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Review

# Cytotherapy using stromal cells: Current and advance multi-treatment approaches

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ABSTRACT

The research in stem cells gives a proper information about basic mechanisms of human development and differentiation. The use of stem cells in new medicinal therapies includes treatment of different conditions such as spinal cord injury, diabetes mellitus, Parkinsonism, and cardiac disorders. These cells exhibit two unique properties: self-renewal and differentiation. The major stem cells been used for approximately about 10–14 years for cellular therapy are mesenchymal stem cells. Mesenchymal stem cells can individualize into many lineage, i.e. into both mesenchymal and non-mesenchymal lineage, such as into osteoblasts, chondrocytes, myocytes, adipocytes, neurons, etc. This review focuses on the history, types of stem cells and their targets and mechanisms of mesenchymal stem cells. Mesenchymal stem cells are the significant futuristic carrier for treating diseases associated not only with regeneration but also immunomodulation.

## 1. Introduction

Stem cells (SCs), the precursor of more than 220 types of cell present in the body, potentiate the growth of multiple type of tissues such as skin, muscles and nerve cells for treating various conditions like cancer, diabetes, wound healing, etc. [1,2]. A SC showed two important characteristics, i.e. cell differentiation and self-renewal [3]. Unlike cancerous cells, division of SC is well controlled, hence it is notable that SCs become specific types of cells which are capable to revive themselves for an extended period of time [4]. After division, new cells may retain as SC or become a specialized cell that act as a part of healthy individual during early life and growth [5]. Hence, they are potential therapeutics used in tissue regeneration and repair [6]. SCs are divided on the basis of potency *viz*. Totipotent cells (TC), Multipotent cells (MC), Pluripotent cells (PC), Oligopotent (OP) and Unipotent (UP). All types of SC can be utilized for medical research, but each of them has their own pros and cons as shown in Table 1 [7]. Scientific investigation on SC has wide potential for the advancement of novel healing treatment to cure many serious injuries and diseases like spinal cord injury (SCI), cardiovascular disease (CVD) and central nervous system (CNS) diseases, etc. [2]. Adult stem cells (ASCs) are obtained from different sources such as bone marrow, umbilical cord blood and are used in the medical treatment due to their differential plasticity [8]. The name PC is used because they can discern into all types of cell whereas PCs showed short- life in foetus prior to their differentiation into specific types of cell [8]. MCs exist in subgroups of a specific germ line and specific tissues thus showing limited differentiation potential [9].

## 2. History

In mid-1800's, it was found that the elementary unit of life is cell, in which some specialized cells produce different types of cell [10]. In the early years of 1900 scientists made an effort to produce mammalian eggs outside the human body, and it was discovered that there were few cells that could generate blood cells (Table 2) [11]. Russian histologist, Alexander Maksimov, in 1908 suggested the name SC for scientific use. The research in human SCs field became more popular after the work of the Canadian scientist Ernest A. Mcculloch and James E [12]. In 1937, Schretzenmyr showed first bone marrow transplant in the existing framework of stem cell transplant (SCT) as SC is noted to be existing in adult's bone marrow. In 1959, first animal was made by *in-vitro* fertilization (IVF), a step towards SCT [8]. In the late 1960s, teratocarcinomas which was found to be originated from mice embryonic germ cell, whereas Embryonal Carcinoma (EC) cells were found as SCs [9]. In 1968, first human egg was produced *in-vitro* and during the same year treatment of Severe Combined Immunodeficiency (SCID) from bone marrow transplant between twins was successfully accomplished [6] In 1978 haemopoietic SCs were discovered. It was proven that Embryonic stem cells (ESCs) of mouse are isolated from the inner cell mass of blastocysts in 1981 [6]. *In-vitro* growth of ESCs of mouse, were developed to inject into mice, which resulted in the formation of teratomas. There are some pluripotent clonal cells called EC cells were

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**Table 1**
SCs therapy pros and cons and their characteristics.

| SC | Description | Example | Pros | Cons |
|---|---|---|---|---|
| MC | Cell of any type within specific germ line or lineage | Fetal tissue, blood, ASC | 1. Less likelihood of rejection when used in transplants.<br>2. Stable cell phenotype<br>3. Low metabolic rate<br>4. Possibility of re-programming and trans differentiation is poorly investigated. | 1. The ability to regenerate and proliferate is limited as compared to embryonic stem cell (ESC).<br>2. In culture, cells cannot be developed for extended periods of time.<br>3. Difficult to discover and clean due to very limited number in each tissue.<br>4. Currently, for generating abundant amount of SC in culture, no technology is available. |
| TC | Cells of any type in the body and placenta | Cells derived from early embryo | 1. Potential to cure conditions like SCI, Parkinsonism, cancer, etc.<br>2. By gaining the knowledge of ESCs proper understanding of development process can be achieved.<br>3. Mostly protocols are established for maintenance of culture. | 1. The process for generating ESC lines is inefficient.<br>2. Destruction of preborn life is unacceptable.<br>3. They can cause tumors. |
| PC in the form of induce pluripotent stem cells (iPSCs) | Cells of any type in the body | Some cells of blastocytes | 1. Somatic cells isolated from donor can be used in large quantity.<br>2. In case of donor or recipient transplants problem of histocompatibility is resolved.<br>3. In drug development process iPSCs are very useful. | 1. Assured reproducibility and its retainment are not defined for differentiated tissue procedures. |
| OP | Some types of cells only | Lymphoid or myeloid SC (adult) | – | – |
| UP | Cells of individual type | Muscle SC adult | – | – |

**Table 2**
Timeline events of SC research.

| Year | History of SC |
|---|---|
| 1978 | SCs were discovered in human cord blood |
| 1981 | First *in-vitro* SC line developed from mice |
| 1988 | ESC lines created from a hamster |
| 1995 | First ESC line derived from a primate |
| 1997 | Cloned lamb from SCs |
| 1997 | Leukaemia origin found as haematopoietic SC, indicating possible proof of cancer SCs |
| 1998 | John Green Hart extracted germ cells from gonadal tissue of foetus before developing PC line |
| 2001 | Scientists showed advancement in cell technology which was close to early stage embryo for the purpose of generating ESC |
| 2006 | Scientists in Chicago found SC like characteristics in umbilical cord blood cells. |
| 2008 | Robert Lanza discovered first human embryonic cells without the destruction of an embryo. |
| 2010 | Person with SCI was first to receive medical treatment derived from human embryonic stem cells (hESCs) |
| 2012 | hESCs showed promising results in treatment of blindness. |
| 2013 | hESCs were produced from fetal cells using therapeutic cloning. |
| 2015 | Preparations of MSCs were available in market. |
| 2016 | Bextra came into the US markets to reduce pain caused by rheumatoid arthritis (RA) and osteoporosis. |

created in between 1984 and 1988 [6]. These cells differentiated into neuron-like cells and other cell types when exposed to retinoic acid. A clonal line of human EC cells that yields tissues from all three primary germ layers, but possess limited replicative and differentiating potential were derived by scientists in 1989 [8]. Cells like ESCs are formed in the centre and they have SC like morphology [9]. The non-human primate and differentiated normally into all the three primary germ layers in 1995-96 [13]. Scientists discovered different cell types could be produced by manipulating adult mouse tissues in 1999 and 2000 [10]. Scientists revealed that cells derived from bone marrow were able to generate nerve or liver cells and those cells present in the brain yield other types of cells [12]. These findings were exciting in the field of SC research, with the promise of better scientific control over SC differentiation and proliferation (Table 2) [10].

From the inner cell mass of human blastocysts, ESCs were isolated, cultivated and developed normally in 1998 and 2000 [7]. They can multiply *in-vitro* for a long period of time and when injected into immune deficient mice, form of all the three germ layers and teratomas [14]. The scientists from Kingston University in England stated about different class of SC, which originate in the umbilical cord, named it cord blood embryonic-like SC in 2005. It is recommended that these SC can separate into most cell types as compared to ASC, resulting in better potential for cell-based therapeutics [14]. Researchers working under Dr. Anthony Atala declared that an advance type of SC had been found and was screened in amniotic fluid in early 2007 [11].

## 3. Class of SC: classification of SCs on the basis of their sources

### 3.1. Embryonic stem cells (ESCs)

In human beings, the organism from the time of implantation within the womb till the end of the second month of gestation is known as an embryo. ESCs are also known as early SC, as their isolation is possible only during early stages of cell, i.e. blastocysts stage (32-cell stage). Blastocyst formation takes place approximately five days after fertilization [15] as shown in (Fig. 1).

#### 3.1.1. Establishing ESC lines

A sperm fertilizes an oocyte to form a TC known as a zygote. After many series of cellular division, generation of the morula occurs with 32–64 TCs. Morula then develops into blastocysts, that is composed of a hollow ovoid of cells. The innermost cells of the blastosphere form