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Frontiers in Stem Cell and Regenerative Medicine Research Volume 4

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Frontiers in Stem Cell and Regenerative Medicine Research

(Volume 4)

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Frontiers in Stem Cell and Regenerative Medicine Research

Volume # 4

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PREFACE

There continues to be tremendous progress in the field of stem cell and regenerative medicine research. The developments promise to change the face of medicine. This 4th volume of '*Frontiers in Stem Cell and Regenerative Medicine Research*' should be of considerable interest to the readers as it presents state-of-the art reviews written by renowned experts in this fast moving field.

Ilham Saleh Abduljadayel presented a comprehensive review in chapter 1 on epimorphic regeneration and retrodifferentiation. Both processes have the capacity to recreate and reconstruct tissue with precise positional integration of cells in such a way that will enable healing without scars. In chapter 2 Fraser *et al*. extensively reviewed the unique genetic programmes that lead to mesendoderm formation and the pathways leading to mesoderm and endoderm specification. They also present examples where mature cell types from both germ layers interact to support their mutual development. These programmes are being employed to direct the differentiation of pluripotent cells *in vitro* into mesendoderm derived cells and tissues. Fraser *et al*. also reviewed the role of stem, progenitor and supportive cells within the hematopoietic tissues as essential elements of regenerative medicine in chapter 3.

Cell-based therapy is an emerging field in veterinary medicine that has been used for developing new therapies for degenerative diseases. In chapter 4 Izadyar *et al*. described different cell based therapies, their risks and benefits and their possible therapeutic use for veterinary medical applications. Mesenchymal stem cells (MSCs) are the most favored cellular candidates for regenerative therapeutics. Bhat *et al*. discussed how MSCs contribute to therapeutic efficiency include facilitating secretion of bioactive factors, induction of cellular recruitment and retention of progenitor faculties in the last chapter.

Knowledge of stem cell and regenerative medicine research continues to move ahead on many fronts. We hope that the readers will enjoy reading about the latest and stimulating development in this hot area in the 4th volume of this series.

We are pleased to place on record our heartfelt thanks to all the authors for their contributions. We are also grateful to the editorial staff of Bentham Science Publishers, particularly Dr. Faryal Sami, Mr. Shehzad Naqvi and Mr. Mahmood Alam for their constant support and great help.

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CHAPTER 1

Retrodifferentiation: From Concept to Bedside Stem Cell Therapy

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Abstract: Epimorphic regeneration is a process by which damaged tissues or severed body parts are restored to the original. This type of sophisticated regeneration is observed in urodeles and fetal mammals. For example, through this process, an amputated limb of a salamander can be restored, by re-growing an exact replica, irrespective of its age. During limb epimorphic regeneration: committed mesenchymal cells at the stump site dedifferentiate, forming a cluster of heterogeneous population of stem cells, known as the blastema. Upon blastema integration, positioning and expansion, constituent cells embark on redifferentiation and remorphogenesis to restore the lost appendage. Similar to epimorphic regeneration is retrodifferentiation in human leukocytes. In response to ligation of monomorphic regions of MHC class II antigens with monoclonal antibody CR3/43, human leukocytes retrodifferentiate into a variety of heterogeneous stem cell types belonging to the mesoderm, ectoderm or endoderm lineage, depending on culture media and conditions. During this process, leukocytes lose lineage-associated markers home and undergo homocytic aggregation, upregulate expression of stem cell antigens, and subsequently redifferentiate to give rise original tissue or, transdifferentiate into a different tissue altogether. The hematopoietic retrodifferentiated stem cells have been shown to engraft an animal host in two proofs of principle clinical studies, demonstrating long-term engraftment and safety in acquired aplastic anaemia, while transient amelioration of beta thalassemia major was also observed. Binding of MHC class II antigens on leukocytes with the monoclonal antibody CR3/43 appears to emulate stress and injury in human tissue *in vitro*, similar to limb amputation in salamander. The ease by which various stem cell types can be generated from human peripheral blood has allowed the design of various kits to guarantee the specificity, sterility and efficacy of stem cells production for various

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clinical and research applications. The robustness and efficacy of the retrodifferentiation process in generating unprecedented quantities of stem cells belonging to the three germ layers will enable organ and tissue reconstruction *ex vivo*, using bio-printing and various scaffold materials. Epimorphic regeneration and retrodifferentiation both have the capacity to recreate and reconstruct tissue with precise positional integration of cells in such a way that will enable us to heal without scars and to understand how to maintain tissue integrity and architecture in the face of a hostile environment.

Keywords: Axolotl, Bioprinting, Blastema, Bone, Dedifferentiation, Ectoderm Endoderm, Epimorphic Regeneration, Hematopoietic, Hepatocytes, Histogenesis, Human leukocytes, Mesenchymal, Morphogenesis, Neurons, Pluripotent, Positional integration, Regeneration, Retrodifferentiation, Salamander, Scaffolding, Stem Cells, Tissue Repair, Transdifferentiation.

INTRODUCTION

The ability to regenerate an entire complex tissue, organ or appendage upon damage is almost nonexistent in higher vertebrates, for instance in an adult human. This is because neither all tissues in the human body are endowed with stem cells that have the ability to proliferate and differentiate to replenish damaged or spent cells nor the adult human body possess sophisticated regenerative processes that enable replacement of body parts lost to severe injury. Most injuries are dealt with simply utilizing repair mechanism which entails closure of the injured site by deposition of fibrous tissue instead of cells. This leads to altering organ geometry and architecture including deterioration in function. In stark contrast, amphibians and particularly a selected group of urodele salamander can re-grow body parts, such as an amputated limb, even when old, in a process known as epimorphic regeneration. In this process, complex mechanisms, including dedifferentiation, innervation, positional integration and re-morphogenesis occur to restore the severed appendage. During the dedifferentiation phase, fully mature specialised cells from various positions around the circumference of the amputate, belonging to the mesenchymal lineage home to the stump site and dedifferentiate. This leads to the formation of a cluster of heterogeneous population of stem cells, known as the blastema. Homing and integration of mesenchymal cells occur according to positional values. This

facilitates alignment and arrangement of cells of different lineages, in a configuration that upon re-morphogenesis permits restoration of the original geometry and architecture of the limb. Elucidation and understanding of epimorphic regeneration, including harnessing similar mechanisms in human, has tremendous applications in regenerative medicine than mere production of stem cells which at best proliferate and differentiate *ex-vivo*, but may fall short of positional integration or morph into tumors when transplanted into humans. The process which has been termed retrodifferentiation [1] is similar to the process of cellular dedifferentiation which facilitates blastema formation in salamander [2].

Retrodifferentiation of human leukocytes into a variety of pluripotent stem cell classes occurs in response to ligation of the monomorphic region of the major histocompatibility complex beta chain, using a monoclonal antibody (clone CR3/43) [3]. Each stem cell type generated is determined by the type of culture media and conditions utilized during retrodifferentiation. Similar to mesenchymal cell dedifferentiation in salamanders, leukocytes lose lineage associated markers, undergo homing and homocytic aggregation, and form heterogeneous stem cell colonies which subsequently redifferentiate into cellular components of the original tissue. Unlike salamander regeneration, retrodifferentiation is capable of transdifferentiation and histogenesis giving rise to entirely different tissues. In this process, mature mononuclear leukocytes can be converted into a variety of stem cell types belonging to the three germ layers: mesoderm, endoderm or ectoderm. Three hour human male retrodifferentiated haematopoietic stem cells (RHSC) have been shown to engraft in minimally irradiated NOD/SCID female mice [4]. Furthermore, 3 hr autologous RHSC were capable of long term engraftment in severe acquired aplastic anemia patients without any form of pre-conditioning therapy [5]. While in beta thalassemia major [6], a genetic blood disorder, the autologous RHSC were only able to ameliorate the course of the disease for six months. The ease by which any stem cell type can be prepared from human peripheral blood *via* retrodifferentiation, enabled the development of kits for the treatment of haematological and degenerative disorders, as a bed side stem cell therapy. In this manner, and in combination with leukopheresis and washing devices, the automation of stem cell production, will guarantee efficiency, sterility and specificity of stem cell infusate. Most importantly, retrodifferentiation

CHAPTER 2

The Mesendoderm: A Wellspring of Cell Lineages for Regenerative Medicine

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Abstract: Regenerative medicine is centred around the premise that progenitor populations can be engineered to give rise to mature cell lineages forming a complex tissue architecture which in turn produces functional organs. The potency of the starting progenitor population is therefore a critical consideration. The mesendoderm is a rare population of cells present in the embryo only at gastrulation. This bipotent population gives rise to the mesoderm and the definitive endoderm and all mature cell types derived from these germ layers. Mesodermal progenitors generate cardiac, smooth and skeletal muscle, as well as the blood and vascular lineages, bone and connective tissue cells. The endoderm is the source of numerous cell lineages with potential utility for regenerative medicine including hepatocytes, pancreatic lineages and the epithelial cells of the respiratory, gastrointestinal and reproductive tracts. The development of numerous organs is dependent upon mesoderm-derived lineages interacting with endodermal-derived cell types. The kidney, adrenal gland, pancreas and genito-urinary tract development all require interactions between mesodermal and endodermal derivative cell types. Here, we describe the unique genetic programmes that lead to mesendoderm formation, the pathways leading to mesoderm and endoderm specification and examples where mature cell types from both germ layers interact to support their mutual development. We will also show how these programmes are being

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harnessed to direct the differentiation of pluripotent cells *in vitro* into mesendoderm-derived cells and tissues which can be used to improve the quality of human life. Finally, we will discuss considerations for combining stem cell differentiation with tissue engineering through 3D bioprinting modalities.

Keywords: 3D bioprinting, Embryonic development, Embryonic stem cells (ESC), Endoderm, Germ layer specification, Induced pluripotent stem cells (iPSC), Mesendoderm, Mesoderm, Regenerative medicine, Tissue engineering.

INTRODUCTION

The complex adult mammalian body is derived from three simple structures early in embryogenesis termed the germ layers. These are: the ectoderm, which forms the skin and central nervous system; the endoderm which gives rise to the epithelial tissues of the viscera such as the respiratory, gastrointestinal and genito-urinary tracts; and the mesoderm, which forms all of the connective tissue, blood, vessels and muscle tissues. These three germ layers, can be first distinguished at the developmental stage termed gastrulation. However, it has been proposed for some time that the mesoderm and endoderm arise from a single cell type with the potential to form both lineages. This cell type, termed the mesendoderm, can be identified in simpler animal models such as the frog embryo, and an equivalent cell type can be generated from mammalian pluripotent stem cells in culture. The mesendoderm is, in the end, responsible for the formation of essentially vast amounts of the body except for the brain, skin (derived from the ectoderm) and other tissues derived from a structure arising later in embryogenesis termed the neural crest.

All of the epithelial tissues contain mesoderm-derived lineages. For example, the gastro-intestinal epithelial tissue has a mesoderm-derived connective tissue component essential in maintaining structural integrity. Indeed, it is now clear that, in many organs, extensive cross-talk must take place between endoderm-derived tissues and mesodermal-derived structures during embryogenesis of organogenesis to proceed. The developing pancreas and liver (endoderm) require signals from underlying blood vessels (mesoderm) to form [1, 2]. Removal of the blood vessels leads to a loss of appropriate signals and failure of pancreatic

development. In contrast, most mesoderm-derived organs lack epithelial structures. For example, the heart, skeletal muscle and bone marrow do not contain endoderm-derived cell types (Table **1**).

Table 1. Organs and cells derived from the mesendoderm.

Organ	Endoderm-derived Lineages	Mesoderm-derived Lineages
Salivary gland	Serous, mucosal and seromucosal epithelial cells	Connective tissue fibroblasts, macrophages endothelial cells, adipose cells
Trachea	Goblet cells columnar epithelial cells	Tracheal cartilage, lymphoid cells, macrophages
Lungs	Type I and II alveolar cells Clara/club cells, Goblet cells	Endothelial cells alveolar macrophages
Stomach	Surface mucous cells mucous neck cells entero-endocrine cells chief cells, parietal cells	Smooth muscle, adipocytes, endothelial cells fibroblasts, lymphoid cells
Liver	Hepatocyte cholangiocyte	Sinusoidal endothelial cell Kupffer cell, hepatic stellate cell
Gastrointestinal tract	Gastric epithelium glands (pyloric, cardiac, fundus)	Mesentric connective tissue fibroblasts smooth muscle, endothelial cells, lymphoid cells
Pancreas	Acinar cells, centroacinar cells pancreatic α, β and δ cells	Capillary endothelial cells connective tissue fibroblasts
Kidney	Tubular epithelial cells	Glomerular endothelial cells, mesangial cells podocytes, capsular stromal fibroblast
Prostate	Cuboidal epithelial cells columnar epithelial cells	Prostatic stroma fibroblasts, smooth muscle connective tissue
Urinary bladder	Urothelium	Smooth muscle, hematopoietic cells, endothelial cells
Bone		Osteocytes, osteoblasts, chondrocytes, endothelial cells, hematopoietic cells, adipocytes
Thymus	Cortical thymic epithelial cells medullary thymic epithelial cells	Thymocytes (developing T lymphocytes) dendritic cells, thymic macrophages
Spleen		Capsule stromal fibroblasts, erythrocytes lymphocytes, sinusoidal endothelium macrophages
Gonads		Leydig cells, Sertoli cells, follicular cells thecal cells

CHAPTER 3

Hematopoiesis and Regenerative Medicine

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Abstract: The hematopoietic, or blood-producing, system resides in the bone marrow of adult mammals. This system regulates the production of billions of new blood cells per day in healthy adult humans. Even slight perturbations of this production can lead to severe pathological conditions. One of the first applications of cellular regenerative medicine in clinical practice was the transplantation of bone marrow cells to generate a new, healthy blood production system in compromised patients. The success of bone marrow transplantation is dependent upon the potency of stem cell and progenitor populations within the adult mammalian bone marrow. The utility of hematopoietic stem cell (HSC) transplant has been extended to the treatment of a broad range of hematological diseases and disorders, as well as in the regeneration of the blood-producing tissue following radiation or chemotherapy. There is a strong push towards the development of vast numbers of mature blood cells *in vitro*. An *in vitro* system resulting in the consistent, large-scale production of patient-specific mature erythrocytes from HSCs or erythroid progenitors could alleviate the pressure felt by blood donation agencies. The cells that support blood cell production in the bone marrow and other organs, known collectively as the hematopoietic niche, are critical in blood cell lineage regeneration. The development of novel regenerative therapies to treat myelodysplastic syndromes, anemia, leukemia and other blood diseases deserves attention. Stem, progenitor and supportive cells within the hematopoietic tissues are essential elements of regenerative medicine. The utility, limitation and promise of these populations in regenerative medicine are described here.

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Keywords: Bioengineering, Blood, Bone marrow, Embryo, Hematopoiesis, Niches, Regenerative Medicine, Stem cells, Transplantation.

INTRODUCTION

A healthy adult human produces over 2 million new red blood cells per second or nearly 2 billion per day. This extraordinary rate of cellular production is dependent upon a hierarchy of stem, progenitor and maturing cell types forming in the hematopoietic organs. Hematopoietic stem cells (HSCs) are very rare cells capable of giving rise to all of the major blood cell types when transplanted. These characteristics have led to HSCs being one of the cell types most frequently transplanted for clinical treatment. Once HSCs have been transplanted from donor to recipient, these cells home to the bone marrow where they reside and give rise to the massive number of blood cells required to maintain human health. HSCs also give rise to a broad variety of blood cell lineages. These range from gas transporting erythrocytes (the most common form of blood cell in mammals) to megakaryocytes producing platelets; granulocytes (neutrophils, eosinophils and basophils) offering immune protection against bacteria, fungi and parasites; and the lymphocytes capable of forming an immunological memory of pathogen exposure. Specialized tissue macrophages and dendritic cells are also derived from HSCs. HSCs therefore have a profound capacity for regenerating the blood compartment, which comprises approximately one fifth of all cells in the healthy adult human. The remarkable capacity of HSCs to give rise to the entire hematopoietic system in recipient animals and patients has led to utilization of these cells in regenerative medicine. HSC transplantation can be performed from transplanting a patient's own stem cells (autologous transplants) or from transplanting a donor's cells (allogeneic transplants). Both these techniques are used commonly in medicine today and are often the only life saving or prolonging treatment available to these patients.

Significant challenges lie ahead in hematopoietic regenerative medicine, and we will discuss some of these in this chapter. In contrast to other stem cell types, such as embryonic or induced pluripotent stem cells, we cannot currently maintain HSCs *in vitro* in the stem cell state for an indefinite period. There are also

significant challenges in finding appropriately matched HSCs for transplantation, and mitigating the many complications associated with HSC transplantation. Sourcing matched volunteers for blood donations for red blood cell and platelet transfusions is a challenge globally. In some clinical cases, the problem is due to defects in the hematopoietic niche, the supporting cells which maintain HSCs as stem cells. Developing novel systems to obtain patient-specific HSCs and progenitors as well as novel methods for modifying and enhancing the HSC niche, will dramatically improve the health outcomes of a vast number of patients suffering from hematopoietic and related diseases.

Here, we will discuss the link between blood cell generation and regenerative medicine. In contrast to other systems, the hematopoietic system is more diffusely scattered throughout the body. Regenerative therapeutic treatment will vary according to patient needs and may include regeneration of failing bone marrow, replacement of a deficient or defective thymus to produce T cells; re-construction of a spleen or other hematopoietic tissue; or the generation of mature circulating cells from an *ex vivo* or *in vitro* expanded progenitor population such as functional red blood cells, mature platelets or granulocytes to supplement immunodeficient individuals.

This discussion will proceed in four sections. Firstly, the hematopoietic system will be introduced. Secondly, the niches which regulate blood cell generation and constant production will be described. The application of HSC transplantation to the treatment of a range of human diseases is one of the major forms of regenerative medicine and will be discussed at length in the third section. Finally, focusing all of these studies onto future directions, we will discuss the application of novel technologies such as induced pluripotent stem cells and tissue engineering of blood producing tissues to the treatment of hematological disorders.

AN INTRODUCTION TO HEMATOPOIESIS

Hematopoiesis is the production of blood cells initiated in the early embryo and maintained throughout life. Maintenance of a homeostatic state requires the genesis and consistent life-long production of a broad palette of blood cell types.

CHAPTER 4

Cell-based Therapy in Veterinary Medicine

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Abstract: Cell-based therapy is a growing field in veterinary medicine and has created a lot of hope and excitements for developing new therapies for degenerative diseases that otherwise cannot be treated by traditional medical approaches. Clinical studies in dogs, cats and horses show promising results indicating that stem cells and other cell-based products may facilitate tissue repair and improve quality of life in companion animals. In this review, different cell based therapies, their risks and benefits and their possible therapeutic use for veterinary medical application will be discussed.

Keywords: Companion animals, Degenerative diseases, Stem cells, Veterinary medicine.

RECENT ADVANCES AND APPLICATIONS OF CELL THERAPY

Cell therapy is the administration of live cells to the body of a recipient for treatment of a medical condition. It could be for replacement of absent cells like infusion of red blood cells to overcome anemia, administration of platelets for emergency thrombocytopenia, or application of T lymphocytes for regulation of the immune system and cancer therapy. This type of cell therapy is called cell replacement therapy and is commonly used in medical and veterinary medical protocols. Cell therapy can also be used for regenerative medical applications. In that case, stem cells and progenitor cells with the ability to produce other cells will be used. A good example is the administration of bone marrow cells, which contain hematopoietic stem cells for regeneration of the blood. This therapy can help reestablish hematopoiesis and regenerate blood in patients undergoing

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cytotoxic treatments such as chemotherapy or radiotherapy. Cell products with regenerative potential can regenerate cells, tissues and organs, to restore or establish normal function. In addition to live cells, regeneration could also be triggered by proteins and growth factors, extracellular matrices, scaffolds and small molecules, but these effects are generally transient, and repeated treatments are required.

The nomenclature to identify and describe various cells is to use the cluster of differentiation (abbreviated as CD) distinction. It refers to protein structures (or antigens) embedded on the outer membrane of cells. The system was first described to identify basic immune cells and since has been applied to many cell types relevant for the immune system. Over the past 30 years, data generated by the Human Leukocyte Differentiation Antigens Workshops have led to the characterization and formal designation of more than 400 CD molecules. These CD molecules are commonly used as cell markers, allowing the identification and isolation of leukocyte populations, subsets and differentiation stages. Some of these markers are commonly expressed by other cells including stem cells (Table **1**).

Table 1. Some of the important CD molecules and their expression profile.

CD1	The first-named CD; this complex glycoprotein is expressed in immature T-cells, some B cells and other, specialized immune cells in the skin.
CD3	A multimeric protein complex, known historically as the T3 complex, and is part of the T cell receptor.
CD4	A molecule on a mature “helper” T lymphocyte cell surface.
CD8	A molecule on a mature “cytotoxic” T lymphocyte cell surface.
CD19	A molecule on a mature B lymphocyte cell surface.
CD34	A monomeric cell surface antigen that is selectively expressed on hematopoietic progenitor cells.
CD90	Also known as Thy-1. CD90 is expressed on neuronal cells, a subset of CD34+ cells, activated endothelial cells and mesenchymal stem cells.

The types of cells used in cell therapy can be mature cells, such a T-cells or dendritic cells, to adult stem cells isolated from a fresh tissue source. An up and coming exciting use of mature cells is that of regulatory T-cells (Tregs) in therapeutic applications. CD4+Foxp3+ Tregs are long-lived cells that suppress

immune responses *in vivo* in a dominant and antigen-specific manner. Tregs confer long-term protection against auto-inflammatory diseases in mouse models and have been shown to be effective in suppressing alloimmunity in models of graft-*versus*-host disease [1]. CD4+ Foxp3+ Treg therapy is now at the point to evaluate its safety and efficacy within preclinical testing in humans [2, 3].

Another interesting mature cell type being explored for cell therapy is the dendritic cell. Dendritic cells are highly specialized, bone marrow-derived antigen-presenting cells that induce or regulate innate and adaptive immunity. In general, dendritic cells express CD11b and CD11c, although there are many more markers to identify subsets of dendritic cells. Since the mid-1990s, dendritic cells have been used in clinical trials as cellular mediators for therapeutic vaccinations of patients with cancer. As sentinel members of the innate immune arm, dendritic cells secrete protective cytokines (Table **2**) in response to signals of inflammation [4]. Interleukins (ILs) are specific types of cytokines that are produced by leukocytes for regulating immune responses. IL-6 and IL-12 are particularly important because they play roles in establishing a local immune response. For example, IL-6 secreted from dendritic cells has immunosuppressive properties and IL-12 augments CD8 T cell activation. Dendritic cells capture process and present antigens *via* the major histocompatibility complex to naïve T-cells at lymphoid organs, thereby inducing adaptive CD4+ and CD8+ T-cell-mediated immune responses [5, 6]. Dendritic cell based therapeutic immunotherapies with oncogene inhibitors in patients appear to be the method of choice. Human clinical trials investigating targetable tumors are underway in renal cell carcinoma, prostate cancer, breast cancer and melanoma [7, 8].

Table 2. Some of the important Cytokines produced and their function.

Cytokine	Full Name	Characteristic
IL-2	Interleukin-2	Promotes T cell expansion, used in immunotherapy to support large numbers of tumor-infiltrating lymphocytes with anti-cancer activity.
IL-6	Interleukin-6	Multifunctional cytokine involved in modulating various physiological events, such as cell proliferation, differentiation, survival, and apoptosis.
IL-10	Interleukin-10	Produced by cell types that mediate anti-inflammatory activities, induce regulatory T-cells, and are involved in immunosuppression and tissue repair.

CHAPTER 5

From Trials to Therapeutics: Are Mesenchymal Stem Cells Promising in Cellular Therapy?

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Abstract: Mesenchymal stem cells (MSCs) are today, the most favoured cellular candidates for regenerative therapeutics. Though discovered early in the 1960s, only recent decades have witnessed extensive research involving MSCs. MSCs, termed as multipotent mesenchymal stromal cells in 2006, by the International Society of Cellular Therapy have gained greater acceptance in view of their ubiquitous presence in tissues, exemption from ethical concerns, clonogenic potential, trilineage differentiation, versatile plasticity and ability to orchestrate host tissue interactions. Biological properties of MSCs that contribute to therapeutic efficiency include facilitating secretion of bioactive factors, induction of cellular recruitment and retention of progenitor faculties. Researchers, however continue to be intrigued by variability in the *in vivo* identity of MSCs which is influenced by various factors that include tissue of origin, age of MSCs, number of isolates and isolation efficiency, associated metabolic disorders, foetal or adult status, gene expression, protein and transcription factors and allogenic or autologous extract . Although early results in clinical studies are promising, transformation of MSCs into a mature clinically viable option would mean a patient wait.

Keywords: Cellular therapy, Critical limb ischemia, Crohn's disease, Graft *versus* host disease, Mesenchymal stem cells, Osteogenesis imperfecta, Telomere, Tissue repair, Wharton's jelly, Wound healing.

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INTRODUCTION

Successive failures of embryonic stem cells and induced pluripotent stem cells have potentiated the research utilization of mesenchymal stem cells (MSCs). As defined by the International Society of Cellular Therapy, these multipotent, plastic adherent spindle-shaped cells can be propagated through multiple passages in cell culture and differentiated into osteogenic, adipogenic and chondrogenic lineages under permissive conditions [1]. Conventionally isolated from the bone marrow, over the past couple of decades, the isolation of MSCs has been possible from virtually every tissue [2] exhibiting similarity in morphology and, to a certain extent in surface marker profile [3]. Culture-expanded MSCs may lose some of these markers but continue to remain multipotential [3].

By virtue of a variety of biological properties exerted either individually or in combination MSCs have contributed to therapeutic effects in a variety of disease conditions (Fig. **1**). The distinguishable properties include capability to: differentiate into different cell lineages, homing and migration to sites of inflammation and injury, secrete bioactive molecules and promote repair, produce immunomodulatory effects by interacting with the immune cells [4].

Though all MSCs were previously regarded as having low immunogenicity, in view of the low expression of MHC class I and II along with other co-stimulatory molecules such as CD40, CD80, and CD86, recent studies have suggested that allo MSCs may not be as immune-privileged [5] as previously reported except for a few foetal origin MSCs [6], such as those from Wharton's jelly [7].

Owing to the ease of isolation and expansion, MSCs have been studied and have undergone trials in a diverse range of clinical conditions ranging from graft *versus* host disease, autoimmune diseases such as Crohn’s disease, cardiovascular diseases such as acute myocardial infarction, stroke and orthopaedic applications including bone and cartilage repair [8]. Primitive MSCs isolated from foetal and perinatal tissues, umbilical cord, placenta, and amniotic fluid have been found to possess longer telomeres [9], higher proliferative potential [10], greater colony-forming capacity, and ability to readily differentiate into bone and muscle [11] and in addition, into non-mesenchymal cells such as neural [12] and hepatic cells

[13]. Increasing age of the MSC may limit the ability to be expanded, leading to rapid senescing in culture and restricted differentiation capacity. In addition, differentiation capabilities, growth kinetics, and yield vary significantly between MSC cell populations from different tissue sources, impacting their clinical utility [14].

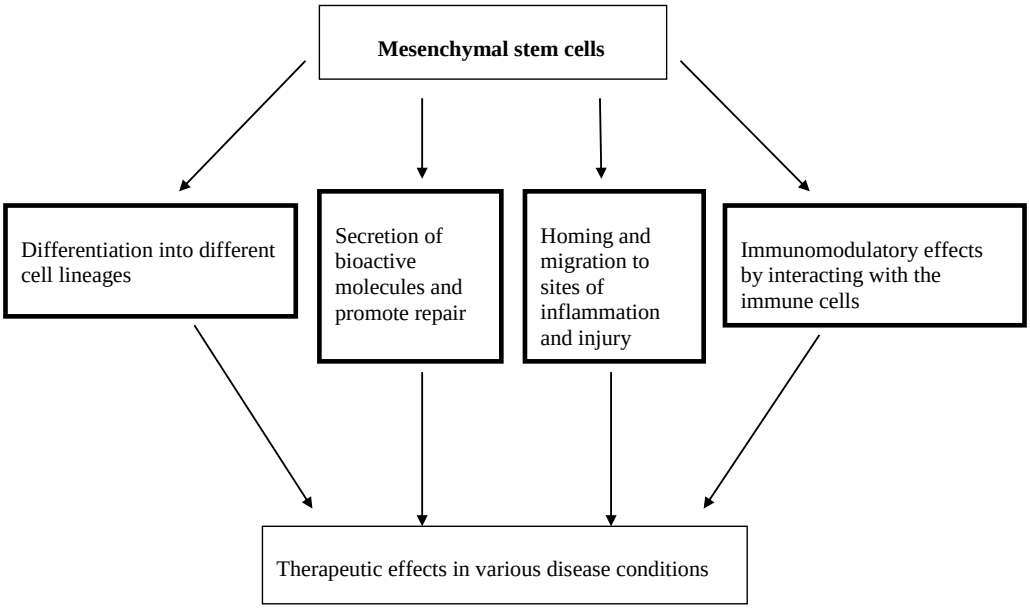

Fig. (1). A schematic diagram of the biological properties of MSCs.

Safety profile of MSCs has been encouraging with no reports of any major health concern in the various human disease settings and clinical trials conducted [15]. Further studies to evaluate tumor formation and genomic integrity are though necessary, the results from current studies have demonstrated no solid evidence of malignant growth or cellular transformation induced by chromosomal inconsistencies [16]. However there is concern about acquired mutations that may induce transformation as a result of prolonged culture.

The lack of standard validated protocols for cell isolation, expansion, and quality control hinder the monitoring of the clinical effectiveness of MSC-based therapy [14]. The absence of governmental regulatory policies at both local and global levels may impact the advance of MSC-based therapeutics into the clinic [17].

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ATTA-UR-RAHMAN, *FRS*

Atta-ur-Rahman, Ph.D. in organic chemistry from Cambridge University (1968), has 1020 international publications in several fields of organic chemistry including 727 research publications, 37 international patents, 68 chapters in books and 188 books published largely by major U.S. and European presses. He is the Editor-in-Chief of eight European Chemistry journals. He is Editor of the world's leading encyclopedic series of volumes on natural products "Studies in Natural Product Chemistry" 50 volumes of which have been published under his Editorship by Elsevier during the last two decades.

Prof. Rahman won the UNESCO Science Prize (1999) and was elected as Fellow of the prestigious Royal Society (London) in July 2006. He has been conferred honorary doctorate degrees by many universities including (Sc.D.) by the Cambridge University (UK) (1987). He was elected Honorary Life Fellow of Kings College, Cambridge University, UK, conferred the TWAS (Italy) Prize and the Austrian government has honoured him with its high civil award ("Grosse Goldene Ehrenzeischen am Bande") (2007). He is Foreign Fellow of Chinese and Korean Academy of Sciences, Foreign Fellow of the Chinese Chemical Society and former President of Pakistan Academy of Sciences.

SHAZIA ANJUM

Dr. Shazia Anjum is the Professor of Chemistry Department and the Director of Cholistan Institute of Desert Studies, the Islamia University of Bahawalpur, Pakistan. She is an experienced medicinal and natural product chemist. She has authored and co-authored more than 105 research papers, a US patent, has edited 04 books and has published 02 chapters in the international books. She has accomplished the synthesis of several naturally occurring aminoglycosides- that can be used as antibiotics. Dozen of students have completed their MS degrees under her supervision and couple of others are pursing for their MS/PhD degrees.

As recognition of her contributions to science, she has been awarded with 03 International awards like Fellowship from Islamic World Academy of Sciences, Postdoctoral fellowship from the Ministry of Culture and Education, Spain and a Young Chemist Award from the Third World Academy of Sciences, Italy. She is also a recipient of several national awards.