STEM CELL THERAPY IN OCULAR DISEASES

ESSAY

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By

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Abstract

This essay is a review of literature on the use of stem cells in the management of ocular disorders. Stem cell therapy is emerging as a potentially revolutionary new way to treat disease and injury, with wide-ranging medical benefits. It aims to repair damaged and diseased body-parts with healthy new cells provided by stem cell transplants. Diseases and disorders with no therapies or at best, partially effective ones, are the lure of the pursuit of stem cell research.

A stem cell is a cell that has the ability to divide (self replicate) for indefinite periods-often throughout the life of the organism. Under the right conditions, or given the right signals, stem cells have the potential to develop into mature cells that have characteristic shapes and specialized functions.

Key Words :

Acidic fibroblast growth factor - *Basic fibroblast growth factor* – *Bromodeoxyuridine*.

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Abbreviations

aFGF : *Acidic fibroblast growth factor*
AMD : *Age-related macular degeneration*
AMT :*Amniotic membrane transplantation*

bFGF : *Basic fibroblast growth factor*
BM : *Bone marrow*
BrdU : *Bromodeoxyuridine*

c-CLAL : *cadaveric conjunctival limbal allograft*
c-KLAL : *cadaveric keratolimbal allograft*
CLAU : *Conjunctival limbal autograft*

E16.5 : *Embryonic day 16.5*
EGF : *Epidermal growth factor*
ERG : *Electroretinogram*
ESC : *Embryonic stem cell*
EVELAU : *ex vivo expanded limbal autograft*

FGF : *Fibroblast growth factor*

GFP : *Green fluorescent protein*
GM : *Growth medium*

HAM : *Human amniotic membrane*
HESC : *Human embryonic stem cell*
HIF-1α : *Hypoxia-inducible factor-1α*
HLA : *Human leucoyte antigen*

HPCLK : *Homologous penetrating central limbokeratoplasty*

HSC : *Hematopoietic stem cell*

ICM : *Inner cell mass*

IGF-I : *Insulin like growth factor I*

IPE : *Iris pigment epithelium*

IPL : *Inner plexiform layer*

KEP : *Keratoepithelioplasty*

LCAT : *Limbal-conjunctival autograft transplantation*

Lin^- : *Lineage negative*

Lin^+ : *Lineage positive*

lr-CLAL : *conjunctival limbal allograft*

1r-EVELAL: *living-related ex vivo expanded limbal allograft*

LRC : *Label retaining cell*

LSCD : *Limbal stem cell deficiency*

MEF : *Mouse embryonic fibroblast*

MSC : *Mesenchymal stem cell*

MTX : *Methotrexate*

$NaIO_3$: *Sodium iodate*

NMDA : *N-methyl-D-aspartate*

OCP : *Ocular cicatricial pemphigoid*

ONL : *Outer nuclear layer*

P11 : *Post-natal day 11*

PMC : *Postmitotic cell*

RCS : *Royal college of surgeons*

RP : *Retinitis pigmentosa*

RPE : *Retinal pigment epithelium*

RT PCR : *Real time polymerase chain reaction*

SC : *Stem cell*

SEZ : *Subependymal zone*

SJS : *Stevens-Johnson syndrome*

TAC : *Transient amplifying cell*

TDC : *Terminally differentiated cell*

VEGF a : *Vascular endothelial growth factor a*

Stem Cell Therapy in Ocular Diseases

Introduction

The two main prerequisites for good vision are the clear optical focusing system (cornea, lens, and intraocular fluids) which are designed to bring visual images to a focus on the retina and the intact neural system, which detects and transmits images in coherent fashion from the retina, through a series of neural pathways, to the visual cortex, where they are perceived and interpreted.

It is no wonder that the focus of an immense amount of research has been on the two parts of the eye that are essential for clear vision (the cornea and the retina). Therefore recent interests in ocular stem cell research have concentrated wholly on these two major components of the ocular system

Stem cell therapy involves the introduction of healthy new stem cells to, potentially, repair and replace damaged or lost cells. This therapy, often referred to as "Regenerative Medicine" provides much promise for the treatment of what was previously regarded as incurable diseases.

Stem cells (SC) are different from other cells of the body in that they have the ability to self-renew and to give rise to multiple cell types. With this ability, they have been used to replace defective cells/tissues in patients who have certain diseases or defects. Their sources in the eye are: the limbus (source for corneal stem cells), bulbar and forniceal

conjunctiva (for conjunctival stem cells), the ciliary epithelium, retinal progenitor cells and the embryonic stem cells (for the retina) as well as the umbilical cord stem cells and the bone marrow stem cells. However, the embryonic stem cells can be the source of stem cells for all the ocular tissues. [1]

During the 1990's the research focus for many debilitating diseases was focused on gene therapy, which involves putting certain genes into cells in a patient. Today, the focus has shifted to research on how to put stem cells into patients.

The greatest advances in ocular stem cell biology and treatment have been in relation to the cornea and conjunctiva, which forms the ocular surface. The ocular surface is an ideal region to study epithelial stem cell biology, because of the unique spatial arrangement of stem cells and their daughter cells, which are called “transient amplifying cells”. Under certain conditions, the limbal stem cells may be partially or totally depleted resulting in varying degrees of stem cell deficiency with resulting abnormalities in the corneal surface. Such deficiency of limbal stem cells leads to "conjunctivalization" of the cornea with vascularization, appearance of goblet cells, and an irregular and unstable epithelium. This results in ocular discomfort and reduced vision. [2] Advances in microsurgical techniques and the understanding of the role of the limbal stem cells have led to great improvements in both visual acuity and quality of life for these patients. [3]

Nowadays trials have been adopted to introduce stem cells in the treatment of retinal diseases. At present, no therapies are available to patients for preventing or reversing the retinal degeneration that occurs in

these diseases. Implantation of neural progenitor cells into the eye may be a means by which to retard or even reverse degeneration of the retina. [4]

The recent identification and characterization of neural progenitors with stem cell properties has opened new avenues that may be useful for treating functional impairments caused by the death of specific neural cell populations. Neuronal degeneration is the cause of debilitating visual impairment associated with prevalent ocular diseases, such as retinitis pigmentosa (RP), age-related macular degeneration (AMD), retinal detachment, and glaucoma. Neural stem cells may help to restore vision in patients who have these diseases, by repopulating the damaged retina and/or by rescuing retinal neurons from further degeneration. [5]

They could be surgically transplanted into the eyes or drugs could be developed to activate suitable populations of stem cells naturally present within the patient's body. Once in the retina it is hoped that the new retinal cells will mature and incorporate within the existing tissue. This process may be helped naturally by the degenerating retina as the damaged retinal pigment epithelium (RPE) secretes cytokines attracting bone marrow (BM) derived stem cells. Thus BM stem cells may serve as endogenous source for tissue regeneration after RPE damage. [6]

Aim of the work:

The aim of this essay is to review the literature handling the role of stem cells in the management of ocular surface disorders as well as retinal diseases.

What Are Stem Cells?

In 1998, for the first time, investigators were able to isolate stem cells from early human embryos and grow them in culture. In the few years since this discovery, evidence has emerged that these stem cells are, indeed, capable of becoming almost all of the specialized cells of the body and, thus, may have the potential to generate replacement cells for a broad array of tissues and organs. Thus, this holds the promise of being able to repair or replace cells or tissues that are damaged or destroyed by many of our most devastating diseases and disabilities. [7]

Stem cells (SC) can be defined as any cell with high capacity for cell renewal extending throughout adult life. They make up from 0.5% to less than 10% of total cell population. [8] They are unspecialized cells that can self-renew indefinitely and that can also differentiate into more mature cells with specialized functions. In humans, stem cells have been identified in the inner cell mass of the early embryo; in some tissues of the fetus, the umbilical cord and placenta; and in several adult organs. In some adult organs, stem cells can give rise to more than one specialized cell type within that organ (for example, neural stem cells give rise to three cell types found in the brain neurons, glial cells and astrocytes). [9]

Stem Cell Niche:

Given the life-long importance of stem cells, they must be tucked safely from harm's way. It is widely believed that the maintenance of stem cells is controlled by their particular microenvironments (or

"niches"). Stem cells are usually confined to their 'niche' where the microenvironment supports and maintains the stemness of stem cells and affords a degree of protection. The 'niche' represents the collective influence of other local matrix cells, the extracellular matrix, its vascularity, basement membrane characteristics and prevalent growth factors and other cytokines. [10]

The importance of the niche is perhaps best exemplified by experiments in which the fate of embryonic stem cells (ESCs) is monitored following their subcutaneous injection into nude mice. ESCs isolated from a blastocyst-stage mouse embryo can be propagated indefinitely in tissue culture without losing their pluripotent potential. However, when faced with a foreign environment of surrounding in vivo tissue, ESCs form ugly multicellular tumor masses, known as teratomas, which contain a multiplicity of cell types. Without the appropriate microenvironment of specific intercellular interactions and cellular organization, the ESC can become an undesirable beast. By contrast, as shown by ***Beatrice Mintz*** and ***Martin Evans in the 1970's***, when injected instead into the center of a recipient mouse blastocyst, analogous to their native niche, ESCs resume normal behavior and contribute to generating all of the tissues of a healthy normal chimeric offspring. Taken together, these findings imply that it is the combination of the intrinsic characteristics of stem cells and their microenvironment that shapes their properties and defines their potential. [11]

Stem cells are able to survive throughout the lifetime of the organism, while maintaining their number, producing populations of

daughter cells that can proceed down unique pathways of differentiation. [12] Following stem cell division, only one of the daughter cells can re-enter the niche, while the other daughter cell enters a less favourable environment that does not protect the cell from entering the pathway of terminal differentiation. The daughter cell(s) that step outside the stem cell pool are destined to divide and differentiate with the acquisition of features that characterize the specific tissue. Such a cell is called "**transient amplifying cell**" and is less primitive than its parent stem cell. It is believed in some quarters that there exists a window of opportunity during which some of these cells (transient cells) can revert to the stem cell pool as stem cells. Transient amplifying cells divide more frequently than stem cells but have limited proliferative potential and are considered the initial step of a pathway that results in terminal differentiation. They differentiate into **'postmitotic cells**' and finally to **'terminally differentiated cells'**. Both postmitotic and terminally differentiated cells are incapable of cell division. All cells except stem cells have a limited life span and are destined to die. [10] This is the most particular, and not so well understood characteristic of stem cells, which is the capacity for asymmetric cell division. This property allows on daughter cell to remain a stem cell while the other daughter cell is more differentiated. [8] The two daughter cells acquire different developmental potentials, either by unequal segregation of cell fate determinants or because of differential influences from their surroundings. Structural proteins, in particular cytoskeletal components, are important for partitioning of cell fate determinants. [13]