news

Sourcing natural killer cells for antitumor immunotherapy

Jane Bradbury, janeb@sciscribe.u-net.com

Human embryonic stem cells (hESCs) might one day provide treatments for cancer, report Minnesota-based scientists Dan Kaufman and Jeffrey Miller. The researchers and their colleagues have converted hESCs into natural killer (NK) cells, a type of immune cell that can destroy cancer cells [1]. It will be several years, warn Kaufman and Miller, before hESC-derived NK cells will be ready to try in patients but hESCs could provide an unlimited source of NK cells for cancer therapy.

NK cells for cancer killing

Unlike T and B lymphocytes, components of the adaptive immune system that make specific responses to foreign antigens, NK cells (part of the innate immune system) kill cells that have lost expression of major histocompatibility complex class I molecules. Tumor cells often downregulate class I expression, explains Miller, Associate Director of Molecular and Cellular Therapeutics in the Department of Medicine and Cancer Center, University of Minnesota, USA, 'and we have known for about 30 years that NK cells purified from the blood can kill some tumor targets'. Attempts to treat cancer by boosting endogenous NK activity in patients with cancer have proven ineffective, however, possibly because NK cell activity is inhibited by receptors on the tumor cells that the NK cells recognize as self.

To circumvent this problem, Miller recently tested NK cells isolated from the blood of closely related donors. These, he reasoned, would be different enough from the host's cells to be able to recognize and kill tumor cells efficiently. In a small Phase II trial, Miller and co-workers found that donor haploidentical NK cells survived in patients with acute myeloid leukemia (AML) for about a month and induced remissions in some patients for whom standard therapy had failed [2].

The stem cell option

Miller now plans to test whether umbilical cord blood might be a better source of NK cells for cancer immunotherapy than adult blood. Cord blood contains more hematopoietic stem cells – cells that renew themselves but also differentiate into specific types of blood cell – than adult blood. 'We hope to start testing the safety of NK cells produced from HLA half-matched cord blood in patients with AML in the next few months', says Miller. 'If cord blood proves to be a better source of NK cells for tumor therapy than adult blood, then hESCs may be an even better source.'

Embryonic stem cells can differentiate into any cell type present in the adult body. The first hESC lines were isolated in 1998 but, says Stephen Minger, Director of the Stem Cell Biology Laboratory at King's College London, UK, 'large numbers of lines have been freely available for only 3–4 years so researchers are only just learning how to persuade them to differentiate down specific pathways. hESCs may eventually provide unlimited cells for regenerative medicine – for example, neurons to repair nervous system damage – and highly enriched human cell populations for use in drug screening and toxicology.'

By deriving functional NK cells from a hESC line in a two-step process, Kaufman, an assistant professor in the Stem Cell Institute of the University of Minnesota, USA, is working towards a third potential use of hESCs, that of a source of cells for cancer immunotherapy [1]. The NK cells we have derived, says Kaufman, 'express inhibitory and activating receptors typical of mature NK cells and can kill human tumor cells in culture'. He now plans to test whether these NK cells can kill human tumor cells implanted in animals.

According to Minger, 'designing conditions that generate a highly enriched population of any cell type that may have therapeutic potential from hESCs is a good step forward'. Dario Campana, Professor of Pediatrics at St Jude Children's Research Hospital, Memphis, USA, also comments that the University of Minnesota study is exciting and may help to identify new molecules that regulate NK cell expansion, which could then be used to produce sufficient NK cells for clinical use. Campana himself recently described a method for growing large numbers of NK cells from peripheral blood [3].

Kaufman and Miller both agree that additional work is needed to find ways to make sufficient hESC-derived NK cells for clinical use, but, says Kaufman, 'if we can make the system efficient enough, we might open up the possibility of using hESCs as a renewable source of NK cells that can be matched to individual tumors to improve killing efficiency'.

References

1 Woll, P.S. *et al.* (2005) Human embryonic stem cell-derived NK cells acquire functional receptors and cytolytic activity. *J. Immunol.* 175, 5095–5103
2 Miller, J.S. *et al.* (2005) Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. *Blood* 105, 3051–3057
3 Imai, C. *et al.* (2005) Genetic modification of primary natural killer cells overcomes inhibitory signals and induces specific killing of leukemic cells. *Blood* 106, 376–383

Nanomedicine transforms drug delivery

Catherine Shaffer, cath-shaffer@sff.net

The marriage of nanotechnology and biotechnology has come as a surprise for the older generation. Few expected those two crazy kids to run off together, but, upon reflection, it seems inevitable. Biomolecules represent the ultimate nanoscale 'machines.' It was only a matter of time before engineers attempted to imitate them. Now surprising advances in nanotechnology stand poised to change all the rules for drug discovery. Did you think your compound was insoluble? Did you discard it because it doesn't cross the blood–brain barrier? Think again.

Treatment at the single-molecule scale

Nanomedicine encompasses medical diagnosis, monitoring, or treatment at the single-molecule scale. This new field is so promising that the National Institutes of Health have included a Nanomedicine initiative in the NIH Roadmap.

1359-6446/05/$ – see front matter PII: S1359-6446(05)03655-X

news

By establishing Nanomedicine Development Centers, they hope to encourage the development of technologies that can destroy cancer cells, repair broken cellular machinery, deliver medicines with precision, and more.

In October 2005, scientists gathered in Cambridge, Massachusetts, for a conference on Nanomedicine. Discussions ranged broadly, from imaging technologies to exotic nanomaterials for sealing a surgical field from contamination. One of the presenters was Mansoor Amiji, an Associate Professor at Northeastern University in Boston, Massechussetts. Amiji is working on various strategies for using nanotechnology to deliver drugs or other payloads to target sites in the body. Amiji has already had success targeting cancer drugs to human tumors growing on the backs of nude mice using polymer-based nanoparticles. The particles are about 150 nanometers in diameter and can entrap or encapsulate hydrophobic drugs. Amiji has also developed a gelatin-based nanoparticle that can be used as a safe delivery vector for DNA. He and his colleagues at Northeastern have recently begun working on combination methods for delivering more than one agent to a drug-resistant tumor, in an attempt to reprogram the cell so that it can once more respond to treatment. 'By using the nanotechnology and combining more than one agent, you are able to literally reengineer the whole apoptotic mechanism back into a cell, which...has lost the apoptotic state.'

Molecular imaging

One of the most promising areas of nanomedicine is in optics and imaging. Nano-sized imaging agents that can be targeted to tumors or other areas of interest in the body could provide a faster, less invasive, and more accurate way to diagnose disease. Rebekah Drezek, assistant professor of Bioengineering at Rice University in Houston, Texas, specializes in developing novel optical imaging technologies for *in vivo* tissue pathology. One project in her laboratory focuses on molecular imaging. A fundamental limitation of molecular imaging is the signal to background ratio. When brightly glowing nanoparticles are targeted to diseased tissue, there will be a certain proportion that do not arrive at the target zone, resulting in a background illumination that can make it difficult to identify a low-intensity signal. Says Drezek, 'We're trying to get around that by developing a class of imaging agents that's completely dark and only lights up when a particular molecular event happens.' By using quantum dots attached to gold nanoparticles through a degradable peptide linker, Drezek gets a molecular imaging agent that only changes color when it comes in contact with the correct cleavage enzyme.

Changing the rules in drug discovery

Developments in nanomedicine are distinctly threatening to the traditional paradigm in drug discovery, which is predicated on finding druggable compounds. Poor solubility and limited bioavailability are the major reasons that most compounds do not advance to lead status. Changing the rules at this stage would result in a major reorganization and reconceptualizing of the drug discovery process that could be both expensive and uncomfortable. But the benefits in salvaging millions of discarded compounds are undeniable. A larger hurdle is untangling the regulatory issues surrounding nanomedical devices. In some cases, they could be regulated as drugs. In others, regulation as a device would seem more appropriate. And the safety issues surrounding many of these new nanomaterials are not well understood. Until regulatory agencies respond to the new technologies, there will be some confusion.

Hope for Huntington's from an old antibiotic

Haroon Ashraf, haroonstuff@hotmail.com

US researchers have reported that an antibiotic for internal use might block the action of Huntington's disease in mice and cell culture. Huntington's disease is a hereditary, degenerative, and fatal disease of the brain that causes changes in personality, progressive loss of memory and cognitive ability, and a characteristic uncontrolled jerking motion known as Huntington's chorea. There is no known cure or effective treatment.

Less huntingtin

The Huntington's gene causes the production of a toxic protein, mutant huntingtin, which eventually kills neurons, causing the disease's degenerative effects. The research team led by neurologist Stephen Massa (San Francisco VA Medical Center, California, USA) said Clioquinol, an antibiotic banned for internal use in the USA in 1971 but still allowed for topical applications, interrupted the production of mutant huntingtin. In the first part of their study the team tested the effect of Clioquinol on neurons in cell culture that contained a form of the mutant Huntington's gene [1]. 'We found that not only did cells look better and survive a bit longer when exposed to the drug, but they also seemed to make less of the toxic protein', said Massa.

These tests were followed by animal studies where mice bred to express the toxic huntingtin protein were given 1 milligram of Clioquinol per day in water. After eight weeks of treatment, they had accumulated four times less toxic protein in their brains compared with control mice given water alone. The experimental animals lived 20% longer than the control animals, did better on tests of motor coordination, and had less weight loss, they reported.

Senior lecturer in neuropharmacology David Dexter (Imperial College, London, UK) said that the results backed an increasingly supported hypothesis. 'It is becoming very clear that many neurodegenerative disorders are being associated with altered protein formation and these can often interact with metal ions to produce free radicals and oxidative stress or alternately oxidative stress can cause misfolding of proteins making them toxic.'

'The implications of this work do add some credence to the theory and hence are and important indicator of potential mechanisms and drug targets, said Dexter, who is also scientific director of the Parkinson's Disease Society Tissue Bank.

Efficacy *in vivo*

Massa said that he was cautious about over interpreting the results for Clioquinol, which he decided to try after reading about

1359-6446/05/$ – see front matter PII: S1359-6446(05)03654-8 PII: S1359-6446(05)03685-8