STEM CELLS THERAPY IN MULTIPLE MYELOMA

ESSAY

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Contents

List of Abbreviations

ABMT	Autologous Bone Marrow Transplant.
ASCT	Autologous Stem Cell Transplantation.
CC	Conventional Chemotherapy.
CR	Complete Remissions.
DEX	Dexamethasone.
ED	Early Death.
EFS	Event Free Survival.
EGCs	Embryonic Germ Cells.
ESCs	Embryonic Stem Cells.
G-CSF	Granulocyte-Colony Stimulating Factor.
GVHD	Graft Versus Host Disease.
HDT	High Dose Therapy.
HSCs	Hematopoietic Stem Cells.
HSCT	Hematopoietic Stem Cells Transplantation.
ICM	Inner Cell Mass.
IFM	Intergroupe Francais du Myelome.
MEL	Melphalan.
MM	Multiple Myeloma.
MP	Melphalan plus Prednisone.
MPT	Melphalan Prednisone Thalidomide.

MSCs	Mesenchymal Stem Cells.
OS	Overall Survival.
PBSCs	Peripheral Blood Stem Cells.
PR	Partial Response.
TBI	Total Body Irradiation.
THAL	Thalidomide.
VAD	Vincristine And Doxorubicin.
VGPR	Very Good Partial Response.

List of Tables

List of Figures

Introduction

Tissue engineering has been a topic of extensive research over the last years. The isolation of mesenchymal stem cells (MSCs) and later the embryonic stem cells in conjunction with the advances made in cellular biology, tissue engineering, genetics and recombinant technology has initiated the development of new techniques and new therapeutic strategies allowing treatment of many pathological conditions providing restoration of tissue continuity and function [(1)].

Since the first report detailing the use of peripheral blood-derived stem cells (PBSCs) was published, there has been rapid expansion in the clinical use of these cells as well as a concomitant increase in an understanding of their basic biology [(2)].

Recent developments are revolutionizing our understanding of the potential therapeutic role of what used to be called bone marrow transplantation but is now called hematopoietic stem-cell therapy. Over the past three decades, much empirical knowledge has been accumulated to provide a sound basis for the optimal use of this approach in the treatment of hematopoietic cancers, especially acute myelogenous leukemia, Hodgkin's disease and other lymphomas, and (more recently) multiple myeloma. This

approach has also been used in the treatment of some solid tumors, most notably breast cancer [3].

The failure of conventional chemotherapy to improve the outlook in multiple myeloma has led to the treatment of this disease with high-dose chemotherapy plus autologous stem-cell transplantation. Promising results have been obtained in pilot studies [4-5] and randomized trials comparing autologous stem-cell transplantation with conventional chemotherapy in patients with newly diagnosed myeloma have been reported. These studies demonstrated the superiority of autologous stem-cell transplantation over conventional treatment in terms of the response rate and event-free survival, but the effects on overall survival were unclear. A survival benefit was observed in French and British trials [6].

High-dose chemotherapy with rescue of the bone marrow by an autologous hematopoietic-cell transplant is regarded as the standard of care for newly diagnosed myeloma in patients less than 65 years of age [7].

Stem cell biology

The term stem cell is used most often by the press when referring to embryonic stem cells, which are undifferentiated cells that have been isolated from an embryo. But in reality there are many different types of stem cells with varying levels of potency and ability. All stem cells however must share three common properties.

All stem cells must be:

1) Capable of renewing and dividing for extended periods of time.
2) Unspecialized.
3) Able to give rise to specialized cells.

Stem cells are unspecialized, meaning that they do not participate in the functions performed by the cells that they give rise to. For example, hematopoietic stem cells do not transport oxygen through the bloodstream, although they give rise to the blood cells that do [(8)].

When stem cells give rise to specialized cells the process is called differentiation. This process is directed by internal signals encoded in the cells genes, and external signals which include chemicals, physical interactions with neighboring cells, and specific molecules in the cells microenvironment [(9)].

Unlike many specialized cells, stem cells have the ability to replicate themselves an unlimited number of times over the lifespan of an organism. Normally a cell divides into two identical daughter cells, each of which inherits a complete copy of the chromosomes from the original cell, this is called symmetric division. Symmetric division occurs in specialized cells and embryonic stem cells, as each daughter cell is an exact copy of the parent [10].

Conversely, when an adult stem cell divides one daughter cell will become a stem cell (and remain "immortal") and the other will go through the process of determination where it will gain a specific function, this is called asymmetric division. Asymmetric division allows for the renewal of specialized cells while maintaining a constant supply of new stem cells to continue the cycle [10].

Stem Cell Potencies:

A stem cell is often described in terms of its potency or the number of different kinds of specialized cells that it has the ability to produce (Figure 1). The fertilized egg or zygote is considered to be the ultimate "stem cell" (technically it is not a stem cell because it does not renew itself) because it is totipotent, meaning

it has the ability to give rise to any embryonic or adult tissue cell, including germ cells, the placenta, and embryonic membrane.

As the zygote continues to divide its potency diminishes. At around 5 days, a blastocyst forms consisting of an outer layer and an inner cell mass. The inner cell mass contains embryonic stem (ES) cells. These cells are pluripotent with the ability to make almost all kinds of cells in the body [(11)].

An adult human has multipotent stem cells capable of making various kinds of cells of one tissue, for example hematopoietic stem cells (HSCs) that are capable of forming the cellular components of blood. In addition adults also have unipotent stem cells within certain tissues that are usually capable of forming only that same type of cell. Cells in this category include neuronal stem cells, and skin stem cells [(11)].

Traditionally scientists believed that no adult stem cells were pluripotent, making them less useful in medical treatments than embryonic stem cells. However, increasing evidence suggests that some adult stem cells, especially those found in bone marrow, may retain pluripotency [(11)].

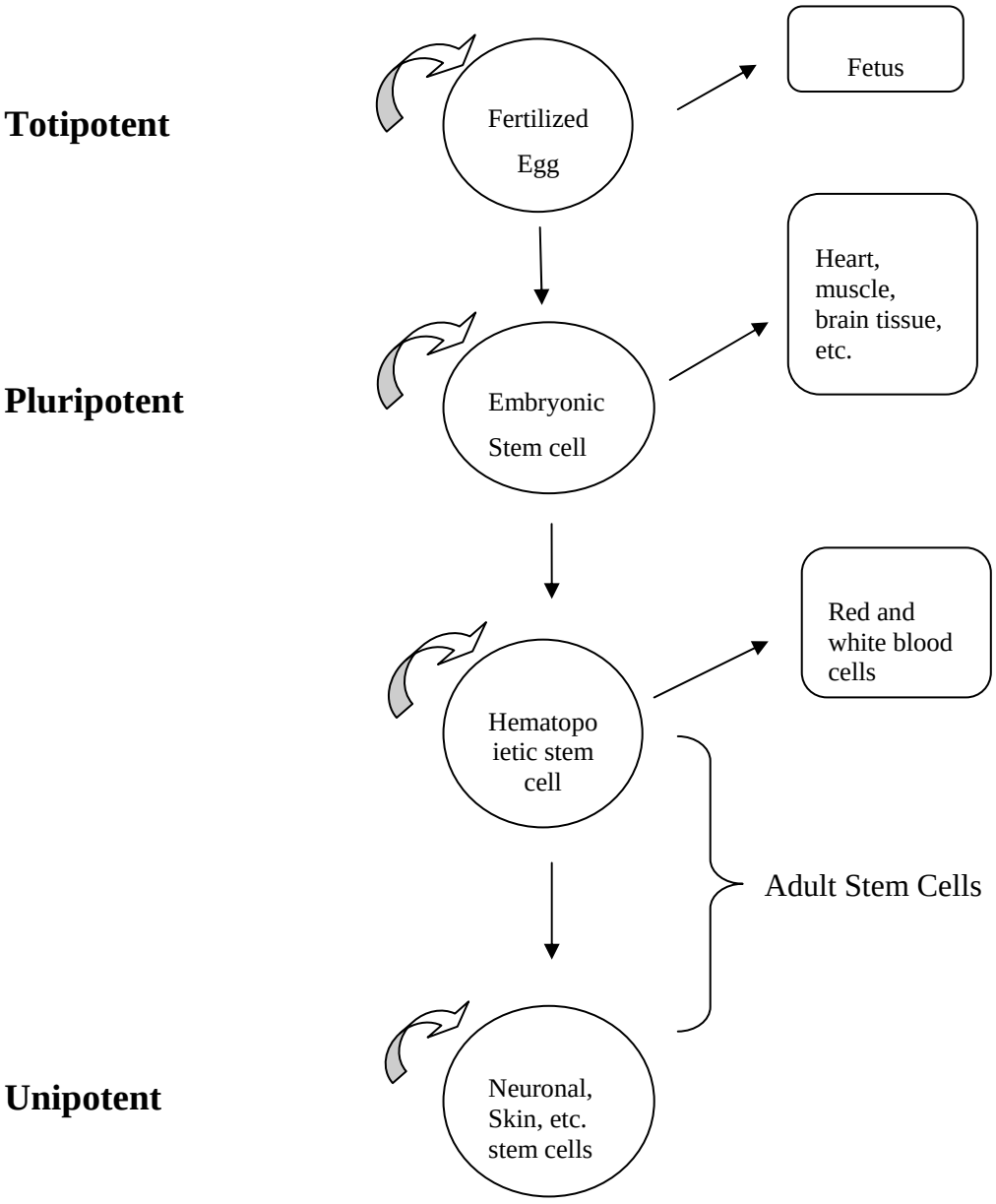

Figure (1): A diagram of diminishing stem cell potency as the fertilized egg develops into a specialized adult cell [(11)].

Embryonic Stem Cells and Embryonic Germ Cells:

Embryonic stem (ES) cells are defined by their origin in the blastocyst stage of the embryo. ES cells are pluripotent, not totipotent because unlike the fertilized egg, ES cells cannot by themselves produce a new organism. At this early stage they still have the ability to become any of the cells of the human body, but they are not totipotent as they can no longer become a part of the embryonic membrane or the placenta [(12)].

As the zygote divides, the daughter cells produced are called blastomeres. When there are about 4-16 cells, they clump together to form a cluster called a morula. When number of cells reaches 40-150 blastomeres they form a hollow sphere, or blastocyst, the cavity of this sphere is called a blastocoele. The outer cells of the blastocyst, the trophoblast, will eventually form the embryonic membrane and placenta, while the inner cell mass (ICM) or embryoblast will form the embryo (Figure 2).

The ICM is then further divided into three germ layers, the ectoderm, mesoderm, and endoderm. Each of these layers will eventually develop into all of the tissues of the adult organism. Embryonic stem cells are derived from these inner cells of the blastocyst, at an early stage of the embryo before it is implanted in the uterine wall [(13)].

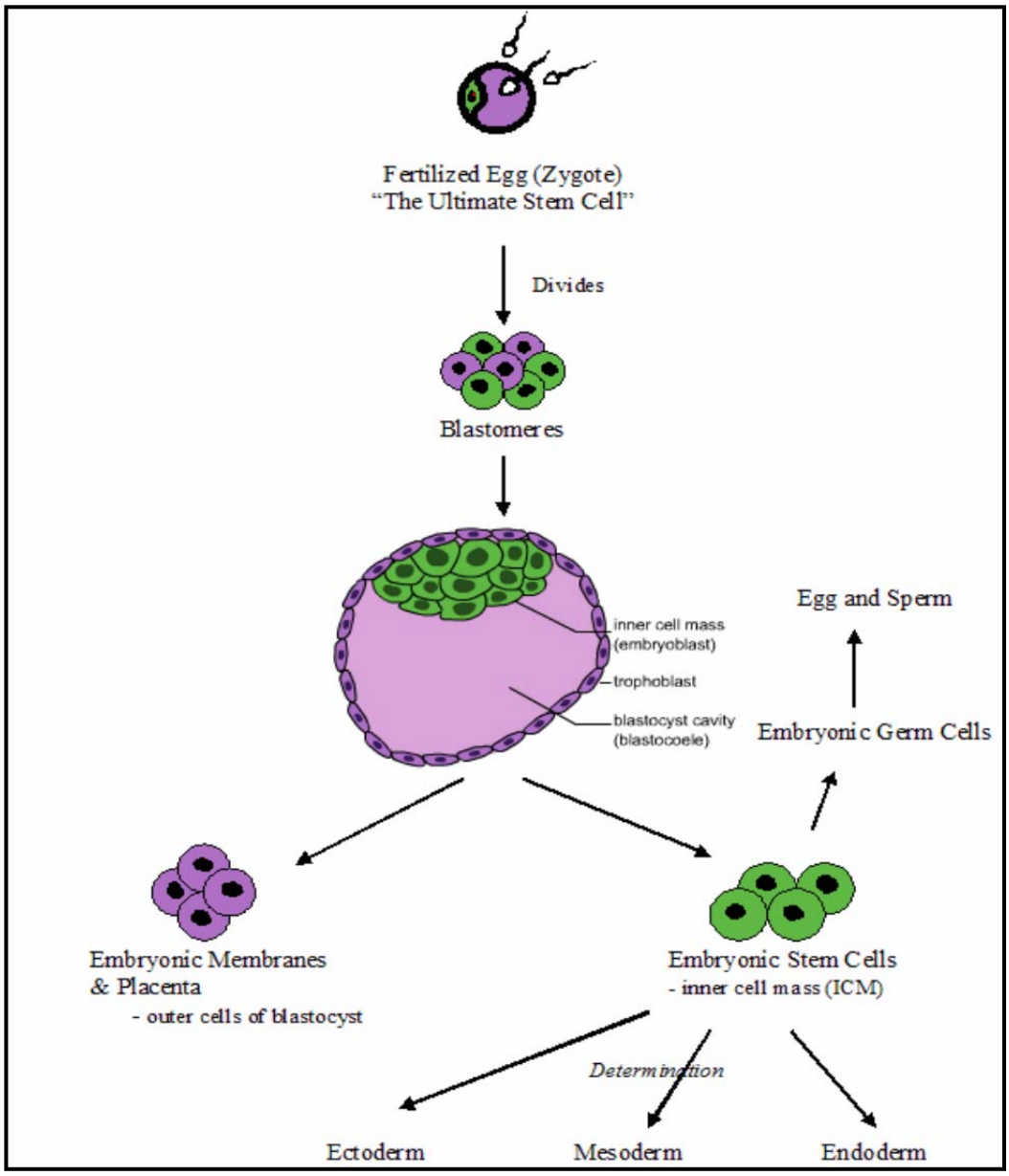

Figure (2): The development of the fertilized egg as it divides into blastomeres which then form the blastocyst from which embryonic stem cells are isolated [13].

Embryonic stem (ES) cells can theoretically proliferate indefinitely. To this point researchers have maintained undifferentiated ES cells in culture for more than a year and up to 300 population doublings. However, if the ES cells are allowed to clump together to form embryoid bodies they will begin to spontaneously differentiate into different types of specialized cells.

It is unclear at this time what causes a stem cell to remain undifferentiated. Transcription factors such as Oct-4, expressed by human and mouse ES cells in vivo, as well as the cell cycle of the cell, are thought to play a role in maintaining the stem cells undifferentiated state [(14)].

Embryonic germ (EG) cells are isolated from the embryo or fetus, specifically from the gonadal ridge, and eventually form the germ cells of the organism. EG cells, derived from the primordial germ cells found in the gonadal ridge, are closely related to ES cells. Both are pluripotent, replicate for an extended period of time, and generate both male and female cell cultures. However, EG cells cannot be maintained in culture as long as ES cells and they do not produce teratomas, which are germ cell tumors made up of cells from all 3 germ layers, when injected into colonies of mice cells with compromised immune systems [(14)].