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COMMENTARY

Adoptive Cell Transfer to Enhance Patients Immunity Against Cancer

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ABSTRACT

Cancer is an abnormality of cells in which cells are proliferating in an uncontrolled manner due to some unwanted mutations. Any cells from any part of body can be cancerous and may form tumors later on. These tumors develop tumorsphere and their microenvironment modulate T cells as a survival mechanism and these immune cells failed to identify the cancerous cells, allowing them to metastasis. A number of therapeutic approaches such as radiotherapy, chemotherapy etc. are being applied in clinical practices to remove tumors or kill tumor cells. Cell therapy has shown a promising potential in last two decades in cancer treatment as some cells such as mesenchymal stem cells have tumor tropism and induce apoptosis in cancer cells. Recently, immunotherapeutic approaches have been considered the gold standard and it has been shown that T cells isolated from the cancer patient can be trained to target cancer cells. In this process, chimeric antibody receptor (CAR) and T-cell receptor (TCR) are introduced on the T cell surface to enhance T cells function and their transfer in the patient's circulatory system result in the identification and killing of cancerous cells. This approach has been known as the adoptive cell transfer or adoptive cell therapy (T cells) and has shown 99% promising results in 243 clinical trials done so far. Clinical trials are going on to determine its efficacy in cancer treatment and a number of pharmaceutical firms are developing adoptive T cells as drugs to treat cancer in our daily routine clinical practice. Results obtained yet, have shown the perspective of adoptive cell therapy as the future approved cancer therapy.

Keywords: Adoptive Cell Therapy, Adoptive T-Cell Transfusion, Cell Therapy, Clinical Trials, Cancer Therapy

Cancer is the second largest cause of mortality around the world causing millions of deaths every year (1). It is caused when cells failed to follow the cell cycle checkpoint pathways and start dividing in an uncontrolled manner. Millions of cells are dying daily, and these cells are being replaced by newly divided cells to regulate body functions normally. By some unwanted mutations, the cells skip the controlled and regulated division mechanism and start developing massive structures containing cancer cells called tumors (2, 3). As these mutations are making cells abnormal or cancerous, T cells of body are aimed to kill the cancerous cells whenever they developed in any part of the body.

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OPINION

Commercialization of Stem Cell Therapeutic Research: Bridging a Big Gap

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ABSTRACT

Stem cell therapeutic research is passing through a transition phase between laboratory research and health industry. According to the US data registry of clinical trials, more than 4776 studies have been registered, 2882 have been completed whereas 1894 studies are in process. Surprisingly, in spite of having huge research, there are two commercialized stem cell therapeutic products in global market and these two products are also not approved by FDA. As it has been discussed in literature, stem cells have been considered as promising candidates to treat non-curable diseases like cancer etc. More than 80% successful clinical trials have been done showing no or little side effects with much better efficiency than pharmacokinetics but still stem cell research is far from being commercialized. The major reason of stem cells non-commercialization is the gap among clinicians, researchers, industry experts and policy makers. A multibillion dollar grants and a very strong communication system between doctors, researchers, industrial experts, policy makers, regulating authorities, are the pre-requisite to commercialize stem cell therapy.

Keywords: Current good manufacturing practice (cGMP), commercialization of stem cells, cellular therapy, clinical trials, non-curable diseases

Stem cell therapy has been recommended as a novel way of treatment for various diseases like cardiovascular, diabetic, neurological diseases, spinal and orthopaedic injuries, etc. A number of optimization techniques have been approved for clinical studies using stem cells [1, 2]. In recent years, stem cell therapy has been considered as a promising candidates in regenerative medicine to replace or regenerate damage tissues via differentiation [3] or paracrine effects [4]. 4776 studies are registered on US registry for clinical trials (www.clinicaltrials.gov) till 2014. The geographical distribution of these clinical trials are given in Figure 1.

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Commentary

Developments toward an Ideal Skin Substitute: A Commentary

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Abstract

Skin grafting always has been considered a challenging task for the researchers and tissue engineers from its first introduction in 1871 by Reverdin. Skin substitutes, composed of degradable synthetic or biological components, are being considered as emergency replacements/grafts to the damaged skin. A number of technical developments in this filed have led to development of several skin substitutes, such as Biobrane®, Integra®, OrCel®, Suprathel® etc which are available for clinical utilization. From these, some characteristics, including infection resistance, water loss prevention, long shelf life, easy to store are set as criteria for assessment of the products. Post grafting problems associated with available skin substitutes questioned their reliability and reject them as an ideal skin substitute. Innovative tissue engineering approaches based on biological scaffolds and clinical grade stem cells could be an attractive alternative for available skin substitutes.

***Keywords*:** Tissue engineering, allografts, xenografts, epidermis, keratinocyte cultures, Skin Substitutes

Introduction

Skin is the largest protective organ of the human body, making up to 15% of the body weight. It acts as a functional barrier against the invasion of germs, body fluid loss, etc. (Lai-Cheong and McGrath, 2013). Skin is composed of three basic layers of epidermis, dermis and hypodermis. Epidermis is the outermost layer which is mainly composed of proliferating and non-proliferating keratinocytes (Arda et al., 2014). Accidental damaging of the skin, cutaneous wounds and burnings result in the severe and life threatening complications to the patients (Blais et al., 2013). Immediate replacement of the skin remained a clinical practice since the 19th century in the form of epithelial cell grafts (Reverdin, 1871). The limited amount of epithelial cells and donor sites are the major challenges in advantageous skin grafts. Conceptual approaches in the development of an ideal skin substitute for immediate replacement of damaged or wounded skin have remained as clinical interests for researchers, globally (Boyce, 2001; Balasubramani et al., 2001). Investigations in this area have resulted in introduction of the first skin substitute in 1981 by Burke and his colleagues (Burke et al., 1981). To date, a number of biological and synthetic skin substitutes are commercially available i.e. Biobrane®, Integra®, OrCel®, Suprathel® etc. Synthetic components are mostly organic polymers which are degradable and provide a regenerative environment for tissue regeneration. Biological skin substitutes are cellular products containing proliferative keratinocytes (Whitaker et al., 2008; Heimbach et al., 1988; Eisenberg and Llewelyn, 1998; Uhlig et al., 2007). Combinatory approaches using skin substitutes and dermal components i.e. fibroblasts have been applied for better wound healing (Eisenberg et al., 1998; Still et al., 2003; Veen et al., 2010). Better understanding of cellular and molecular mechanisms in skin regeneration is needed for the development of an ideal skin substitute (Bielefeld et al., 2013).

Classification of Skin Substitutes

Several skin substitutes are currently available for a variety of clinical applications. They can be classified into different categories, based on different criteria (Atiyeh et al., 2005; Horch et al., 2005). Almost all commercially available skin substitutes have been classified under the following three main headings (Ferreira et al., 2011).

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Effects of Iron Salts on Rhamnolipid Biosurfactant Production

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ABSTRACT

In this research, previously identified *Pseudomonas aeruginosa* (IMBB Strain) was re-streaked onto a fresh nutrient agar slants and stored at 4° C for further use. Iron limited mineral salt medium with the prescribed composition was used for the production of biosurfactants. Three different salts, namely ferrus chloride, ferrus sulfate and ferrous ammonium sulfate, were selected to analyze their effect on rhamnolipid production. The experiments were designed in three batches containing varying concentrations of ferrous chloride, ferrous sulfate and ferrous ammonium sulfate with one control flask. The produced rhamnolipid was detected physically and chemically by surface tension measurement and Orcinol assay, respectively. There was highest yield of Rhamnolipid of 3.81 g/L when the medium of Manitol was varied with 0.008 g/L of ferrous sulfate. The Rhamnolipid production using 0.004 g/L ferrous chloride was estimated as 1.85 g/L.

INTRODUCTION

Biosurfactans are structurally diverse group of surfactants (surface active compounds) produced by living organisms (microorganisms) and contain both hydrophobic and hydrophilic moieties that reduce surface tension and interfacial tension between individual molecules at the surface and at interfaces respectively (Lin *et al.,* 1998). Biosurfactants have applications in a wide variety of industrial processes involving emulsification, foaming, detergency, wetting, dispersing or solubilization. There is almost no modern industrial operation where properties of surfaces and surface active agents are not exploited (Fiechter, 1992). Biosurfactants attracted attention as hydrocarbon dissolution agents in the late 1960s and their applications have been greatly extended in the past five decades as an improved alternative to chemical surfactants (carboxylates, sulphonates and sulphate acid esters) especially in food, pharmaceuticals and oil industry (Banat *et al.,* 2000.). The reason for their popularity as high value microbial products is primarily because of their specific action, low toxicity, higher biodegradability, effectiveness at extreme temperature, pH, salinity, widespread applicability, and their unique structures which provides new properties that classical surfactants may lack (Kosaric, 1992).

Biosurfactants possess the characteristic property of reducing the surface and interfacial tension using the same mechanism like chemical surfactants. Unlike chemical surfactants which are mostly derived from the petroleum and feedstock, these molecules can be prepared by the microbial fermentation processes using cheaper agro-based substrates and waste materials. During the past few years biosurfactant production by various

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REVIEW

Engineered Cell Therapy: A Successful Approach to Treat Cancer

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ABSTRACT

Cancer is the abnormality which happens in the cell cycle, resulting in uncontrolled cell division and is the second largest cause of deaths in the world accounting 13% of all deaths followed by the cardiovascular diseases. Finding a therapeutic solution for cancer is a continuous process. A number of therapeutic approaches like chemotherapy, preventive therapies, radiation and magnetic therapy, adjuvant therapy, Immunotherapy, gene therapy, cell transplantation therapy, Hyperthermia and surgery are under research in order to treat cancer. Targeted therapy is the most preferred way to treat cancer globally and researchers are focusing on the different ways of targeted therapy. Gene therapy with its first approved drug for cancer (Gendicine™) in China revolutionized the cancer drugs but a number of questions in scientific community around the world and its rejection in European and American market raised question marks on its authenticity as cancer drug. Successful clinical trials for mesenchymal stem cell (MSCs) and engineered cells based therapy against cancer emerged the concept of gene and cell therapy for cancer and a number of clinical trials also produced successful results in this case. Engineered cells are new agents of targeted cancer therapy and have been considered by researchers, as a promising therapeutic candidates. Engineered cell therapy (combination of gene and cell therapy) as a part of targeted therapy of cancer may provide a valuable resource. T-Cell engineering has faced successful results, whereas MSC engineering is passing through a transition phase. Successful engineering of MSCs could be a hope for cancer patients in near future.

Keywords: Cancer therapy, stem cell transplantation, cancer statistics, cancer mortality, cancer prevalence

Malignancy always remains a big challenge for life science researchers as being the leading cause of death worldwide. According to the GLOBOCAN 2012 & WHO, 8.2 million people died (about 13% of all deaths) just because of cancer in 2012 and these deaths are predictable to continue rising, with an estimated 13.1 million deaths in 2030 from which, the majority are caused by lung cancer.

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(Mini Review)

FACTORS AFFECTING THE RHAMNOLIPID BIOSURFACTANT PRODUCTION

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ABSTRACT

Rhamnolipids are the best studied glycolipids having excellent surface activity. Their utilization in various application areas of environment, health, food, cosmetic, oil industry etc., have made it the potential candidates that could replace the chemically synthesized surfactants because these are derived from the natural source, in a pure form and they have low toxicity levels. The production of rhamnolipids dependent on several environmental and nutritional factors and the highest yield of rhamnolipids are estimated at 6 g/L with specific parameters. Effects of multivalent ions, nutritional factors and environmental conditions are described by many researchers to find out its enhanced production (Desai and Banat, 1997). In this mini review, some nutritional, environmental and compositional factors are studied and estimated that how the production of rhamnolipids enhanced and which kind of effects these factors have on its production.

INTRODUCTION

Rhamnolipids, a kind of extra-cellular glycolipids composed of L-rhamnose and 3-hydroxyalkanoic are produced by the *Pseudomonas aeruginosa.* Rhamnolipids were found for the first time in *P. pyocyanea* grown on glucose and was the first report of link between a sugar and a hydroxylated fatty acid (1). There is no any field, which is excluded in the application area of rhamnolipids. Increased demands and high cost of rhamnolipids compelled the scientists to increase its production and to find out the ways which affects its high yield. Researchers are focusing on the factors to enhance its production by changing the environmental conditions and parameters (2). Their wide applications make it an interesting candidate to find out its relationships in its maximum production.

Effect of Nitrogen: Nitrogen or metal ion-dependent regulation plays a prominent role in the synthesis of biosurfactants. The synthesis of rhamnolipids in *P. aeruginosa* is exhausted of nitrogen and commencement of the stationary phase of growth has been observed (3).

Effect of Multivalent: The limitation of multivalent cations also causes over production of biosurfactants. Iron limitation stimulates biosurfactant production in *Pseudomonas aeruginosa* (3).

Effect of Carbon Sources: Micro-organisms utilize a variety of organic compounds as the source of carbon and energy for their growth. Water soluble carbon sources such as glycerol, glucose mannitol and ethanol used for rhamnolipid production by *Pseudomonas aeruginosa* as mentioned in Table-1 (4).

Only glycerol behaved differently, as the rhamnolipid level decreased sharply when

REVIEW

Stem Cell Therapy for Neurodegenerative Diseases: Strategies for Regeneration against Degeneration

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ABSTRACT

Neurodegeneration is a general term for the progressive loss of structure and/ or function of neurons, gives rise to dysfunction or death of neurons. Neurodegenerative diseases including Alzheimer´s disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), spinal cord injury (SCI) and brain ischemia (BI) occur as a result of neurodegenerative processes leading to different degrees of paralysis and loss of sensation and cognition in the patients. Unfortunately, no successful cure for neurodegenerative disorders has been developed so far, and most of the currently available pharmacological therapies are mainly palliative.

In recent years, stem cells have provided a great opportunity to develop potentially powerful innovative strategies to cure neurodegenerative diseases. Stem cells transplantation is capable of restoring injured neuronal tissue by replacement of the damaged cells via using directly differentiated cells or by protecting of existing healthy neurons and glial cells from further damage, or by repairing through providing a conductive environment in favour of regeneration. Here we have brought together some of these examples, discuss possible therapeutic means using different types of stem cells, mainly adult stem cells (ASCs), to treat neurodegenerative diseases.

Keywords: Neurological disorders, Stem cell therapy, Genetically modification, Paracrine effects, Differentiation, Combinatorial treatment, Cell cartridge

Neurodegenerative diseases are divided into acute cases, like spinal cord injury (SCI) and brain ischemia (BI), in which different types of both neurons and glial cells restricted to the stroke site are lost over a short period of time (1, 2), and chronic cases such as Alzheimer disease (AD), Parkinson disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple

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Meeting Report

1st Symposium on Y-Chromosome Human Proteome Project

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Abstract

Chromosome-centric human proteome project (C-HPP) is a recent initiative to rationalize and analyze gene-protein and protein-protein interactions in normal and disease conditions. This initiative is aimed to generate the proteomic atlas explaining the molecular architecture of the human body and was initiated in response to the hurdles identified during analyzing the human genome project (HGP). A need for the experimental observation of translated proteins was felt to analyze precisely what is going on in the cell. 25 countries around the world are participating in the C-HPP. This symposium report will introduce the Y-chromosome HPP which is undergoing in Iran by eminent molecular biologists of Royan Institute, Tehran and its collaborates.

Keywords: Human Y-Chromosome

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Introduction

The human proteome project (HPP) is a systematic global effort to analyze the molecular behavior of translated proteins, their distribution and localization, and interactions and functions in the human body. In 2011, complete directions of the project such as its future exploration and its current status were explained (1). After finalizing the directions and targets, scientists explained that this project will be the effective integration of proteomics data into a genomic framework that will help us understand complex biological systems and to predict protein-based solutions to chronic diseases as it will catalog the proteins encoded by the genome as shown in figure 1 (2). Twenty-three pairs of human chromosomes along with the mitochondrial chromosome are divided among 25 countries around the world. X- and Y-chromosomes are independently assigned to Japan and Iran respectively (Table 1). Journal of Proteome Research has assigned a specific annual issue C-HPP (12:1, 2013 and 13:1, 2014) to uncover the key developments in C-HPP and the current status of overall project has also been discussed in both issues (3, 4).

In line with research activities of Y-C-HPP, the first Y Chromosome Proteome Project Symposium was held in Royan Institute. More than 200 students and researchers attended this symposium. In this report, the scientific program of the symposium has been categorized into 4 sections. First section was regarding the introduction of Royan Institute and the role of the Islamic Republic of Iran in Y-HPP. In section two, the invited speakers discussed the need for C-HPP and presented a 2014-update on XY-HPP. The third section was the presentations of students and researchers on the work they are under taking and highlighting their current results and future directions. The last section was the panel discussion among the speakers and participants.

Molecular biological research in Iran

It is for the first time that an Islamic country

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Original Research

Adipose derived mesenchymal stem cells express keratinocyte lineage markers in a co-culture model

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Abstract: Cutaneous wound healing is a complex type of biological event involving proliferation, differentiation, reprograming, trans/de-differentiation, recruitment, migration, and apoptosis of a number of cells (keratinocytes, fibroblasts, endothelial cells, nerve cells and stem cells) to regenerate a multi-layered tissue that is damaged by either internal or external factors. The exact regeneration mechanism of damaged skin is still unknown but the epithelial and other kinds of stem cells located in skin play crucial roles in the healing process. In this work, a co-culture model composed of adipose derived mesenchymal stem cells and keratinocytes was developed to understand the cellular differentiation behaviour in wound healing. Human mesenchymal stem cells were isolated from waste lipoaspirates. Keratinocytes were isolated from neonatal rats skin as well from human adult skin. Both types of cells were cultured and their culturing behaviour was observed microscopically under regular intervals of time. The identity of both cells was confirmed by flow cytometry and qRT-PCR. Cells were co-cultured under the proposed co-culturing model and the model was observed for 7, 14 and 21 days. The cellular behaviour was studied based on change in morphology, colonization, stratification, migration and expression of molecular markers. Expression of molecular markers was studied at transcriptional level and change in cellular morphology and migration capabilities was observed under the invert microscope regularly. Successfully isolated and characterized mesenchymal stem cells were found to express keratinocyte lineage markers i.e. K5, K10, K14, K18, K19 and Involucrin when co-cultured with keratinocytes after 14 and 21 days. Their expression was found to increase by increasing the time span of cell culturing. The keratinocyte colonies started to disappear after 10 days of culturing which might be due to stratification process initiated by possibly transdifferentiated stem cells. It can be concluded that mesenchymal stem cells can regenerate the damaged skin if transplanted to damaged area but for their successful differentiation and enhanced regeneration, they need a population of keratinocytes *in situ* which need further experiments for validation of co-culture model and its potential for being used in clinics.

Key words: Cutaneous wound healing, Keratinocyte lineage, Adipose-derived mesenchymal stem cells, Regenerative medicine, Co-culturing model.

Introduction

Human skin is responsible to protect the human body from being damaged by the fluctuations of external environment. These variations are damaging the skin regularly and skin homeostasis is maintained continuously via a complex regeneration process of cutaneous wound healing. It has been discussed that a number of cellular (keratinocytes, keratinocyte stem cells, fibroblasts, mesenchymal stem cells) and molecular components such as extracellular matrix (ECM) are involved in regeneration of damaged skin and this process is being followed by a strict regulation of a cascade of events involving inflammation, proliferation, differentiation and remodelling to regenerate a multi-layered tissue. All cells involved in healing process are highly intercommunicated to create a healing microenvironment for precise regeneration. Stem cells as being the critical healing agents are either recruited or differentiated for the generation of a multi-layered skin and maintenance of healing microenvironm (1-4). Reliable keratinocyte culturing and characterization techniques (5), better understanding of the molecular mechanisms in the regulation of epidermal stem cells and wound healing (6), techniques to accelerate basement membrane formation and vascularization and induction of mesenchymal stem cells towards keratinocyte-like cells have been studied to explain the complexity of wound healing mechanism but the puzzle yet remains unsolved (7, 8). Cellular proliferation and differentiation have been termed as crucial steps in wound healing and skin homeostasis maintenance (9). A number of other approaches such as cadaver skin grafting, application of skin substitutes, use of growth factors etc have been applied for skin regeneration but post grafting problems including infection, graft rejection, inadequate healing, short shelf life etc. are yet associated problems with available grafting techniques (10).

Stem cells, especially mesenchymal stem cells (MSCs) could be a gold standard to treat cutaneous

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LETTERS TO THE EDITOR

Commercialization of Gene Therapy Drugs

Sir,

Gene therapeutic research was considered a risk based approach and faced many challenges in the past, as many ethical issues arose particularly after the first death caused by gene therapy in 1999.[1] However, the journey of this research continued with difficulties from 1989 till it achieved its first success in 2000, with successful treatment of two children.[1] In 2004, the production of Gendicine[2] (Adenoviral-P53 for different cancers) in China, and its demand in neighboring countries (http://www.financialexpress.com/news/gene-therapy-could-be-here -soon/687507/0) for clinical practices, stepped up the gene therapeutic research worldwide. More than 1000 cancer patients from all over the world, were treated without facing any side effects or ethical problems from 2004 to 2008.[3] This breakthrough resulted in the development of various gene therapeutic drugs like ADVEXIN/INGN 201 (Ad5CMV-P53 for a variety of cancers)[4] and TG1042 (adenoviral-mediated IFN gamma gene for tumours)[5] and also proved as a significant step in the revision of terms and conditions of ethical committees worldwide. Finally, in late 2012, GLYBERA (alipogene tiparvovec for lipoprotein lipase deficiency (LPLD) was approved by European Commission (EC) as the first gene therapeutic medicine in Europe for cardiovascular diseases.[6] Production of gene therapeutic drugs like Gendicine, Advexin, TG1042 and Glybera has revolutionized the biopharma industry.

This temptation resulted in about 900 clinical trials worldwide till 2004.[1] By the end of 2012, circa 1900 clinical trials of gene therapy were reported. Most of these were focused on cancer (64.7%) alone, followed by monogenic hereditary diseases (8.7%), cardiovascular diseases (8.4%) and infectious diseases (8%). Details of various other groups of diseases, which have been trialed by gene therapy, are shown in Figure 1.[7] The production of gene therapeutic drugs and their availability in global markets helped to show that gene therapy is no longer a dangerous therapy. Criticism always remains a common phenomenon over all breakthroughs in the world. As the research of gene therapy has passed from a very critical point, is it not the time to apply these breakthroughs in our daily routine clinical researches to have better results and analysis? If still we will not consider these drugs, then how can we predict the future of gene therapy research?

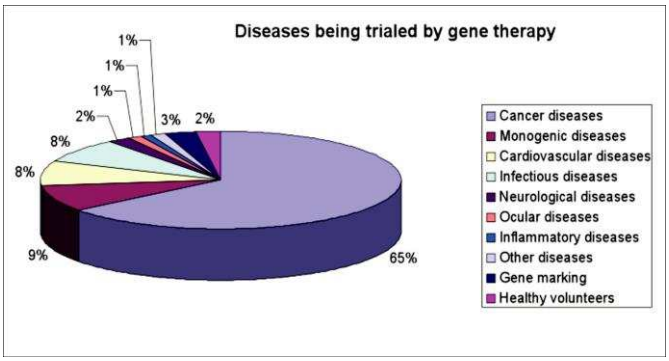

Figure 1: Diseases being trialed by gene therapy from 1989-2012.

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Glial cell derived neurotrophic factor induces spermatogonial stem cell marker genes in chicken mesenchymal stem cells

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ABSTRACT

Mesenchymal stem cells (MSCs) are known with the potential of multi-lineage differentiation. Advances in differentiation technology have also resulted in the conversion of MSCs to other kinds of stem cells. MSCs are considered as a suitable source of cells for biotechnology purposes because they are abundant, easily accessible and well characterized cells. Nowadays small molecules are introduced as novel and efficient factors to differentiate stem cells. In this work, we examined the potential of glial cell derived neurotrophic factor (GDNF) for differentiating chicken MSCs toward spermatogonial stem cells. MSCs were isolated and characterized from chicken and cultured under treatment with all-trans retinoic acid (RA) or glial cell derived neurotrophic factor. Expression analysis of specific genes after 7 days of RA treatment, as examined by RT-PCR, proved positive for some germ cell markers such as *CVH*, *STRA8*, *PLZF* and some genes involved in spermatogonial stem cell maintenance like *BCL6b* and *c-KIT*. On the other hand, GDNF could additionally induce expression of *POU5F1*, and *NANOG* as well as other genes which were induced after RA treatment. These data illustrated that GDNF is relatively more effective in diverting chicken MSCs towards Spermatogonial stem cell –like cells in chickens and suggests GDNF as a new agent to obtain transgenic poultry, nevertheless, exploitability of these cells should be verified by more experiments.

1. Introduction

Stem cells have the potential to differentiate into various cell types and could be categorized according to their differentiation potency. Spermatogonial stem cells (SSCs) have been considered as pluripotent stem cells because they are capable of differentiating into almost all cell types in the body (Kanatsu-Shinohara et al., 2004). SSCs have great applications in many fields including developmental biology, germ cell related disorders like male infertility, transgenic technologies in industrial animals like poultries and survival of rare or extinct species.

Thus a priority in stem cell research is to establish optimal conditions for derivation and maintenance of SSCs *in vitro*. Isolation and manipulation of these cells is difficult (Tegelenbosch and de Rooij, 1993; Hofmann, 2008). Although, several studies have reported culturing SSCs in the last few years but their maintenance remains a difficult task (Kanatsu-Shinohara et al., 2003; Momeni-Moghaddam et al., 2013).

Breakthroughs in stem cell research have shown that stem cells from one type could be transdifferentiated into another type. Several reports illustrated that mesenchymal stem cells could be differentiated into cells expressing the molecular markers of primordial germ cells (PGCs), spermatogonial stem cells and sper-

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MINI-REVIEW

Immortality of cell lines: challenges and advantages of establishment

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Abstract

Cellular immortality happens upon impairment of cell-cycle checkpoint pathways (p53/p16/pRb), reactivation or up-regulation of telomerase enzyme, or upregulation of some oncogenes or oncoproteins leading to a higher rate of cell division.There are also some other factors and mechanisms involved in immortalisation, which need to be discovered. Immortalisation of cells derived from different sources and establishment of immortal cell lines has proven useful in understanding the molecular pathways governing cell developmental cascades in eukaryotic, especially human, cells. After the breakthrough of achieving the immortal cells and understanding their critical importance in the field of molecular biology, intense efforts have been dedicated to establish cell lines useful for elucidating the functions of telomerase, developmental lineage of progenitors, self-renewal potency, cellular transformation, differentiation patterns and some bioprocesses, like odontogenesis. Meanwhile, discovering the exact mechanisms of immortality, a major challenge for science yet, is believed to open new gateways toward understanding and treatment of cancer in the long term. This review summarises the methods involved in establishing immortality, its advantages and the challenges still being faced in this field.

Keywords: cell cycle pathways; cell lines; immortalisation; pluripotency; senescence; telomerase

Introduction

Immortality is established when a cell loses its cell cycle checkpoint pathways. The overriding of natural cellular senescence takes place when inactivation of p53/p16/pRb occurs during immortalisation protocols (Shay et al., 1991). The mechanism controlling cellular senescence and immortalisation was described as a two-stage mechanism (terms are explained in Table 1) according to which telomerase activity is a key factor in the establishment of immortality (Wright and Shay, 1992). Strahl and Blackburn (1996) discussed high activity of telomerase in cellular malignancy and proposed its inhibition as a method for treatment of cancer. Shortly after this proposal, Marusic et al. (1997) studied this activity in the human cancer cells carrying a mutant telomerase gene (HT-cell lines). Extending the work of Morales et al. (1999), Steinert et al. (2000) studied the immortality of cell lines established after introducing the telomerase and its function in the elongation of telomeres and excision of the exogenous genes with their role in M1 and M2 stages (Figure 1).

How to achieve immortality?

Immortality of cell lines could be achieved by different approaches, including ectopic expression of telomerase or telemorase reverse transcriptase (TERT), by mutating the *p53* and *pRb* genes, or introducing the oncogenes, as described in Figure 1. Viral vectors may be used for all the mentioned approaches, that is introduction of TERT and oncogenes or mutating the *p53*/*pRb*, as will be explained in the following sections.

Immortality establishment by telomerase or TERT

Immortality has been achieved by introducing telomerase as well as TERT into the cells (Klingelhutz et al., 1994; Tsai et al., 2010). The elongation of telomeres increases the stability of chromosomes, making the cells immortal (Morales et al., 1999). Chang et al. (2005) managed to overexpress the hTERT in endothelial cells in order to immortalise them. In other efforts fibroblast-like cells,

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RESEARCH ARTICLE

Injectable hydrogel delivery plus preconditioning of mesenchymal stem cells: exploitation of SDF-1/CXCR4 axis toward enhancing the efficacy of stem cells' homing

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Abstract

Clinical applications of mesenchymal stem cells (MSCs) rely on their capacity to home and engraft in the appropriate target injury tissues for the long term. However, their homing efficiency has been observed to be very poor because of the lack or modifications of homing factors SDF-1α and CXCR4 receptors. Hence, this study was designed to investigate the homing and retention of pretreated human adipose tissue-derived MSCs (hASCs) from three different delivery routes in response to SDF-1α, released from chitosan-based injectable hydrogels. After stimulation of ASCs with a hypoxia mimicking agent, the expression level and functionality of CXCR4 were analyzed by flowcytometric analysis (FACS), transwell migration assay and qPCR. Then, the homing/retention of pretreated DiI-labeled hASCs were compared through three different in vivo delivery routes, 2 weeks after transplantation in Wistar rats. The cells were tracked histologically by fluorescent microscope and by PCR for human-specific *CXCR4* gene. Results showed CXCR4 has dynamic expression pattern and pretreatment of hASCs significantly up-regulates CXCR4, leading to an increase in migration capacity toward 100 ng/mL SDF-1α in vitro and homing into the subcutaneously implanted hydrogel releasing SDF-1α in vivo. Furthermore, it seems that SDF-1α is particularly important in the retention of ASCs, in addition to its chemoattraction role. In summary, the delivery route in which the ASCs were mixed with the hydrogel rather than systemic delivery and local injection and preconditioning undertaken to increase CXCR4 expression concomitant with SDF-1α delivery by the injectable hydrogel, allowed for further homing/retention of ASCs. This might be a promising way to get better therapeutic outcomes in stem cell therapy.

Keywords: cell delivery routes; chitosan-based injectable hydrogels; drug delivery systems; in situ tissue regeneration; SDF-1/CXCR4; stem cell therapy

Introduction

Mesenchymal stem cells (MSCs) have been termed as promising stem cells for therapeutic applications and have been used in the clinic for the last decade (Wei et al., 2013), in part, because of their multiple beneficial paracrine effects (Chamberlain et al., 2007). Various sources of MSCs have been found (Wei et al., 2013) and among these human

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Abbreviations: AMD3100, 1,1′-(1,4-Phenylenebis[methylene])bis-1,4,8,11-tetraazacyclotetradecane octahydrochloride; BCIP/NBT, 5-bromo-4-chloro-3-indolyl phosphate/ nitro blue tetrazolium chloride; bFGF, basic fibroblast growth factor; BSA, bovine serum albumin; CH-GP-HEC, chitosan-glycerophosphate-hydroxyethyl cellulose; CoCl2, cobalt chloride; CXCR4, chemokine (C-X-C motif) receptor 4; DFX, desferrioxamine mesilate; DMEM, Dulbecco's modified eagle (DME)-medium; D-PBS, Dulbecco's phosphate buffer saline; FACS, fluorescence activated cell sorting; hASCs, human adipose tissue-derived MSCs; LiCl, lithium chloride; MMPs, matrix metalloproteases; MSCs, mesenchymal stem cells; SDF-1α, stromal cell-derived factor-1 alpha; SVF, stromal vascular fraction cells; VPA, valproic acid

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MINI-REVIEW

Mesenchymal stem cell based therapy for osteo-diseases

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Abstract

Stem cell therapy in recent years has gained much attention as the modern therapeutic approach to treat diseases. Mesenchymal stem cells (MSCs) are seen as the most reliable cells applied in therapy over other stem cells because of their versatility. Bone and cartilage diseases (osteo-diseases) are the major target of therapy using MSCs. In this perspective, we have statistically analyzed the data available on clinical trials registry databases regarding the mesenchymal stem cell based therapy for a number of mentioned diseases and paid attention towards the osteodiseases. We report that MSC therapy for osteo-diseases needs optimization in its standards to achieve acceptable results so that we can apply it in daily routine clinical practice.

Keywords: bone and cartilage diseases; cell based therapy; clinical trials; mesenchymal stem cells

Introduction

Stem cells are the specific cells having unlimited proliferation and differentiation capacities. Since their first discovery in 19th century (Reiser et al., 2005), these cells have been applied in cell-based therapeutic approaches in clinics (Brodie and Humes, 2005). From clinically applied stem cells, mesenchymal stem cells (MSCs) have been described as well-characterized stem cells that can be isolated from adult tissues (Jiang et al., 2002). Positive indications of their applications in various diseases have made them clinically promising (Bang et al., 2005, Garcia-Olmo et al., 2005, Kuo et al., 2008, Le Blanc et al., 2008, Nakamizo et al., 2005, Pisati et al., 2007). Many advantages in their application over the embryonic stem cells has made them potential candidates in regenerative medicine (Thomson et al., 1998). Other pluripotent stem cells, for example, induced pluripotent stem cells, are also mainly valuable for research purposes, and remain far from being applied in therapy (Nishikawa et al., 2008). MSCs were first isolated from the bone marrow of guinea-pig (Friedenstein et al., 1970). These cells were considered as bone marrow stem cells, which are very limited in number (Stenderup et al., 2003). MSCs have been isolated from almost all parts of the body, for example, skin (Toma et al., 2005), blood (Campagnoli et al., 2001), umbilical cord blood (Rosada et al., 2003), dentine (Perry et al., 2008), pancreas (Seeberger et al., 2011), adipose (Zuk et al., 2002), liver (Wenceslau et al., 2011), brain, heart, lungs, and kidneys (Salem and Thiemermann, 2010).

Adipose tissue is the largest source of these stem cells as they can be isolated from the lipoasparate in daily routine liposuction (Yoo et al., 2009) and have limited oncogenicity (Vilalta et al., 2008). MSCs derived from different organs should have the following characteristics: self-renewal and differentiation ability to osteocyte, adipocyte and chondrocyte (Zuk et al., 2002); should express CD105, CD90, and CD73 antigens; and should not express CD11b, CD14, CD34, CD45, and HLA-DR1 (Ghannam et al., 2010). Clinical methodology (clinical trial) is the follow-up study of a disease treatment on humans under the supervision of expert scientists. Every clinical study has a strong experimental basis performed on animals. In this perspective, we will discuss clinical trials of osteo-

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The Editorial

Molecular Interactions of lncRNAs: Cellular Fate Determination and Tissue Regeneration

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Summary

LncRNAs (long non-coding RNAs), defined as non-coding RNAs with length ≥200 nt, are responsible to control the degradation process, RNA stability, orchestration, inhibition, transcription and histone modification etc. These RNAs have been termed as the key agents of several vital mechanisms such as development, organogenesis and regeneration of damaged tissues etc. They interact with a number of partner molecules either proteins, RNAs or DNAs. They also control the cellular behaviour of stem cells such as differentiation or self-renewal or their paracrine effects. This editorial is discussing the significance of lncRNAs as therapeutic target in stem cell therapy field.

***Keywords*:** LncRNAs, Regeneration, Molecular interactions, Stem cell fate, Differentiation

LncRNAs (long non-coding RNAs) are defined as the transcripts of greater than 200 nucleotides that lack ORF (open reading frames) and perform a lot of important functions other than coding proteins. RNA polymerase II transcribe them and then they spliced and polyadenalated (Rinn and Chang, 2012). It has been discovered that they are involved in the generation of variety of other nucleic acids such as miRNAs, other-ncRNAs etc (Ogawa et al., 2008; Rogler et al., 2014). LncRNAs have been found to be involved in many known process with interaction of other molecules such as, they are involved in (1) the degradation process when interact with miR-9 (Leucci et al., 2013), (2) enhanced BACE mRNA stability while interacting with miR-485-5p (Faghihi et al., 2010), (3) participates in the orchestration of an intrachromosal loop while interacting with RUNX1 promoter and enhancers (Wang et al., 2014), (4) tether with DNA to recruit inhibitor proteins (Wang et al., 2008), (5) dissociate the preinitiation complex when bind with DHFR promoter (Ponting et al., 2009), (6) form histone modification complex by bridging with PRC2 and the lysine demethylase LSD1 (Tsai et al., 2010), (7) activate the *Dlx5/6* enhancer when cooperate with *Dlx2* homeodomain protein (Feng et al., 2006) and etc.

It has been confirmed that lncRNAs control some vital functions in the development, organogenesis and regeneration of damaged tissues. Their role has been identified in the differentiation and terminal differentiation of somatic stem cells to improve wound healing in traumatic injuries (Beasley et al., 2015; Kretz et al., 2013). It has been discovered that these lncRNAs are involved in the maintenance of stem cells state and to determine the stem cell fate, which lineage it has to adopt and either it has to differentiate or terminally differentiate. As we have discussed here they have very strong molecular interactions with almost all kind of RNAs, DNAs and proteins to play their vital role in cellular behaviour. Every lncRNA has its own specific molecular partners where they interact each other and control the cell fate. A number of cellular mechanisms controlled by lncRNAs in coordination with their partner molecules have been shown in table 1.

Table 1. LncRNAs and their interacted partner molecules to control cellular fate (Flynn and Chang, 2014).

Sr. No.	LncRNA	Partner Molecules	Targeting Cells
1	TUNA/megamind	PTBP1, NCL, hnRNP-K	Neuronal Cells
2	Dix1as	?	Neurons
3	Six3os1	?	Oligodendrocytes
4	TINCR	STAU1	Differentiated Keratinocytes
5	ANCR	?	Skin Stem Cells
6	Braveheart	PRC2	Cardiocytes
7	Fendrr	PRC2 or MLL	Cardiac and Lung Cells
8	Yam1	YY1	Muscle Stem Cells
9	Linc-MD1/miR133	AGO and HuR	Muscle Tisses

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Review

Rhamnolipids: Well-Characterized Glycolipids with Potential Broad Applicability as Biosurfactants

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Abstract

Rhamnolipids are well-studied glycolipids secreted by Pseudomonas aeruginosa *that have been found to have excellent surface activity. Already used in various application areas, including environmental, health, food, cosmetic, and oil industries, rhamnolipids are attractive candidates to replace chemically synthesized surfactants because they are derived from a natural source at high purities and have low toxicity levels. Production of rhamnolipids depends on several environmental and nutritional factors, and the highest yield is estimated to be 6 g/L; recent advances in recovery methods have resulted in 99.9% pure rhamnolipids. Rhamnolipids have several beneficial characteristics: they are easily degradable, nontoxic, nonmutagenic, and have the highest surface-tension-reduction index of any surface-tension reducing agent currently in use. They have broad potential applicability across industries. They can also be used in oil-spill management, environmental management, biodegradation and remediation, the uptake of heavy metals and environmental pollutants, and the production of skin-compatible biochemicals for use in cosmetics. Rhamnolipids have applicability as antimicrobial, antifungal, antiviral, anti-algal, and anti-protist agents. In this review, we summarize the production parameters, properties, and industrial potential of rhamnolipids, as the next generation of biosurfactants.*

Key words: *Pseudomonas aeruginosa*, glycolipids, biosurfactant, rhamnose, β-hydroxydecanoic acid

Introduction

Rhamnolipids are extracellular glycolipids composed of L-rhamnose and 3-hydroxyalkanoic acid that are produced by *Pseudomonas* spp. Much of the research that has been conducted on rhamnolipids to date has focused on determining potential applications. Jarvis and Johnson first isolated and described rhamnolipids from *Pseudomonas aeruginosa* in 1949.[1]

Rhamnolipids are synthesized when one or two rhamnose sugar molecules fuse with one or two β-hydroxy 3-hydroxy fatty acids.[2] There are four types of rhamnolipids: mono-rhamnolipids (Rh1), which contain one rhamnose sugar attached to two molecules of β-hydroxydecanoic acid; di-rhamnolipids (Rh2), which contain two rhamnose sugars attached to two molecules of β-hydroxydecanoic acid; tri-rhamnolipids (Rh3), which contain one rhamnose sugar attached to one molecule of β-hydroxydecanoic acid; and tetra-rhamnolipids (Rh4), which contain two rhamnose sugars attached to one molecule of β-hydroxydecanoic acid.[3] The length of the carbon chains found on the β-hydroxyacyl portion of the rhamnolipids can vary significantly. However, rhamnolipids produced by *Pseudomonas aeruginosa* predominantly contain a 10-C molecular chain.[4] Glycolipids in which one or two rhamnose molecules are linked to one or two molecules of β-hydroxydecanoic acid have been the most studied. The OH^- group of one of the acids forms a glycosidic bond with the reducing end of the rhamnose disaccharide, while the OH^- group of the second acid is involved in ester formation.[5] The Rh1 L-rhamnosyl-L-rhamnosyl-β-hydroxydecanoyl-β-hydroxydecanoate, and L-rhamnosyl-β-hydrodecanoyl-β-hydroxydecanoate, an Rh2, (*Fig. 1*) are the principal glycolipids produced by *P. aeruginosa*.[6]

Pseudomonas species are the main sources of rhamnolipids, with *P. aeruginosa* the primary species to produce rhamnolipids. Sim et al. reported in 1997 that *Pseudomonas pyocyanea* could produce rhamnolipids when grown on glucose.[7,8] Norman-Shaw summarized the known sources and structures of bacterial glycolipids in 1970.[9] *P. aeruginosa* is capable of growing and producing rhamnolipids by metabolizing a range of different carbon sources; however, the highest level of rhamnolipids production results from using vegetable-based oils, including soybean oil and olive oil.[2,10–12] However, many isolates from other bacterial species of varying distance in their taxonomical classification were reported to be rhamnolipid producers.[13,14]

Rhamnolipid biosurfactants can be produced from inexpensive raw materials that are available in large quantities, such as industrial wastes and byproducts.[15] The carbon source, which may come from hydrocarbons, carbohydrates, or lipids, is the most important factor in rhamnolipids production.[16] However, rhamnolipids production also depends on several other environmental and nutritional factors, including nitrogen, multivalent ions, agitation rate, temperature, pH, phosphates, and metals. The highest achievable rhamnolipids yield has been estimated to be 6 g/L with optimized parameters.[17] Olive oil waste has been considered an excellent carbon source for rhamnolipid production, with a

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Abstracts: Current Cancer Research in Iran-2015

Establishment of cancer prevention centers: A perspective

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Abstract

Cancer has been described as the second leading causes of death worldwide estimating 8.2 million deaths in 2012. In the same year, 14.1 million new cases were diagnosed globally with an expected increased rate at 11% according to the data given by GLOBOCAN and WHO. Its diagnosis and targeted treatment is still a mystery for the scientific communities. A drastic increase has been seen in the establishment of cancer research and treatment centers around the world during the last two decades. In spite of having tens of thousands of cancer treatment and research centers, this mystery cannot be resolved. Up to now, it has been proposed that cancer may not be curable but preventable as more than 90% cancers are caused by environmental factors. Natural foods and physical activities are the significant approaches in cancer prevention. Other recommendations based on the WCRF/AICR findings, report focusing on the improvements in social life, smoking cessation, diet changes, early detection and state-of-the-art treatment (http://www.wcrf.org). Cancer awareness, consultation to patient's family and early detection may help to save many lives. It is the necessity of time to increase focus on the development and implementation of effective preventive strategies. A strategic social integrated model for cancer prevention focusing the social integration of multidisciplinary fields is required to stop cancer spreading. Cancer prevention centres should be established to gather the communities working on cancer in different directions because cooperation of bright minds can lead to a better prevention and these centers should provide a platform for oncologists, policy makers, consultants, surgeons, radiologists, molecular biologists and pathologists, to draw preventive strategies because better coordination is better prevention.

Keywords: Cancer prevention, Cancer management

1st International Nastaran Cancer Symposium-2015: Focusing cancer prevention and diagnosis

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Abstract

Deaths caused by cancer are rising in the world and it has been estimated that nearly 10 million persons are died because of cancer till now. Non-invasive approaches of cancer diagnosis is the hot topic of current decade and a number of new diagnostic approaches like detection of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) etc from cancer patients and analysing the tumor size, stage and even the types is under investigation. It also has been proposed that cancer spreading can be stopped by implementing efficient cancer prevention strategies. According to WCRF/AICR recommendations, more than 90% cancers can be prevented if we do improvements in social life style, smoking cessation, diet changes, early detection and state-of-the-art treatment (http://www.wcrf.org). Nastaran Center for Cancer Prevention (NCCP) was established in 2014 in Mashhad, Iran to draw and implement efficient cancer prevention strategies and to achieve this aim. NCCP established a platform of peoples in which we tried to gather peoples from all fields of science and society such as cancer therapists, genetics experts, psycho-oncologists, cell and molecular biologists, policy makers, molecular pathologists and etc. Nastaran Symposium-2015 is the first international cancer symposium organized by NCCP in collaboration with Ferdowsi University of Mashhad and Mashhad University of Medical Sciences (MUMS), Mashhad, Iran. This symposium was aimed to discuss the issues in cancer prevention and diagnosis. One session was also included as targeted and novel therapeutic approaches to treat cancer and it was discussed that cancer prevention should be focused on three steps, primary prevention, secondary prevention and tertiary prevention. NCCP is also working for the upcoming Nastaran Symposium-2016 as the 2nd International Nastaran Cancer Symposium-2016 held in October of 2016.

Keywords: Cancer Prevention and Diagnosis, Nastaran Symposium-2015, Nastaran Symposium-2016, Nastaran Center for Cancer Prevention, Mashhad-Iran.

Probiotics and its effect on cancers (review)

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Extended Abstract

Introduction: One hundred years ago, we ate beneficial bacteria all the time but pasteurization, sterilization and irradiation of food have ended much of that. The concept of probiotics evolved at the

O26- Investigating the Regenerative Potential of Trans-differentiated Adipose-derived Stem Cells (t-ASCs) in Cutaneous Wound Healing

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Abstract

Cutaneous wound healing is a complex type of biological event involving proliferation, differentiation, reprograming, trans/de-differentiation, recruitment, migration, and apoptosis of a number of cells (keratinocytes, fibroblasts, endothelial cells, nerve cells and stem cells etc) to regenerate a multi-layered tissue that is damaged by either internal or external factors. Cell therapy has been proposed as a promising approach to be applied in clinics to have rapid and efficient repairing of wounds. A number of challenges like escape of cells, graft rejection etc are being faced for cell therapy to be a state-of-the-art approach for our daily routine clinical practice. Transdifferentiated stem cells (t-SCs) or keratinocyte-lineage committed stem cells (t-SCs) may show promising response in post-transplantation challenges such as cell escape as these cells have their lineage committed to engraft and develop the epidermis. Increased cell survival and less escape of transplanted cells is the current area of interest in regenerative medicine. **Methods:** Adipose-derived mesenchymal stem cells (ASCs) were cultured for transdifferentiation using three strategies as, 1) ASCs were cultured in keratinocytes conditioned medium (KCM) derived from the culture of rat keratinocytes cultured in keratinocytes growth medium (KGM), 2) co-culturing of ASCs with keratinocytes, and 3) ASCs were cultured in KGM supplemented with differentiation induction factors. ASCs were analysed for transdifferentiation after 7, 14 and 21 days of their culture for keratinocyte specific markers using RT-PCR. Differentiation assay, colony forming assay, and cell proliferation assay were performed to analyse differentiation,

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Research Article

Significance of Cell/Stem Cell Therapy in Wound Care Management

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Summary

Wound care management is a continuous challenging task for researchers and tissue engineers. Skin substitutes (synthetic and natural) have been introduced as emergency replacements/grafts to the damaged skin and a number of problems such as infection, graft rejection, inadequate healing, short shelf life etc. have reduced their clinical importance as being the ideal skin substitutes. A number of novel ideas have been presented in last decades which have focused on the applications of stem cells as ideal candidate in the development of ideal skin substitutes.

Keywords: Cell Therapy, Stem Cell Therapy, Wound Healing, Wound Management

Introduction

Skin grafting processes starting from 1871 by Reverdin, up till now has been considered as a challenging task for researchers and tissue engineers and a number of skin substitutes, containing degradable synthetic or biological components have been introduced and are being considered as emergency replacements/grafts to the damaged skin for example, Biobrane®, Integra®, OrCel®, Suprathel® etc are available for clinical utilization(Irfan-Maqsood and Hemmati Sadeghi, 2013). There are a number of post grafting problems including infection, graft rejection, inadequate healing, short shelf life etc. associated with currently available skin substitutes. This necessitates the need for development of innovative tissue engineering approaches based on biological scaffolds and clinical grade stem cells could be an attractive alternative for available skin substitutes.Reliable and xenobiotic-free keratinocyte culture techniques(Hannigan et al., 1996), better understanding of the molecular mechanisms in the regulation of epidermal stem cells (Li et al., 2007), techniques to accelerate basement membrane formation and vascularization, solution to post grafting problems associated in skin engineering, such as graft contraction, loss of pigmentation and scars formation (Islam and Zhou, 2007; Li et al., 2013; Thiery, 2003) are suggested as main priorities in the field. Graft necrosis, extensive inflammatory reaction, marked foreign-body reaction (FBR), rapid scaffold degradation, abnormal collagen deposition and remodelling still remain the major issues in skin bioengineering (Nakamura and Tokura, 2011; Yan et al., 2010). Problemsassociated with chemical scaffolds, perceive the ideas of biological membranes as alternatives (Mohd Hilmi et al., 2013). Application of stem cells, especially mesenchymal stem cells, along with keratinocytes, and identification of specific antigens for keratinocyte grafts would serve as promising elements in skin bioengineering.

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The Editorial

Stem Cells of Epidermis: A Critical Introduction

Stem cells are the cells having some distinguishing characteristics like longevity, high capacity of self-renewal and differentiation, quiescence and highly error-free proliferation. Almost all stem cells have the potential of lineage reprogramming, i.e. inter-conversion of cell lineages. They also have the potential to differentiate into almost all kinds of cells. These cells have been found in almost every organs of human body. Pool of stem cells found in epidermis is termed as Epidermal Stem Cells (Blanpain and Fuchs, 2006).

Many researchers around the world have reported different kinds of stem cells in skin, based on their cell surface makers, while they have not categorized these cells chronically (De Rosa and De Luca, 2012). It is worth mentioning here that all kinds of stem cells reported in skin, i.e. keratinocyte stem cells, limbal stem cells, hair follicle and bulge stem cells, SG (sebaceous gland) stem cells, and spinous keratinocytes express specific types of cytokeratin protein (e.g. K1, K3, K5, K10, K12, K14, K15, K19 etc.) on their surfaces (Bose et al., 2013; Forni et al., 2012; Ghadially, 2012).

Biologists have defined that almost all of these stem cells share single origin, i.e. Basal Layer of Embryonic Skin. As the embryonic skin passes the developmental stages, the basal layer produces two mother stem cells of skin, keratinocyte stem cells, and so called Limbal Stem Cells (in cornea) (Chee et al., 2006; Lavker and Sun, 2000).

Keratinocyte stem cells give rise to the cells expressing Cytokeratin proteins on their surfaces. So, all the cells expressing cytokeratin are tracked back to these stem cells in origin , while undergone natural lineage reprogramming or differentiation (Potten and Booth, 2002). The stem cells in the basal-layer give rise to keratinocyte stem cells which can be found in the basal layer of the adult skin (Kaur et al., 2004). During the developmental stages, this basal layer, containing keratinocyte stem cells, gives rise to limbal invagination of corneal region, a linage conversion mechanism happens, and the keratinocyte stem cells are naturally reprogramed into the limbal stem cells as shown in figure 1 (Dua and Azuara-Blanco, 2000; Pellegrini et al., 2001).

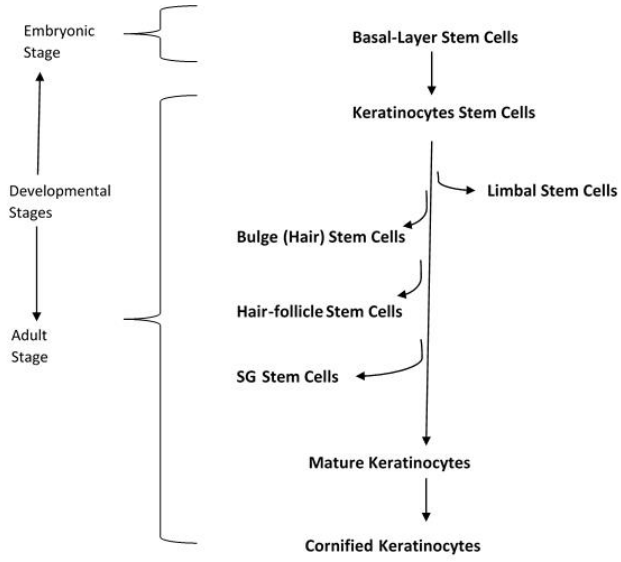

Figure 1: Proposed hierarchy of epidermal stem cells

In basal layer of the epidermis, the keratinocyte stem cells give rise to bulge, hair follicle, and SG stem cells when placode formation takes place.

In future, we need studies to find out which kind of cytokeratin protein is expressed early in these cells. In another word it would be helpful to define the order of cytokeratin expression regarding these lineage developmental processes from embryonic to mature skin and from embryonic basal layer to the formation of cornified epithelial cells.

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