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Stem cell research

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Summary One of the most active areas of research in medicine today is stem cell biology. This review introduces the reader to the field of stem cell biology and its therapeutic potential. More importantly, the potential application of stem cell therapy in acute lung injury will be explored.

BACKGROUND

A stem cell is traditionally defined as a cell that is capable of self-renewing and differentiating into an unlimited number of different cell types.[1,2] Just as importantly, the stem cell needs to exhibit clonality and give rise to a multitude of cells that can actually function. The 'self-renewing' properties of a stem cell can take two forms. The first is symmetrical division, which can give rise exclusively to only stem cells or instead all progenitor cells; progenitor cells (non-self-renewing) are considered more 'committed' in differentiating towards specific cells, such as myocytes or alveolar type II cells, than are pure stem cells. The second form is asymmetrical division, which can give rise to both stem cells and progenitor cells.

The clinical role of stem cells has been limited to reconstituting the haematopoietic system following bone marrow transplantation after chemotherapy and/or total body radiation. More recently, laboratory investigations have suggested the existence of stem cells in other organs, such as the central nervous system,[3–9] lung,[10–12] liver,[13–18] and vascular system.[19–22] In addition, stem cells have been described in muscles,[23–27] gastrointestinal tract[26–29] and pancreas.[30,31]

The science of embryology and the ability to clone cells provide new ways in which tissues might be repaired. Many of the potential uses of stem cells described below are preclinical for repair of the lung. Understanding where the field of stem cell research is moving may shed light on what strategies may in the future be available in the clinical arena.

EMBRYONIC STEM CELLS

Human embryonic stem (hES) cells are obtained from the inner cell mass of a blastocyst (Fig. 1).[32,33] The term 'embryonic stem cell', or 'ES cell', was coined to differentiate cells obtained from embryos as opposed to embryonal carcinoma (or EC) cells, which are derived from tetrocarcinomas.[33,34]

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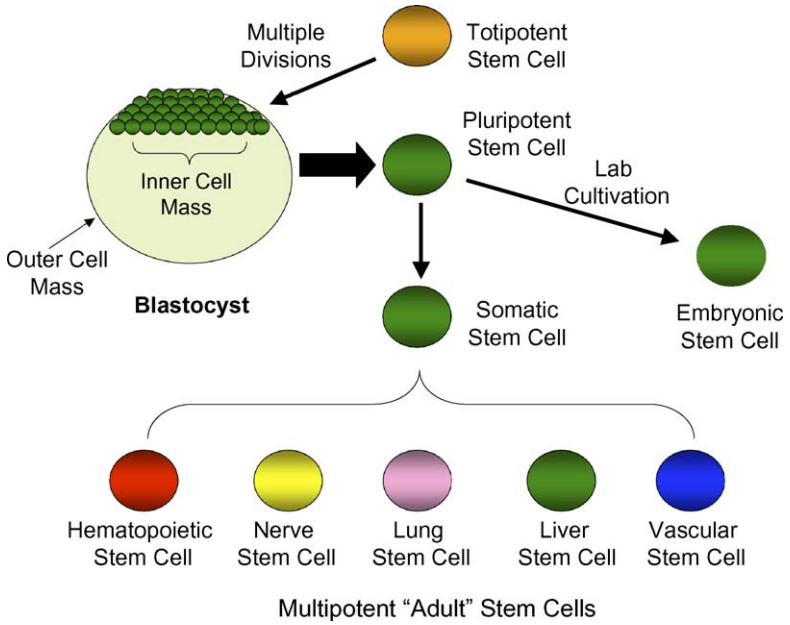

Figure 1 Fertilisation results in the creation of a zygote which undergoes a series of cleavage steps and compaction. Each cell within a zygote is *totipotent* in that each cell is capable of creating an entire being. The blastocyst consists of a hollow vesicle of trophoectoderm surrounding a fluid-filled cavity and a small number of inner cell mass cells. Stem cells derived from the inner cell mass of the blastocyst are *pluripotent* because they are self-renewing and can give rise to all three germ layers of the developing embryo. Cells removed from the inner cell mass and grown in culture are known as embryonic stem (ES) cells. In the living body, pluripotent stem cells differentiate (or restrict their attributes) towards specific organs and become multipotent "adult" stem cells. A *multipotent* adult stem cell is capable of self renewal as well as giving rise to different cell types. Medical therapies are being studied that can harness the transformative or "plasticity" features of multipotent "adult" stem cells as well as the potential of embryonic stem cells.

The hES cell has a prominent nucleus relative to its cytoplasm, distinctive nucleoli and a colony morphology that is similar to that of non-human primate ES cells.[33,35,36] These cells are propagated on a feeder layer of fibroblasts and maintained in a subconfluent state to prevent differentiation. If they are grown in nutritive media without a feeder layer, they will create structures called embryoid bodies, the name being derived from their similarity to the inner cell mass of mouse embryos.[34]

In the undifferentiated state, ES cells express the transcription factor Oct-4. Oct-4 becomes downregulated when the ES cells begin differentiating.[35] The hES cells are *pluripotent* in that they can produce any cell of the three germ layers, but they cannot produce an embryo in the absence of a trophoectoderm. Implanting hES cells into a uterus will not produce a child.[37] Nevertheless, the distinctive features of hES cells include the ability to be maintained in an undifferentiated state when grown in culture for long periods of time. Furthermore, they possess high levels of telomerase and therefore may not be as susceptible to 'proliferative burnout' in comparison to adult multipotent stem cells.[33] Thus, hES cells are attractive candidates for therapeutic tissue regeneration, as well as vehicles for gene therapy.

The study of hES cells in the USA has been limited owing to the restriction of federal funding to 22 fully developed hES cell lines as well as approximately 78 derivations of these lines approved by the Bush administration.[38] These cell lines were created from blastocysts that were discarded from fertility clinics. However, new techniques in isolating ES cells have been developed that may be less controversial and could potentially expand the number of hES cell lines available. For instance, Chung *et al.* demonstrated that a single cell could be removed from the eight-cell stage of an embryo and used to generate ES cell lines while not harming the development of the embryo.[39]

A different approach involves a modification of the nuclear transfer approach termed alternate nuclear transfer.[40,41] In the classic somatic cell nuclear transfer technique, a nucleus is removed from an adult somatic cell (e.g. mammary gland) and transferred into the 'enucleated' egg. The egg is then activated to divide and produce a living animal, such as 'Dolly' the sheep.[42] Alternate nuclear transfer follows the same scheme except that a gene is inactivated or silenced in the somatic nucleus before transfer that prevents any chance that the 'egg' could give rise to a living organism. Cells that are derived from this process could then have the gene reintroduced or activated for further study. An example of a potential target gene is *Cdx2*, which is crucial for the formation of the trophoectoderm.[43] The inhibition of this gene would prevent the development of an embryo and could be used as a target for somatic nuclear transfer and subsequent ES cell line development.