FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY

The Role of Stem Cell In Bone Healing

Essay submitted for partial fulfilment of master degree in orthopaedic surgery

Presented by

Mahmoud Mohamed Osman
M,B.B,CH.

Under supervision of

Prof. Dr.Mamdouh Zaki Saad
Professor of Orthopaedic surgery
Faculty of medicine
Ain shams university

Dr. Mohamed Kamal Assal
Lecturer of orthopaedic sugery
Faculty of medicine
Ain shams university

2011

ACKNOWLEDGEMENT

First and foremost, I would like to express my deepest gratitude and thanks to ALLAH, whose magnificent help was the main factor in accomplishing this work.

My deepest gratitude and indebtedness to Prof. Dr. Mamdouh Zaki Saad, Professor of orthopaedic Surgery, Faculty of Medicine, Ain shams University, for his close supervision, kind instructions, continuous encouragement, perceptive comments and advices those were valuable both in selecting the subject and completing the work.

I would like to express my appreciation and profound gratitude to Dr. Mohamed Kamal Assal, Lecturer of orthopaedic Surgery, Faculty of Medicine, Ain shams University, for his valuable help, illuminating guidance, significant encouragement and meticulous supervision.

Mahmoud Mohamed osman

2011

" قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ"

صدق الله العظيم

{سورة البقرة ، الآية ٣٢ }

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AIF	Anterior Interbody Fusion
ASCs	Adipose-derived stem cells
BMPs	Bone Morphogenetic Proteins
DMEM	Delbecco's modified Eagle medium
ES	Embryonic stem
FGF	Fibroblast Growth Factor
GDFs	growth differentiation factors
GVHD	graft-versus-host disease
hMSC	Human mesenchymal stem cell
HSC	hematopoeitic stem cells
IGF	Insulin-Like Growth Factor
IL	interleukin
OI	Osteogenesis imperfecta
P/S	penicillin/streptomycin
PBS	phosphate-buffered saline
PDGF	Platelet Derived Growth Factor
PLF	PosteroLateral Fusion
PLIF	Posterior–Lumbar Interbody Fusion
RANKL	receptor activator of nuclear factor-κB ligand
SC	stem cell
SVF	The stromal vascular fraction
TGFß	Transforming Growth Factor-ß
TNF-α	tumour necrosis factor-alpha
VEG	Vascular Endothelial Growth Factor
αMEM	alpha minimal essential medium
β-TCP	beta-tricalcium phosphate

Introduction

A facinating revolution is taking place in many fields of medicine, including orthopedic surgery. The stem cell is the focus of this revolution. Applications of stem cell technology have the potential to alter the natural history of musculoskeletal damage and disease processes that, at present, have no attractive therapeutic options.Current treatment regimens for many disabling orthopedic afflictions delays rather than arrests the progression of symptoms, but stem cell technology offers the opportunity to alter their otherwise debilitating course and substantially improve patient outcomes. Although stem cell research is in its early stages, its potential for healing diseased and damaged tissue is both real and vast. An understanding of the fundamental characteristics and processes of stem cell biology will permit the orthopedic surgeon to be actively involved in the development and critique of future clinical applications of this technology and will help each surgeon determine which patients may benefit from stem cell treatment **(*Charley et al., 2008).***

Mesenchymal Stem Cells (MSCs) are nonhematopoietic stromal cells with the capacity of self-renewal and undergoing adipogenic, chondrogenic, osteogenic, myogenic differentiation ***(Toma et al., 2002)***.

MSCs were initially isolated from bone marrow by Haynesworth and colleagues.Subsequently, it was found that adipose tissue, peripheral blood, periodontal ligament, and other connective tissue of human adults were sources of MSCs ***(Trubiani et al., 2005).***

Recently, MSCs have become the most common source for clinical research, such as tissue engineering, trauma repair and oncotherapy. However, in human adult the quantity of MSCs is very low (about 0.001–

0.01%)% of the total number of nucleated cells in the bone marrow and the stemness, the proliferative capacity, the expansion potency and the multipotent differentiation potency of MSCs from bone marrow (BMMSCs) decrease with age **(*Fehrer and* Lepperdinger*, 2005*).**

In contrast to most injury responses that lead to fibrotic scarring and incomplete restoration of tissue structure, bone healing restores both structure and cell composition and in this regard is a true regenerative process. Over the time course of bone healing, multiple cellular lineages that give rise to cartilage, bone, vascular, and hematopoietic tissues that make up a skeletal organ, are all recruited and contribute to the regeneration of the injured skeletal organ ***(Gerstenfeld et al., 2003)a***.

One of the fields for MSC use in regenerative medicine is the treatment of bone defects. First approach to bone repair relied on biodegradable scaffolds impregnated with recombinant bone morphogenetic proteins BMPs, and was designed to induce bone formation through the recruitment of local MSCs (***Lane et al., 1999).***

Aim of work

• The aim of this work is to study stem cells which will facilitate understanding of how these cells differentiate into specialized cells.

• A better understanding of normal cell function will gain understanding and perhaps allow correction of the errors that cause defective bone healing.

• In this study, we will try to approach these issues by studying the molecular and cellular mechanisms of the function of MSCs in bone formation.

Chapter (1)

Human stem cells: sources and clinical applications

The theory of the stem cell

The theory of the stem cell concept can easily be summarised in a simple figure (Figure. 1). There is no universally acceptable definition of the term stem cell. Usually the stem cell is defined as a primitive cell that is capable of dividing to reproduce itself (undergo selfrenewal) and can give rise to a selection of differentiated progeny ***(Fuchs and Segre, 2000).***

Stem cells are a population of embryonic cells, continuously producing cells that can undergo further development within an adult organism. Thus, the adult body retains populations of stem cells, and these stem cell populations can produce both more stem cells and a population of cells that can undergo further development **(*Leskela, 2006).***

These general characteristics are not so easily defined on a molecular level because there are no general markers for stem cells. Stem cell niches are composed of micro environmental cells that nurture stem cells and enable them to maintain tissue homeostasis. The niche also safeguards against excessive stem cell production that could lead to cancer ***(Moore and Lemischka, 2006*).**

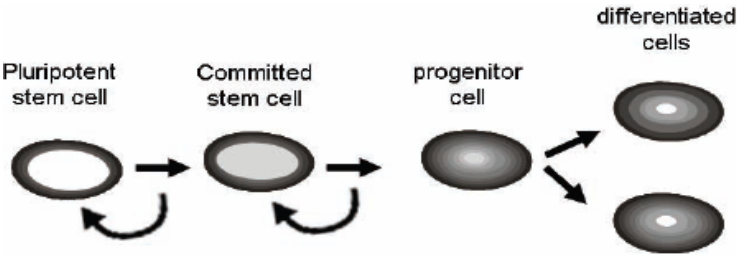

Figure 1: The theory of the stem cell. A pluripotent stem cell gives rise to self-renewal and to different lines of committed stem cells. These produce line specific progenitors which can give rise to usually several differentiated cells ***(Fuchs and Segre, 2000).***

Stem cells can be categorised anatomically, functionally, or by cell surface markers, transcription factors, and the proteins they express. One division of stem cells is between those isolated from the embryo, called embryonic stem cells, and those in adult somatic tissue, called adult stem cells. Stem cells are traditionally categorised by potency, which specifies the ameliorative potential of the cell type ***(Rao and Mattson 2001).***

Totipotent stem cells are produced from the fusion of an egg and sperm cell. The zygote and the cells derived from the first two divisions are able to form the embryo as well as parts of placenta.

Pluripotent stem cells are the descendants of totipotent cells. The cells are from the inner cell mass of the blastocyst and are able to form all cell types derived from the three germ layers— mesoderm, endoderm, and ectoderm ***(Rao and Mattson 2001).***
These three germ layers are the embryonic source of all cells of the body (figure 2: differentiation of human tissues) ***(Slack, 2000).***

Multipotent stem Cells have a wide repertoire of differentiation, including most cells in a particular tissue or organ and that are usually found in adult tissues ***(Rao and Mattson 2001).***

The terms ***bipotent*** and ***unipotent*** will be used to describe stem cells that generate two or one class of differentiated progeny, respectively ***(Rao and Mattson 2001).***

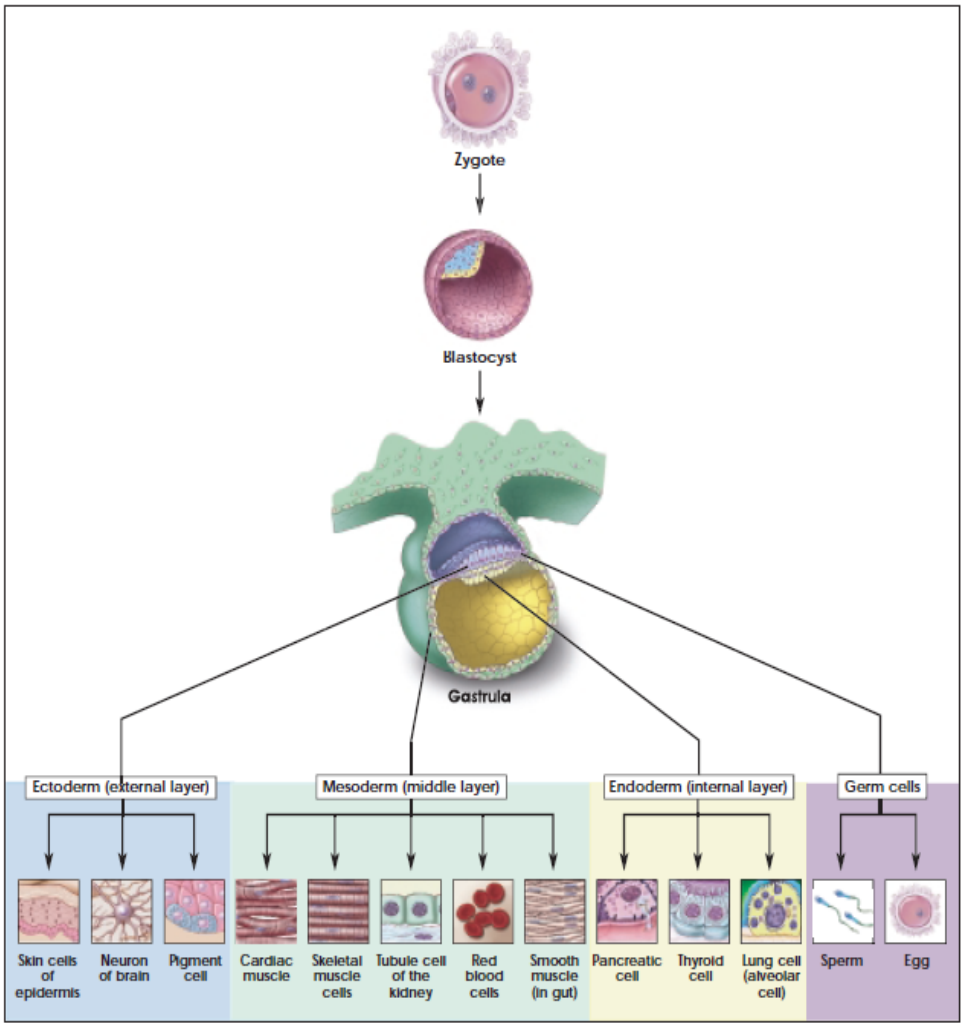

Figure 2: Differentiation of human tissues *(Slack, 2000)*.

It was generally believed that the progeny of a stem cell undergoes an irreversible change at a very early stage that makes them permanently committed to a specific downstream pathway of differentiated progenitors, committed progenitors, and lineage-committed cells.

However, the definition of a stem cell beyond this point of differentiation has been questioned by recent findings relating to multipotent adult stem cells and the concept of plasticity in which the eventual phenotypic fate of these cells is governed by the local environment and it is suggested that these cells are able to change lineages even after a substantial differentiation along a specific lineage (***Orkin and Zon, 2002).***

Stem cells are generally considered to possess certain properties that distinguish them from normal, fully differentiated cells. These properties include the capacity to remain in a quiescent, undifferentiated state until an appropriate stimulus causes them to divide (asymmetrically) and differentiate along multiple tissue lineages, and the ability to undergo many more replicative cycles than normal, fully differentiated cells ***(Tuan et al., 2003).***

Asymmetric division refers to cellular division that produces a daughter stem cell with all of the properties of the parent stem cell and a second cell that is committed to a tissue lineage. In this way, stem cells both differentiate and self-perpetuate, creating a pool of cells with the ability to selfrenew and to produce cells of the host tissue type ***(Deasy et al., 2001).***