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Therapeutic potential of adult stem cells

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ABSTRACT

The aim of cell-based therapies is to replace or repair damaged tissues and organs. A diverse number of disorders are amenable to this approach, including haematopoietic, neurological and cardiovascular diseases, as well as bone defects and diabetes. Central to the success of cell therapy is the necessity to be able to identify, select, expand and manipulate cells outside the body. Recent advances in adult stem cell technologies and basic biology have accelerated therapeutic opportunities aimed at eventual clinical applications. Adult stem cells with the ability to differentiate down multiple lineages are an attractive alternative to human embryonic stem cells (hES) in regenerative medicine. In many countries, present legislation surrounding hES cells makes their use problematic, and indeed the origin of hES cells may represent a controversial issue for many communities. However, adult stem cells are not subject to these issues. This review will therefore focus on adult stem cells. Based on their extensive differentiation potential and, in some cases, the relative ease of their isolation, adult stem cells are appropriate for clinical development. Recently, several observations suggest that multipotential adult stem cells are capable of producing a whole spectrum of cell types, regardless of whether or not these tissues are derived from same germ layer; highlighting the opportunity to manipulate stem cells for therapeutic use.

1. Stem cells: definition and lineage potentials

Stem cells are defined as cells with extensive self-renewal capacity and the ability to multilineage differentiate into a wide variety of cell types. There are three types of stem cells: embryonic, germinal and somatic. Somatic stem cells are also known as foetal/adult stem cells or tissue-derived stem cells. However, stem cells possess varying degrees of potential, including the totipotency of the zygote, the pluripotency of embryonic stem cells, the multipotentiality of stem cells foetal or adult tissue, such as adult mesenchymal stem cells (hMSC), and the unipotentiality of a specific cell type, such as epidermal stem cells.

Embryonic stem cells differ from somatic cells not only in their different lineage potentials, but also in the mechanism by which they proliferate. Stem cells can divide symmetrically (embryonic stem cells) or asymmetrically (germinal and adult stem cells). Adult stem cells are present in most tissues and are responsible for the replenishment of those tissues throughout life. Stem cells divide asymmetrically to maintain their number in the tissue, while at the same time giving rise to cells committed to becoming differentiated tissues and organs (Fig. 1).

The differentiation potential or plasticity of a stem cell is its ability to produce progeny that express various mature phenotypes. The maintenance of many tissues and organs is achieved by tissue-specific stem cells. In general, stem cells divide very rarely, but in the presence of an appropriate stimulus from, for example, an increasing demand for cells, they proliferate and differentiate. This situation is observed, for example, in the transit amplifying cells in the epidermis.

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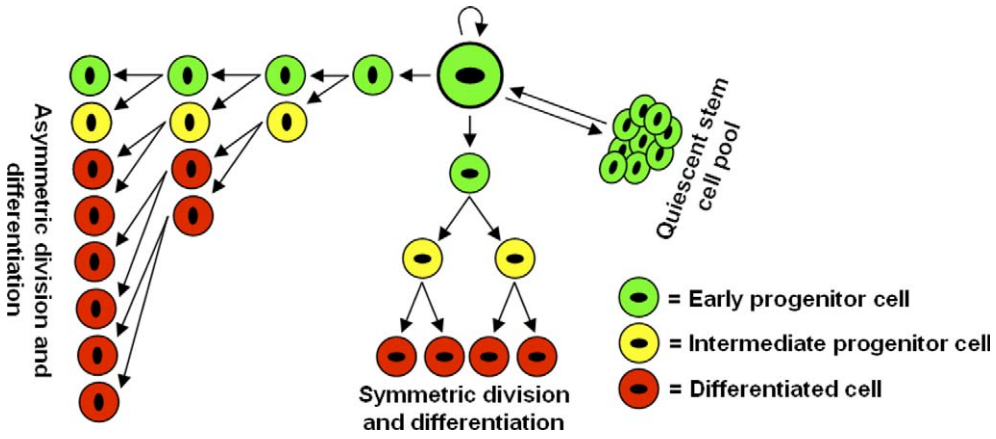

Fig. 1 – Symmetric and asymmetric divisions. When cells divide symmetrically each daughter cell is identical and retains the potential of the parental cells. When cells divide asymmetrically, one of the daughter cells remains a stem cell with the other entering the process of differentiation.

Tissue progenitor (adult stem cells), or transit amplifying cells, provide an expanded population of a proliferating tissue that differentiate into more mature cells with specific functions and eventually cease to proliferate.

A good example of a tissue-derived adult stem cell is found in the bone marrow. Bone marrow is a mesoderm-derived tissue consisting of a complex haematopoietic cellular cell system supported by stromal cells embedded in a complex extracellular matrix. There is increasing evidence to suggest that bone marrow contains two types of stem cells: haematopoietic stem cells (HSCs) and mesenchymal stem cells (hMSC), both of which are multipotential cells. Interestingly, hMSC have the ability to differentiate, both in vivo and in vitro, into a variety of adult mesenchymal tissues, such as bone, cartilage, adipose and muscle.[1] Thus, hMSC have the potential to be used in the treatment of a diverse variety of clinical conditions.

2. Stem cells and cell therapy

The general principle for stem cell therapies is to exploit the natural ability of the human body to heal tissues in part through regeneration. One simple example of this process is the natural growth of new skin to repair a grazed knee. However, the challenge is how to apply this concept to tissues, such as bone, neural tissue and muscle. The simple question is whether one can take normal healthy cells from the human body and use these to replace diseased or damaged cells. The answer may be rather more complex, but stem cell biology is reaching a stage where it can already offer insight into new therapeutic avenues.

Stem cells are ideal candidates for use in regenerative medicine, tissue engineering (including gene therapy) and cell replacement therapies, due to their broad lineage potential[2] (Table 1). As can be seen from Table 2, stem cell therapies have the potential to impact on major killers, such as heart and brain disease. Adult mesenchymal stem cells can give rise to bone, cartilage, adipose and muscle cells and tissues. This ability, coupled with their relative ease of isolation from bone marrow, e.g. iliac crest makes them suitable reagents for the treatment of a diverse variety of clinical conditions, including heart disease and bone-related applications.[3,4] Neuronal stem cells (NSC) are another attractive reagent for regenerative medicine and drug discovery. Neuronal stem cells are relatively easy to isolate and expand in culture. Neural stem cells can be isolated from brain and/or spinal cord. Furthermore, these cells are able to differentiate into func-

Table 1 – Ideal properties of stem cells for transplantation

Desirable property
Easily obtained and purified
Maintain their multipotential lineage capacity
Show directed differentiation
Autologous to the patient
Possible to genetically modify cells
Possible to expand cell numbers in culture
Non-tumourigenic

Table 2 – Some examples of clinical applications of stem cell therapies

Stem cell	Clinical application
Mesenchymal stem cells	Heart disease (e.g. myocardial infarction) Bone defects and fractures Osteoarthritis Cancer (cellular delivery of therapeutics)
Neuronal stem cells	Degenerative neurological disorders (e.g. Parkinson's disease, Alzheimer's disease) Central nervous system injury (e.g. spinal cord injury, traumatic brain injury)
Epidermal stem cells	Skin substitutes for ulcers Burn wounds Corneal repair
Haematopoietic stem cells	Haemophilias Thrombocytopaenia Sickle cell anaemia

tional astrocytes, oligodendrocytes and neuronal cells. There are a number of neurological disorders amenable to cell-based therapies, including many neurodegenerative conditions, such as Parkinson's disease and Alzheimer's disease, as well as trauma injuries to the brain and spinal cord.

3. Stem cells as delivery vehicles for cancer therapeutics

Systemic delivery gene therapy has a promising future, but is limited at present by numerous events including immune detection, non-specific accumulation in normal tissues and poor permeation. It would therefore be a significant advantage if engineered vectors could be localised to the sites of specific tissue before being released. One solution is to use cell-based carriers that preferentially home into the targeted tissues or cancer site, to serve as a delivery platform for therapeutic agents. The identification of reservoirs of multipotential stem cells within adult tissue provides exciting prospects for novel therapeutic approaches, such as cell-based tissue engineering and stem cell mediated gene therapy. During tumour formation in particular, tissue remodelling occurs, with mesenchymal cells contributing to the stromal support element of the tumour.

Studeny and colleagues suggested that hMSC are ideal candidates for cellular delivery vehicles, which can home into the tumour stroma and deliver therapeutic agents.[5] Furthermore, Moore and colleagues demonstrated that systemically transplanted endothelial progenitor cells home into brain tumours with a high specificity. Recent studies have demonstrated the capacity of stem cells to engraft and participate in muscle repair after systemic delivery.[6] All these studies indicate the great potential of stem cells in clinical application as well as for specific delivery vehicles for injury or tumour sites.

4. Realising the potential of adult stem cells: can stem cells be expanded to clinically useful numbers?

Stem cells have a limited mitotic potential; thus, generating sufficient cells in the laboratory for therapeutic purposes can be problematic (Table 1). One way to overcome this barrier is to use genetic manipulation to extend the replicative lifespan of stem cells, through the introduction of genes involved in controlling replicative lifespan. For human cells to achieve immortalisation they must overcome replicative senescence. The most efficient method for achieving this is to use ectopic expression of the human telomerase reverse transcriptase (*hTERT*) gene.

Recently, a number of groups have successfully demonstrated that *hTERT*-expressing stem cells continue to proliferate and maintained ability to differentiate into lineage cells of the origin.[1,7–10] Simonsen and colleagues demonstrated that mesenchymal stem cells can be immortalised with the *hTERT* gene and still maintain their functional characteristics. Furthermore, Roy and colleagues have shown that neuroepithelial cells isolated from the human foetal spinal cord can be immortalised by retroviral expression of the *hTERT* gene and give rise to specific types of functional neurones.

The successful immortalisation of adult stem cells with retention of full differentiation capacity may be of considerable benefit to bio-manufacturing processes that require long-term or large-scale cultures of adult stem cells. However, the long-term culture of adult stem cells immortalised with telomerase may have safety issues, as it has been shown recently that telomerase-modified hMSCs can acquire neoplastic potential.[7,11]

5. Immortalising stem cells: the potential to generate cancer stem cells

One of the crucial features that distinguish a cancer cell from a normal cell is its ability to divide indefinitely. The, capacity for self-renewal links neoplastic growth with stem cell biology[12,13] and cancer may be considered a disease of dysregulated cellular self-renewal capacity. Indeed, there is accumulating evidence to suggest that some cancers at least may arise from stem cells, suggesting that stem cells are targets for neoplastic transformation (Table 1).

Cancer stem cells have been isolated recently from breast and brain tumours.[14–18] Furthermore, human leukaemia cells and their normal counterparts share common molecular mechanisms governing proliferation, supporting the concept that the normal haematopoietic stem cell is a target for transformation.[19,20] Interestingly, the hMSC is also target for neoplastic transformation.[7] The neoplastic potential of the hMSC is only detected after introduction of the *hTERT* gene. The transduced cell line shows alterations characteristic of neoplastic development, such as contact inhibition, anchorage independence and in vivo tumour formation in severe combined immunodeficiency (SCID) mice. Together, these findings support the existence of cancer stem cells.

6. Conclusion

The manipulation of adult stem cells to develop new clinical approaches to disease treatment is exciting and realistic. Whilst the oncogenic potential of telomerase immortalised stem cells suggests some caution may be necessary using current technologies, the considerable therapeutic potential of stem cells cannot be ignored. To realise the potential of stem cell therapeutics will require a thorough understanding of stem cell biology in parallel with technologies designed to manipulate stem cells in vitro.[21] Taking advantage of the body's ability to repair itself makes sense and, perhaps in the not too distant future, regenerative medicine will take its place in mainstream clinical practice.

Conflict of interest statement

None declared.

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