New stem cells by reprogramming

By ‘de-programming' existing specialised cells it might be possible to create cells which resemble embryonic stem cells, bypassing many of the ethical and moral objections to using human embryos.

Researchers are discovering new ways to help ‘de-program' specialised cells so that they can be re-programmed to form a range of different types of tissue, an international meeting of stem cell biologists was told. If this approach can be made to succeed, it could circumvent many of the ethical and moral objections that have been raised to using human stem cells derived from embryos – the ‘blank' cells (‘toti- or ‘pluripotent') that have the potential to turn, or differentiate, into multiple types of specialised cell and which could be used to treat many diseases where cells are not functioning correctly.

Professor Keith Campbell of the University of Nottingham in the UK presented new findings on cell de-programming to an international meeting in Milan (30 September – 2 October, “Challenges in Stem Cell Differentiation and Transplantation”) organised by the European Science Foundation's EuroSTELLS stem cell programme and one of ESF's Member Organisations, the National Research Council (CNR) of Italy.

Embryonic stem cell therapy relies on the fact that in the early stages of the development of the embryo, cells retain the ability to differentiate into every type of cell in the body. In theory an embryonic stem cell could be coaxed to grow into a liver cell or pancreatic cell, for example, and therefore could be used to repair or replace diseased or damaged tissue.

Many hurdles

However, many hurdles remain to be cleared, both scientific and ethical. Professor Campbell, who works as part of a EuroSTELLS consortium, told the Milan meeting, “There are many challenges associated with using embryonic cells. Furthermore if the entire population were to be served by the sorts of treatments envisaged, we would need huge numbers of embryonic cell lines in order to cover the wide range of immunological types present in the population to prevent or reduce rejection.”

One possible way around these problems is to produce ‘personalised' cell populations. This approach would entail removing cells from an individual that have already differentiated and de-program them so that they revert from being specialised cells to becoming ‘blank' cells, similar to embryonic stem cells. They could then be re-programmed into a new type of cell and transplanted back into the person donating the cells, therefore preventing rejection.

The key to this approach is to repackage the cell's genetic material. When a stem cell differentiates into a specialised cell, the genetic code – the sequence of genes on the DNA contained within the chromosomes – remains the same. What alters is the way that the DNA is packaged.

Various ‘epigenetic' modifications take place, in which the DNA is folded and twisted, and with certain molecules bolted onto it which have the effect of exposing some regions of the DNA and masking others, ultimately have an effect on how the genetic code is expressed. De-programming would require the genetic material to be unpacked, reverting to its original state before the cell became differentiated.

Somatic cell nuclear transfer

Such de-programming is feasible – the creation of cloned animals such as Dolly the sheep is achieved by a process called somatic cell nuclear transfer (SCNT), in which the nucleus of a differentiated adult cell is removed and placed into an unfertilised egg cell, termed an oocyte, whose own genetic material has been extracted. Various biochemical factors within the egg cell's contents – its cytoplasm – somehow unravel and ‘clean up' the DNA contained within the transferred nucleus, making it equivalent to an embryonic stem cell, which can then divide and proliferate and form all the other types of cell needed to make a new organism.

“What causes this kind of reprogramming? We do not know,” said Professor Campbell. “But it is clear that it involves some factors within the cytoplasm of the egg cell.”

The entire process of transferring a nucleus from one cell into another cell is fraught with potential pitfalls, and Professor Campbell's team has been working on ways to improve the success rate of SCNT.

For example when the nucleus is removed from the oocyte, inevitably some of the cell's cytoplasm is also extracted. The Nottingham researchers have been analysing the proteins that are removed inadvertently to see if these might be important in de-programming the introduced genetic material.

Caffeine a key

The team has also shown that de-programming of the somatic cell nucleus can be improved if caffeine is present in the cytoplasm of the oocyte. This appears to have a key effect on two enzymes called kinases that possibly helps to open up the donated nuclear material, exposing it to the important de-programming factors present in the oocyte cytoplasm.

Another approach that the Nottingham researchers have adopted is to expose the donor cells to the oocyte cytoplasm before the transfer occurs. “It is clear that protein molecules within the oocyte cytoplasm can deprogram the genome, so we are asking if it is possible to use the protein from an egg directly on the cell whose nucleus is to be transferred,” Professor Campbell said. The team has shown with eggs from amphibians that it is indeed possible to invoke a range of epigenetic changes in the nucleus of the donor cells which, said Professor Campbell, “push the epigenetic profile towards that of the stem cell.”

Professor Campbell said, “Ultimately this work is aimed at investigating whether we can bypass the need for a human embryo. If we can take a differentiated cell and drag it back to the state it was in the embryo then we could solve a lot of the current problems.”

EuroSTELLS is the European Collaborative Research (EUROCORES) programme on “Development of a Stem Cell Tool Box” run by the European Medical Research Councils (EMRC) Unit in the European Science Foundation. ESF provides scientific coordination and support for the networking activities of funded scientists through the EC FP6 Programme, under contract no. ERAS-CT-2003-980409. Research funding is provided by the participating national organisations.