STEM- CELL TRANSPLANTATION IN OCULAR SURFACE DISORDERS

ESSAY

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LIST OF ABBREVIATIONS

bFGFFibroblast growth factor

BM basement membrane

BMZBasement membrane zone

c-CLAL cadaveric-Conjunctival limbal allograft

CINConjunctival intraepithelial neoplasia

CLAU Conjunctival limbal autograft

COP Corneal precursors

CSACyclosporin A

ECM Extracellular matrix

EVELAU Ex vivo expanded limbal autograft

ECCE Extracapsular cataract extraction

FACSFluorescine activated cell sorting

HAHyaluronan

IHC Immunohistochemistry

ICCEIntracapsular cataract extraction

KLALkeratolimbal allograft

KPro keratoprothesis

LESCLimbal epithelial stem cells

lr-CLALliving related-Conjunctival limbal allograft

LRC Latent retaining cells

MACS Magnetic activated cell sorting

OCPOcular cicatricial pemphigoid

OSD Ocular surface disease

OSST Ocular surface stem cell transplantation

PAS Periodic acid-schiff stain

PK Penetrating keratoplasty

PMC Postmitotic cells

SC Stem cells

SEM Scanning electron microscopy

SJS Stevens - Johnson syndrome

SPARC Secreted protein acidic and rich in cysteine

SSCE Sequential sector conjunctival epitheliectomy

SSCE Sequential sector conjunctival epitheliectomy

SSEA-4 Stage specific embryonic antigen 4

TACs Transient amplifying cells

TGF-β Transforming growth factor β

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Introduction

The epithelium covering the cornea at the front of the eye is maintained by stem cells located at its periphery, in a region known as the limbus. A lack or dysfunction of these so-called limbal stem cells (LSCs) results in the painful and blinding disease of LSC deficiency. **(Sajjad et al,2006**)

Stem cells are present in all self-reviewing tissue and have unique properties. The epithelia of ocular surface although anatomically continuous with each other at the corneoscleral limbus, the two cell phenotypes represent quite distinct subpopulations. Stem cells for the cornea are located at the limbus. The microenvironment of the limbus is considered to be important in maintaining stemness of the stem cells. They also act as a "barrier" to conjunctival epithelial cells and prevent them from migrating on to the corneal surface. **(Sangwan, 2001)**

Much hope has been placed on the potential use of these cells to restore sight, particularly in those conditions in which other established treatments have failed and in which visual function has been irreversibly damaged by disease or injury.

At present, there are many limitations for the immediate use of embryonic stem cells to treat ocular disease, and as more evidence emerges that adult stem cells are present in the adult human eye, it is clear that these cells may have advantages to develop into feasible therapeutic treatments without the problems associated with embryonic research and immune rejection. **(Puangsricharern and Tsang ,1995)**

Severe ocular surface disease is a clinical term applied to conditions resulting from injury or disease of either limbal stem cells (which form the source of regenerating the corneal epithelium) and/or the conjunctiva (which harbors the mucin-secreting goblets cells) that are essential for an ocular surface integrity. **(Holland et al ,1996)**

The common conditions leading to either loss or hypo function of limbal stem cells include chemical or thermal burns, Stevens–Johnson disease, ocular cicatrizing pemphigoid, multiple surgeries, and conditions that could lead to insufficient stromal microenvironment to support stem cell function including aniridia, congenital erthrokeratodermia, neurotrophic keratitis, or chronic limbitis. The disease manifests as epithelial defects, chronic inflammation, keratitis, vascularization, and fibrosis, ultimately resulting in corneal blindness. **(Dua et al, 2000)**

Limbal Stem Cell Corneal Transplantation surgically replaces critical stem cells at the limbus.

Host stem cells normally reside in this area. Transplantation is done when the host stem cells have been too severely damaged to recover from disease or injury.

Conditions such as severe chemical burns, Stevens-Johnson syndrome, and severe contact lens over wear may cause persistent non-healing corneal epithelial defects.

These defects result from failure of these stem cells to produce sufficient epithelial cells to repopulate the cornea. If untreated, persistent non-healing corneal epithelial defects are vulnerable to infection, which can lead to scarring, perforation, or both.

Under these circumstances, a corneal transplant, which replaces only the central cornea and not the limbus, is insufficient; stem cells are needed to produce new cells that repopulate the cornea, restoring the regenerative capacity of the ocular surface.

Corneal Limbal Stem Cells can be transplanted from the patient’s healthy eye or from a cadaveric donor eye. **(Koizumi et al, 2001)**

There is great interest in the biology of adult stem cells because of their capacity to self-renew and their high plasticity. These traits enable adult stem cells to produce diverse mature cell progenitors that actively participate in the maintenance of homeostatic processes by replenishing the cells that repopulate the tissues/organs during a lifespan and regenerate damaged tissues during injury. **(Murielle and Surinder, 2006).**

The causes of limbal stem cell transplantation failure can be categorized as early and late. The main causes of early failure include immunologic rejection, inflammation, eyelid abnormalities, and aqueous and mucin deficiency. Acute rejection typically occurs between 2 and 12 months following transplantation. Review of the literature demonstrates several reports of acute stem cell transplant rejection. **(Thoft and Sugar,1993)**

Late causes include sectoral conjunctivalization, low-grade rejection, late acute immunologic rejection, and stem cell transplant exhaustion. **(Schwartz and Holland, 2002)**

Major advances in the biology of corneal stem cells have been achieved. However, the therapeutic use of these stem cell types has the disadvantage of needing an intact stem cell compartment, which is usually damaged. In addition, long ex vivo culture is needed to generate enough cell numbers for transplantation. In the near future, combination of advanced biomaterials with cells from abundant outer sources will allow advances in the field. For the former, magnetically aligned collagen is one of the most promising ones. **(Regen, 2006)**

Aim of the work

The aim of the work is to review the role of stem-cell transplantation in ocular surface disorder.

In this review, pathophysiology of ocular surface disorders with limbal stem cell deficiency**.** Working is attempted together with new published data concerning: Concept, techniques, and future of stem cell transplantation in this type of ocular surface disorders.

Anatomy of the ocular surface

The tissues at the ocular surface include the cornea, conjunctiva, and the intervening zone of the limbus. The primary function of the entire region is to refract and transmit light to the lens and retina. Although the cornea and its surface tear film constitute the tissue actually performing the tasks, the limbus and conjunctiva support the cornea in these important functions. **(Gipson and Surgrue, 1994).**

Corneal Epithelium:

The corneal epithelium is stratified, squamous and non-keratinized consisting of five to seven layers which represent 10% of the corneal thickness ***(Ehlers, 1970).***Thickness has been measured accurately by high frequency ultrasound and was found to be 50-90 um ***(Reinstein et al., 1994).***

The basal cells form the deepest layer of the epithelium and stand in a palisade-like manner in perfect alignment on a basal lamina. They form the germinative layer of the

epithelium and are continuous peripherally with that of the limbus. These cells are columnar (10 um wide and 15 um tall) with rounded heads, flat bases and oval nuclei oriented parallel to the cells' long axis. Multiple branches of the trigeminal nerve terminate as free unmyelinated nerve endings between cells of the basal layer ***(Kenyon, 1987).***

The second epithelial layer (the **"wing"** or"**umbrella**" cells) consists of polyhedral cells, convex anteriorly, which cap the basal cells, and send processes between them. The long axes of their oval nuclei are parallel to the corneal surface ***(Mathers and Lemp, 1989).***

The next two or three layers are also polyhedral and become wider and increasingly flattened towards the surface. The surface cells have the largest surface area and this is greater in the periphery compared to the centre. They retain their nuclei which project backwards leaving the surface perfectly smooth and do not show keratinization ***(Bron et al.,***

1997).Figure (1) demonstrates the differentiation of basal cells into wing cells and finally to superficial cells.

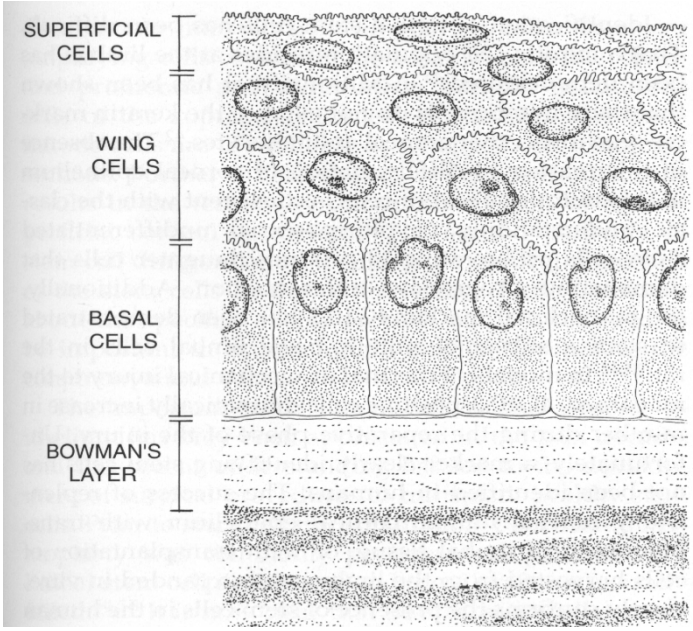

Fig. (1)

A Schematic drawing of corneal epithelium showing the differentiation of proliferative basal cells into wing cells, and finally to superficial cells (Tsubota et al., 2002).

Ultrastructural Features of Epithelial Cells

The epithelial cells contain the usual organelles of actively metabolizing cells. Mitochondria are small and scarce in the basal cells but are moderately abundant in the wing and middle cell layers. There is a highly glycogen