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GUEST EDITORIAL

The promise of stem cell therapy for eye disorders

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Stem cell biology is a fast-emerging field that offers promise of cell-based tools for the treatment of a wide range of recalcitrant diseases that are not amenable to other forms of therapy. By definition, stem cells are cells with a capacity for unlimited or prolonged self-renewal and can produce at least one type of differentiated cell associated with the tissue.[1] The term 'cell therapy' is not limited to application of stem cells alone but encompasses a large gamut of rapidly developing scientific disciplines, including stem cell biology, immunology, tissue engineering, molecular biology, biomaterials, transplantation biology, regenerative medicine and clinical research. Blood transfusions and bone marrow transplantation are prime examples of the successful application of cell-based therapies. Recent advances in cellular and molecular biology have expanded the potential applications of this approach to other medical fields like ophthalmology, cardiology, neurology, dermatology, dentistry and orthopaedics.

Another recent concept that is challenged by the developmental biologists is the phenomenon of 'plasticity' in adult stem cells, which has immense clinical potential in cell replacement therapy and regenerative medicine.[2] The classic example of such adult cells is the bone marrow mesenchymal stem cell, which besides differentiation into bone, cartilage, smooth muscle and skeletal muscle, has also been reported to trans-differentiate into skin, liver and brain cells (neurons and glia).[3–5]

In cardiology, cell therapy was introduced to improve the remodelling following myocardial infarction using bone marrow-derived stem cells and skeletal myoblasts with varying success.[6] Different mechanisms have been proposed to explain the beneficial effects of cell-based therapy, which include cell trans-differentiation, cell fusion and release of paracrine growth factors or probably multiple mechanisms. Similarly, efforts are being made to search for alternative sources of cell therapy for diabetes mellitus, stroke, spinal cord injuries and other diseases. Preclinical experimental studies have included the application of human stem cells from various sources including the brain, bone marrow, umbilical cord and adipose tissue.

STEM CELL THERAPY FOR THE EYE

In ophthalmology, reconstruction of the ocular surface in patients suffering from intractable blinding ocular surface disease has become possible with the advent of techniques of *ex vivo* expansion and transplantation of limbal epithelial stem cells onto the cornea.[7–9] Different groups have used different techniques and substrates to cultivate the limbal cells with almost similar clinical outcomes of about 50 to 70 per cent success at the end of three to five years. The advantages of the technique developed by the group in India[9] include use of denuded human amniotic membrane, feeder cell free method, use of autologous serum, submerged technique of culturing and use of cultured monolayered epithelium generated within 10 to 12 days of cultivation. This cost-effective technique could be translated into an extended clinical trial of treating 450 patients at tertiary eye-care centres in a developing country like India. The patients who underwent subsequent corneal transplantation for visual rehabilitation provided a unique opportunity for documenting the *in vivo* survival and stratification of transplanted cells, thus fulfilling the most important criteria of successful cell therapy that can rarely be documented in other systems. This system provides proof of integration and functional restoration after cell therapy, without causing any harm to the recipient. Although the clinical outcome of this new technique is well established,[10,11] there are still many unanswered questions. These include rigorous characterisation of limbal stem cells, the mechanism and factors influencing the homing of stem cells from transplanted epithelium to limbal niche, and the long-term survival of transplanted cells.

Another challenge in eye disease is the treatment for irreversible photoreceptor loss in many retinal conditions. Repair of such damage by cell transplantation is one of the most feasible types of central nervous system repair; photoreceptor degeneration initially leaves the inner retinal circuitry intact and new photoreceptors need to make only single, short synaptic connections to contribute to the retinotopic map. So far, brain- and retina-derived stem cells from foetal and adult tissues transplanted into adult retina have shown little evidence of being able to integrate into the outer nuclear layer and differentiate into new photoreceptors.

Approaches to treating this disease include:

1. replacing the defective gene
2. introducing a drug or agent that either retards or arrests the premature cell death in the photoreceptors
3. introducing electronic chips
4. replacing the damaged cells by cellular therapy.

Gene therapy is aimed at counteracting the defective gene by substituting it with the normal gene material at the target site. Though successful visual recovery has been reported with gene therapy in canine models,[12] challenges remain in identifying a safe and reliable vector for clinical application and its long-term success. Introduction of trophic or survival factors into the eye, directly or through implants, is another novel way of retarding the premature cell death. The challenge lies in delivering the drug to the appropriate site in a safe and a sustained manner. Electronic chips, similar to those used for audio aids, have shown exciting results but the technology is still in its infancy.

These developments permit us to think optimistically of growing retinal tissue using appropriate cells, conditions and engineering techniques, which, if they clear the scientific and ethical hurdles, would pave the way for clinical application in the near future. We would need to identify the stem cells that would replace the photoreceptor and other cells of the retina, multiply/grow them in sufficient quantities, organise them into functional units, introduce them at the site in an appropriate way, allow them to survive and integrate into the host, so that ultimately, they function appropriately in a safe manner. The following cells have been proposed to have the proliferative potential to regenerate neuronal cells and photoreceptors: embryonic stem cells, retinal progenitor cells from foetal or post-natal retina, progenitor cells from the iris and ciliary body and bone marrow stromal cells.[13–15]

In summary, the advances made in the field of stem cell biology have contributed immensely to the field of ophthalmology, which has now taken a lead role in translational research. Whenever available, use of autologous tissues with minimal and no expansion is one of logical choice for cell therapy, thus obviating the ethical hurdles that are raised with the use of embryonic or foetal stem cells. The eye is one of the perfect organs where cell therapy can be monitored and hence, it comes as no surprise that it would be considered as a perfect model for providing proof of concept of such novel forms of cell therapy.

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