ADULT STEM CELLS

Introduction

1. In response to increasing research in stem cells and clinical prospect for their use in the treatment of diseases, the Singapore National HSR-BAC has been set with the task of setting guidelines for the use of stem cells from various sources.

2. Stem cells are cells that can differentiate into different kind of cells each exhibiting different characteristics such as skin, bone, liver, heart and nerve cells etc. Adult stem cells are those that can be found in adult tissues. Bone marrow has long been regarded as the source of adult stem cells. Recently, stem cells have been found in specific tissue such as in the hippocampus of the brain, and olfactory bulb. It is generally believed that the embryonic stem cells have the most potential to derive into all kinds of cells. Going down the differentiation path from the embryonic stem cells are bone marrow stem cells, tissue-specific stem cells, lineage-specific precursor cells, and then terminally differentiated specific cells. Stem cells have the tendency to be maintained in culture for long period of time, with the capacity for expansion into large cell numbers for therapeutic purposes. However, the control of the differentiation path becomes more difficult the further upstream is the stem cell. Therefore, embryonic stem cells have been the most difficult to produce a pure population of cells for therapeutic applications. On the other hand, precursor cells can be induced to become the desired terminally differentiated cells in one step induction. These cells normally have less capacity for cell expansion. Also, it has been difficult to isolate such precursor cells (e.g. hippocampal neurons from the brain) from the patients. Therefore, it has been appealing to have the stem cells that can be taken from relatively abundant source such as the bone marrow, periosteum, fat tissues and induce them to differentiate into specific types of cells under suitable environment and conditions. Adult stem cells taken from tissue biopsy, fat tissue as the leftover of cosmetic surgery or from cadaver has been explored as the abundant source of adult stem cells as well. Some examples of the adult stem cells are hematopoietic stem cells that produce all types of blood cells, skin epithelium and epithelium of the small intestine, neural stem cells, and mesenchymal stem cells that can differentiate into cells of the musculoskeletal system.

3. The balance between the scientific and clinical promise of stem cell research and ethical controversies, national funding and biomedical development in this area are crucial as Singapore seeks to maintain high ethical and moral standard in its development of Biomedical research. The policies set forth is to avoid the negative consequences that may come with market-controlled research by not only assessing the priority of the research but also ensuring institution and implementation of strict guidelines for stem cells research, its application and commercialization.

Source of Adult Stem Cells

- Live donors or patients:
    i. Bone Marrow-derived Stem Cells:
    - Researchers in Philadelphia achieved a billion-fold increase in a few weeks for bone marrow stem cells in culture. With Adult bone marrow stem cells now discovered to be very versatile as many researchers have been able to generate all kinds of tissue, it is also important that researchers have found ways to generate large amounts of adult

bone marrow stem cells for research. This creates an abundant supply of cells for research and will be useful in subsequent development of supplies for treatment and other research and therapeutic applications.

David Colter *et al.*; "Rapid expansion of recycling stem cells in cultures of plastic-adherent cells from human bone marrow"; *Proceedings of the National Academy of Sciences*, USA 97, 3213-3218, March 28, 2000.

ii. Periosteum-derived Stem Cells:

Periosteum responds to dynamic fluid pressure by proliferating In vitro, *Journal of Orthopaedic Research, Volume 17, Issue 5, 1999, Pages 668-677*
Saris D.B.F.; Sanyal A.; An K.-N.; Fitzsimmons J.S.; O'Driscoll S.W.

Periosteally derived osteoblast-like cells differentiate into chondrocytes in suspension culture in agarose, *Anatomical Record, Volume 259, Issue 2, 1 June 2000, Pages 124-130*
Bahrami S.; Stratmann U.; Wiesmann H.-P.; Mokrys K.; Bruckner P.; Szuwart T.

Bone and cartilage formation in diffusion chambers by subcultured cells derived from the periosteum. *Bone 1900;181-8*

iii. Fat tissues-derived Stem Cells:

Tissue engineering of bone and cartilage using rat adipo-derived stem cells, *Tissue Engineering, Volume 6, Issue 6, December 2000, Page 689*
Huang, J. I. ; Beanes, S. R. ; Zhu, M. ; Lorenz, H. P. ; Benhaim, P. ; Hedrick, M. H.

Multilineage cells from human adipose tissue: Implications for cell-based therapies, *Tissue Engineering, Volume 7, Issue 2, April 2001, Pages 211-228*
Zuk, Patricia A.; Zhu, Min; Mizuno, Hiroshi; Huang, Jerry; Futrell, J. William; Katz, Adam J.; Benhaim, Prosper; Lorenz, H. Peter; Hedrick, Marc H.

Multi-lineage cells from human adipose tissue: Implications for cell-based therapies, *Tissue Engineering, Volume 6, Issue 6, December 2000, Page 655*
Zhu, M.; Zuk, P. A.; Mizuno, H.; Huang, J.; Futrell, J. W.; Katz, A. J.; Benhaim, P.; Lorenz, H. P.; Hedrick, M. H.

Multi-lineage cells isolated from liposuctioned adipose tissue undergo osteogenesis in vitro and in vivo, *Tissue Engineering, Volume 6, Issue 6, December 2000, Page 689*
Zuk, P. A.; Chaudhari, S.; Katz, A.; Benhaim, P.; Lorenz, H. P.; Hedrick, M. H.

- Cadaveric Tissues: Cadavers are potential source of stem cells. Scientists managed to extract immature progenator cells from cadavers.

Fred Gage's group in UCSD; "Progenator cells from human brain after death"; *Nature*, 411: 42-43

Potential Applications of Adult Stem Cells

- Bone marrow stem cells shown to form **liver** tissue. This can be very useful as liver transplants are scarce. The patient's bone marrow stem cells could potentially be used to form liver tissue that would also be rejected by the patient compared with foreign donor organ liver tissue.

Neil Theise *et al.*; "Liver from Bone Marrow in Humans"; *Hepatology* 32, 11-16, July, 2000.

- Bone marrow stem cells have also been shown to generate **neurons**. This could be useful in generating the brain tissue to replenish dopamine producing cells which are deficient in Parkinson Syndrome patients.

J. Sanchez-Ramos *et al.*; "Adult Bone Marrow Stromal Cells Differentiate into Neural Cells in Vitro"; *Experimental Neurology* 164, 247-256.

- A team at the Albert Einstein College of Medicine in New York took rat stem cells from the cortex and injected them into the brains of both normal adult rats and those damaged by stroke. Stroke patients could potentially recover much better from a stroke with the help of stem cells which would form new mature brain neurons.

- Also, other tissues that have been found to be possibly many other types of tissue. Researchers with Osiris Therapeutics and Johns Hopkins University have shown that adult stem cells from human bone marrow have the capacity to regenerate not only more bone marrow, but also numerous other tissue types as well. In culture, the cells were stimulated to form either **bone, cartilage, or fat cells**. The cells appear to have the potential to form other tissues as well, including **tendon and muscle.**

M.F. Pittenger *et al.*; "Multilineage potential of adult human mesenchymal stem cells"; *Science* 284, 143-147, April 2, 1999.

- Apart from bone marrow, other researchers have been successful in isolating stem cells from periosteum and fat tissues, and have demonstrated the pluripotency of these cells to differentiate into bone, cartilage, ligament, tendon and heart muscle cells.

- Bone marrow stem cells have been shown by Drs. Margaret Goodell and Karen Hirschi at Baylor College of Medicine to stem cells taken from the bone marrow of an adult mouse and transplanted into the bone marrow of another adult mouse had the capability to transform into **blood vessels and cardiac muscle.** This could potentially help millions of heart attack victims with damaged cardiac muscle and prevent heart failure.

Margaret Goodell and Karen Hirschi ; The Journal of Clinical Investigation. June 1, 2001

Technical controversies

4. There have been controversies that adult stem cells can be a replacement for embryonic stem cells. In general, the adult stem cells seem to be limited in proliferation

capabilities and the breadth of applications. The source of the cells is also relatively limited. On the other hand, increasing evidences have documented that adult stem cells can give rise to cells beyond their normal developmental lineages so that they are more plastic than previously believed. Since the adult stem cells can be more readily induced to produce relatively pure populations of terminally differentiated cells for therapeutic applications, these adult stem cells would have more immediate applications and interest from the industrial sectors. Therefore, the guidelines that regulate the research and applications involving these cells are also more urgently needed.

Scientific and Medical Considerations

5. Stem cells are found in the body, some more differentiated and committed than others. When stem cells divide, some progeny develop into specific cell types while others remain as stem cells, for the repair of tissues that have undergone wear and tear. These stem cells are capable of continuously reproducing themselves and serve to renew tissue throughout an individual's life.

6. Although feasible, the following should be prohibited:

i. ***Hybrid*** cloning - human (or animal) embryos generated asexually by somatic cell transfer or similar cloning techniques where the nucleus of an adult human cell is introduced into an enucleated human or animal ovum (ES cells). This may be considered as either adult-hybrid or embryonic (hybrid) stem cells.

Although there is much promising research and studies suggesting that it is scientifically and technically limited, there is no legal restriction or ethical guideline for this sort of hybrid cell, consent and risks. Although the source is part adult, its hydrid nature alters the ethics governing its development, use and application.

ii. ***Reprogrammed Adults Cells***
The derivation of stem cells from reprogrammed adult cells must also be monitored as our knowledge and understanding of cell and organ develop.

iii. ***Mixing of human and animal tissues***
Should not be permitted. Must be in compliance with International Regulations and Acts.

7. The need for an Ethical Oversight and Review Committee at the National and Instituitional level and compliance by the private sector with these recommendations is essential.

Legal and ethical issues

8. Since adult stem cells do not involve Human Embryos, the major issues would involve informed consent and analysis of risks associated with the use of such cells in various applications. (NIH guidelines)

9. Provision should be made for not only hydrid, unforeseen but also case-by-case circumstances in aspects relation to the retrieval to the application and all intermediary stages of stem cell research.

Religious Perspective

10. As a multiracial country, Singapore is posed with numerous traditional and religious beliefs. The retrieval, processing and application of stem cells must comply with the general beliefs of these sectors. This may include the following:

- Respect for the dead
- Avoidance of cadaveric tissues and cell retrieved from cadavers

It is recommended that a study on the reactions of different relevant religions towards these issues be commissioned.

Other issues

- Financial issues such as how the public funding can be used for such research:

- Restricted research such as the definitions and scopes of research activities that certainly cannot be carried out such as intentionally removing biopsy samples from patients without well-informed consent for research purpose only.

- Identifier and ownership issues such as who owns the cells and how to track the source of these cells, which tend to tremendous commercial implications later.

- Guidelines for Informed Consent:
  Guidelines for the use and application of ***biopsy*** or ***Cadaveric tissue*** must be in accordance with stem cells research and international organ-tissue retrieval and donation Act. Guardian and proxies of the deceased must have an accurate account of their role in relation to the deceased. The organs or tissues must be offered with ***no commercial or financial interest*** on the part of the guardians or proxies. Written and informed consent must be obtained from the donor.

- Safety:
  - Precaution to ensure non-oncogenic nature of cell, tissues or organs transplanted or risk of tumors after transplantation.
  - Disease-free
  - Genetically sound- unpredictable mutations
  - Regulation of Human cellular and tissue-based products
  - Purity of the products

- Oversight of the implementation of the guidelines
  An Oversight and Review Committee is crucial and reports of misconduct should be anonymously submitted to encourage individual responsibility in ensuring the highest possible standard is maintained. Free, voluntary and unanimous reporting of misconduct must be supported. The national biomedical research funding bodies

should also monitor and ensure strict adherence to guidelines and standards across the country. The National Bio-ethics Oversight and Review Committee would provide the public with additional assurance that research on stem cells are undertaken appropriately. An analogous division to the Criminal Practice Investigation Beureau, a biomedical body looking into breach and misconduct in stem cell research should be set up. This is important as unforeseen outcomes may arise such as hyrid cells created which may no longer be from either the adult or embryo and is allowed to develop. Hence, the duties of the Committee should include:

i. A review of research protocols
ii. Certification that the research proposed is in accordance with approved protocols
iii. Public Registry of approved protocols
iv. Database of national and private research sponsors for stem cells research.
v. Track the history and ultimate use of the stem cell and its products
vi. Establish requirements and guidelines for funding bodies and private sponsors.
vii. Report annually to the HSR-BAC on the current state of the science of stem cell research, emerging ethical or social concerns associated with ethical research and the adequacy and appropriateness of the recommendations at the time.

- Development of GCP protocol for safe procurement, transportation of tissues and transplantation.

- Guidelines for laboratory to avoid cross contamination and infection.

- Regulations on the prohibition of cross-species experimentation and clinical applications of such experiments that involve human materials.

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