Stem Cells/ Regenerative Medicine and Bioethics

Regenerative Medicine

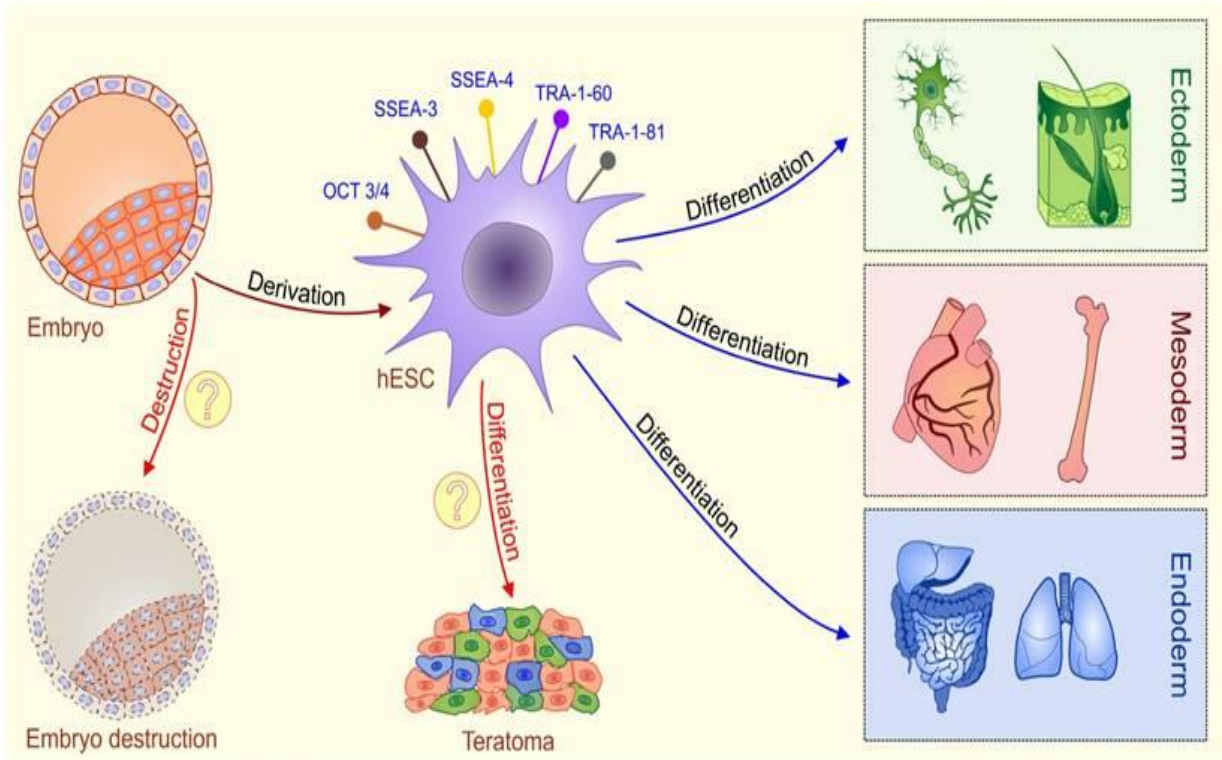
- Regenerative medicine is an emerging interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of the cells, tissues or organs to restore impaired function eg; congenital defects, disease, trauma and aging
- Combination of several technological approaches eg; gene theraphy, stem cell transplantation, tissue engineering, reprogramming of cells and tissues
- Next phase of tge organ transplantation and replacement therapies
- Aims to provide the elements required for in vivo repair, to design replacements, to stimulate regenerative capacities of the body

Stem Cell Therapy

- Stem cells have raised tremendous expectations among the medical doctors, researchers, patients, and the general public due to their capacity to differentiate into a broad range of cell types.
- Stem cell researchers are engaged in different endeavors,
  - treating genetic disorders
  - generating new stem cell-derived human tissues
  - biomaterials for use in pharmacy genomics and regenerative medicine.
- Therapeutic potential of stem cell-based therapy in the treatment of degenerative, autoimmune and genetic disorders
- Probably the most serious problem facing the field of regenerative medicine today is the challenge of effective translation and development of viable stem cell-based therapies

hESC-based Therapy

- hESCs are stem cells derived from the pluripotent inner cell mass of the pre-implantation embryos
- hESCs express typical pluripotent stem cell markers
- hESCs have capacity to differentiate into cell types of all three germ layers [endoderm, mesoderm, and ectoderm] under *in vitro* and *in vivo* conditions.
- hESCs hold great promise in understanding of early human embryology and for developing the cell replacement strategies for the treatment of human diseases.



- Research with embryonic stem cells (ESCs) is highly debated and many people have strong opinions about it. It comes down to how the human blastula is viewed.
- ESCs are primarily made from cells found in a human blastula, one of the earliest stages of human life. A fertilised egg grows into a blastula (made of ~100 cells), which can only survive for a short time before it must be implanted in a womb.
- Blastulas used in research are typically made artificially in a laboratory or fertility clinic.

Ethical and safety concerns regarding hESC-based therapy

- The ethical dilemma involving the destruction of a human embryo was and remains a major factor that has slowed down the development of hESC-based clinical therapies.
  - **Moral status of the embryo**
- Whether it is morally acceptable to pursue novel therapies for curing illnesses at the expense of destroying an early human embryo?
  - individual opinions so deeply rooted in basic moral beliefs
- This ethical dilemma is portrayed in different legislation that exists throughout the world regulating hESCs research
  - Legal in UK, illegal in Italy
- The ethical debate surrounding the harvest of hESCs has made research on this topic controversial, and as a result, the majority of studies were focused on animal models

Ethical and safety concerns regarding hESC-based therapy

- Informed consent
  - Differ from other informed consent status because many regenerative medicine therapies are availebleonly through clinical trials; individuals should decide whether or nor to enroll in such trial
  - Potential risks of those experiments are mostly unknown
- Decision-making capacity
  - Innovative nature- how individuals comprehend?
  - Duty to inform patients for every step and risks
- Therapy versus enhacement
  - Also a method for enhancing normal function
- Transplantation ethics
  - regenerative medicine therapies will involve the transplantation of cells, tissues, organs or bioartificial constructs in the body
  - Ethics of procuring donor materials – organ transpalntation
  - Patient safety

- Beside ethical concerns, safety issues regarding hESC-based therapy are the main problem for their clinical uses.
- The plasticity that permits hESCs to generate hundreds of different cell types also makes them difficult to control after in vivo transplantation

- Some people see destroying a blastula for its cells as destroying an unborn child.
- Others feel that a blastula is not exactly a child just yet, because unless a blastula is imbedded in the uterus wall, it will never have the chance to develop into a baby.
- Every year fertility clinics create many blastula that are destroyed because they are made insurplus.
- Supporters of ESC research generally feel that using cells from these surplus blastula for research and developing medical treatments, which could help improve and save people's lives, is much better than throwing them away.
- Many research institutions have created Embryonic Stem Cell Research Oversight Committees (ESCROs) to review hESC and iPSC research; others rely on their institutional review boards or their animal care and use committees or both.

Induced Pluripotent Stem Cell (iPSC)

- iPSC are very similar to hESCs in terms of karyotype, phenotype, telomerase activity and capacity for differentiation.
- iPSCs are considered morally superior to hESCs since their generation does not require destruction of embryos
- Current ethical controversies regarding stem cell-based therapy are focused on the unlimited differentiation potential of iPSCs which can be used in **human cloning**, as a **risk for generation of human embryos** and **human-animal chimeras**.
- Since **undesired differentiation** and **malignant transformation** are major safety issues regarding transplantation of iPSCs and iPSC-derived cells, protocols for differentiation of iPSCs should be optimized in order to ensure the purity of iPSC-derived populations of differentiated cells before their clinical use.

- In research with iPSCs as well as with other types of stem cells, it is essential that preclinical studies in animal models and other media be sufficient to justify the progression to clinical trials.
- Toxicity and the risk of tumorigenicity must be assessed for all stem cell-based products, especially when genetically modified, in order to minimize the risks of harm as far as feasible before moving to humans
- Concerns about the research use of animals - especially non-human primates - in preclinical research, including iPSC research
  - At the same time, researchers are increasingly aware that good animal models are often unavailable or inadequate to predict effects in humans.
- Clinical trials of iPSCs and other highly pluripotent stem cell interventions generally enroll patients as subjects at all trial stages, as using healthy volunteers may raise safety concerns or compromise the value of the data.

- Disclosure and discussion of uncertainty with potential subjects in stem cell trials are essential in order to reduce the incidence of therapeutic misconception
- information transparency also helps protect the integrity of the research process and the safety of patients in the face of increasing global availability of unapproved and unproven stem cell ‘treatments’

Highly multipotent stem cells: biobanking, disease modeling, and drug discovery

- Some applications of stem cell research, such as disease modeling, drug discovery and testing, cell line banking, and commercialization of stem cell therapies, also give rise to ethical considerations specific to the field
- The creation and use of disease-specific iPSC lines, both alone and in combination with regenerative medicine products (for example, to produce ex vivo organoids), are essential components of disease modeling and drug discovery.
- ‘Body-on-a-chip’ types of three-dimensional organoid arrays hold great promise for improving drug development, disease modeling, and pharmacogenomic research, by lowering costs, speeding results, and increasing the safety and potential efficacy signaling of first-in-human trials, and considerable research is under way
  - questions of consent

- iPSC lines are derived from the somatic cells of identifiable individuals, disclosing to those individuals the planned and envisioned uses of iPSCs derived from the cells they have donated and obtaining consent from them are critical for the creation and sharing of cell line research libraries and the future uses of biomaterials derived from previously donated biospecimens
- In particular, the development of public and other broadly accessible biobanking models for stem cells derived from umbilical cord blood, amniotic fluid and placental tissue, urine, and adipose tissue holds promise for easy collection of good allograft matches for a large percentage of the population but also requires attention to ethical and policy issues

- Like many novel biotechnologies, gene- and cell-based and regenerative medicine interventions and products can be extraordinarily costly and time- and labor-intensive to develop and use.
- Justice requires attention to the costs of developing stem cell therapies and making them available, with the goal of reducing unfair disparities in access.
- Cost is a standard distributive justice concern.

Justice considerations are addressed in stem cell research and therapy in several ways.

- the biobanking policy and practice
  - collection, storage, and use of stem cells of different types
- the health of the public takes place in a market system with its attendant pressures of competition and commercialization
- the minimization of risks of harm
- the importance of information disclosure and informed consent
- the potential for overpromising, overexpectations, and the therapeutic misconception
- the pressure from disease constituencies and commercial entities to move quickly into the clinic, too often at the expense of understanding basic mechanisms

General Ethical Issues

- Clinical translation
- Safety, efficacy, affordability, access
- Commercialization
- Oversight of new stem cell technologies
- Stem cell tourism
- The dynamic of exploiting socioeconomic inequity between nation states - dominated by certain few and powerful countries
- Domestic markets for unproven cell therapies are thriving
- Patient rights & access to treatment
  - who is able to access treatments and how
  - Right-to-Try movement

References

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