cellular thymidine kinase expression is upregulated and in cells with dysregulated growth-factor-receptor signalling (both common features of tumour cells).

Putting these two approaches together therefore provides a means to target tumour cells and deliver a cytolytic agent in a synergistic manner. The synergy is due, in part, to the replication of vaccinia virus in CIK cells being delayed for more than 48 hours after infection, allowing the CIK cells time to reach the tumour site before releasing the lytic virus.

The authors used non-invasive bioluminescence imaging to track vvDD-infected CIK cells following transfer to mice bearing tumours. Importantly, two days after intravenous transfer, vvDD-infected CIK cells were detected at the tumour site and were barely detectable in other parts of the body. Moreover, vvDD-infected CIK cells were shown to penetrate deeper into the tumour mass than vvDD delivered alone.

Next, the authors tested the antitumour efficacy of the combination therapy compared with each therapy alone. Injection of immunodeficient mice bearing established human peritoneal tumour xenografts with CIK cells alone could extend the survival of the mice by 8 days. Injection of vvDD alone increased survival by 15–16 days. By contrast, the combination therapy resulted in a complete response in all mice with no relapse for the duration of the study (90 days). This efficacy of the combination therapy was also seen in immunocompetent mice bearing mouse breast cancers. In this case, injection of vvDD-infected mouse CIK cells resulted in complete responses in six of eight mice, whereas injection of mouse CIK cells and vvDD separately (but on the same day) resulted in a complete response in only one of eight mice.

Although the animal models are encouraging, further studies will be required to determine whether this combination approach will translate to humans.

Lucy Bird

ORIGINAL RESEARCH PAPER Thorne, S. H., Negrin, R. S. & Contag, C. H. Synergistic antitumor effects of immune cell-viral biotherapy. *Science* 311, 1780–1784 (2006)