Somatic cell nuclear transfer in therapeutic clonning: An alternative in the treatment of genetic disorders

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In 1958 Gurdon *et al* reported the discovery that mature cells can be reprogrammed to become pluripotent, thus opening the door to therapeutic cloning. Since then much has been said and done regarding somatic cell nuclear transfer (SCNT). Adapting the method to mammals supposed a big challenge, and did not happen until the cloning of Dolly in 1997. Several attempts have followed since trying to adjust protocols to primates, with poor success rates, specially in humans where reprogrammed cells usually stopped soon after reaching the 8-cell stage. It was only as recently as of May 2013 that Tachibana *et al* successfully obtained for the first time derived Nuclear Transfer Stem Cells (NT-ESC), overcoming a decades-long biology hurdle.

The Technique

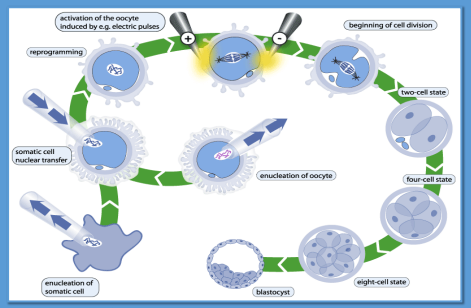

Figure 1: Steps in NT-ESC generation. In human, blastocyst would rarely spawn and degenerate due to premature oocyte activation or poor quality.

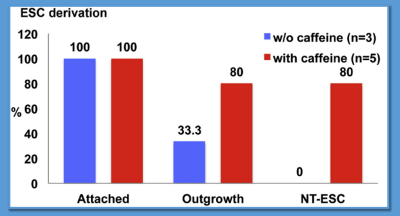

Figure 2. Tachibana *et* al reported increased development efficiency and quality of the human NT-embryos following the addition of caffeine, which prevented early activation of the oocyte. At the same time, only the caffeine group was able to generate for the first time derived stem cell lines in Homo sapiens.

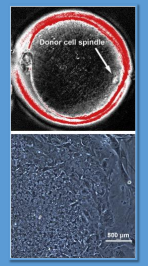

Figure 3. Enucleated oocyte after donor nuclei injection, and derived NT-ESC in culture.

Applications

- Reproductive Cloning

Figure 4. Dolly, first cloned mammal.

Possible uses include transgenic generation for disease modelling, preservation of thoroughbred livestock and better compatibility in xenotransplants.

Malformations due to epigenetic disregulation and low efficiency rates pose a significant hindrance.

- Therapeutic cloning

Potential therapies for degenerative disorders by introducing autologous (therefore immunologically compatible) stem cells free from the disease.

Specially important in mitochondria related disorders.

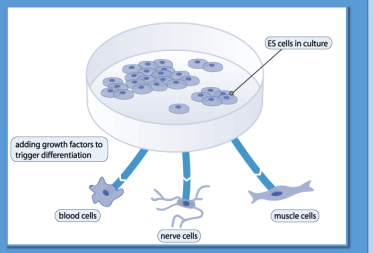

Figure 5. NT-ES cells are able to differentiate to virtually every cell in the body.

Possible therapies

- Wakayama *et al* generated domanergic neurons from a tail biopsy in Parkinson model mice and cured syntomatology after an autologous transplant.

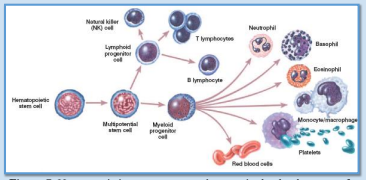

Figure 7. Hematopoietic precursors are a key part in the development of the immune system.

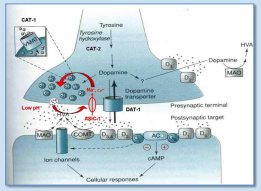

Figure 6. Parkinsonian mice show progressive degeneration of dopaminergic neurons.

- In another study, Rideout and collegues successfully restored immune function in immunodeficient mice.

Alternatives – iPS cells

- Developed in human in 2007, they consist of somatic cells engineered to express pluripotency factors.
- High propensity to form teratoma.

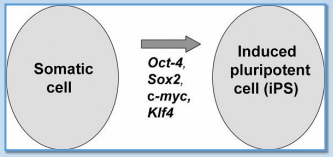

Figure 8. Pluripotency factors are normally inactive in somatic cells and can be reactivated. Genetic engineering of the cells results in de-differentiation and restored pluripotency.

Conclusions

As research on human SCNT was hindered during decades due to both sub-optimal methods and ethical concerns over oocyte sources, parallel research was successfully conducted on human induced pluripotent cells (iPS). This 7-year head start makes it unlikely for NT-ESC to replace iPS, although the former appear to be more effective in erasing the epigenetic memory of the somatic nuclei in mice, and offer the unique possibility of treating mitochondrial related disorders. Thus, more research is required comparing how are NT-ES and iPS cells different between them and standard ES.

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