

Functional Cells, Maintenance Cells, and Healing Cells

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Henry E. Young, Chief Science Officer, Dragonfly Foundation for Research and Development, 1515 Bass Rd, Suite E (Corporate Office), Macon, GA 31210, Tel: 478-319-1983; Fax: 478-743-0280; E-mail: young.hey1@yahoo.com; Website: www.researchdesigns.org.

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Citation: Henry E. Young, Mark O. Speight, Asa C. Black Jr, et al. Functional Cells, Maintenance Cells, and Healing Cells. Stem Cells Regen Med. 2017; 1(1) 003: 1-4.**ABSTRACT**

Development of a multicellular organism is accomplished through a series of events that are preprogrammed in the genome. These events encompass cellular proliferation, lineage commitment, lineage progression, lineage expression, cellular inhibition, and regulated apoptosis. The sequential progression of cells through these events results in the formation of the differentiated cells, tissues, and organs that constitute an individual [1]. Although most cells progress through this sequence during development, a few cells leave the developmental continuum to become reserve precursor cells. The reserve precursor cells are involved in the continual maintenance and healing of the tissues and organs throughout the life span of the individual. Until recently it was generally assumed that the precursor cells in postnatal individuals were limited to lineage-committed unipotent progenitor cells specific for various cells, i.e., neuroblasts for neurons, myoblasts for muscle, hepatoblasts for hepatocytes. However, recent studies [1-3] demonstrated the presence of two categories of precursor cells that reside within the organs and tissues of postnatal animals. These two categories of precursor cells are maintenance cells and healing cells. These reserve precursor cells provide for the continual maintenance and repair of the organism after birth.

Keywords

Function, Differentiated Cells, Maintenance, Progenitor Cells, Healing, Stem Cells, Animals, Mammals, Humans.

The human body is composed of trillions of cells. These cells can be divided into three basic groups: functional cells, maintenance cells, and healing cells. The functional cells comprise the majority of the 220 different cell types in the body. Functional cells are composed of both differentiated parenchyma and stroma. Functional cells are telomerase negative and thus have a defined lifespan before they are genetically pre-programmed to age and die [4,5]. They function on a day to day basis for sensory input from the outside world, regulation of internal function, gas exchange, nutrition, waste removal, defense, energy storage, reproduction, support, ambulation, etc. A few examples of functional cell types include retinal cells, neurons, beta-cells of pancreatic islets, monocytes, hepatocytes, adipocytes, sperm, marrow secretory cells, fibrocytes, chondrocytes, osteocytes, and myocytes. Functional cells comprise

approximately 50% of all cells of the body and are located within specific organs and tissues throughout the body.

Maintenance cells support the functional cells on a day to day basis. As the functional cells wear out and die the maintenance cells proliferate, differentiate, and assume the function of the worn out and dead functional cells. Maintenance cells are also telomerase negative and thus have a defined lifespan before they are genetically pre-programmed to senesce and die [4-6]. Maintenance cells decrease in number with increasing age of the individual. A few examples of maintenance cells are mature adult progenitor cells (MAPCS) [7,8], neuroblasts [9,10] epidermal stem cells [11], pancreatic progenitor cells [12], hematopoietic stem cells [13], hepatic oval cells [14], marrow stromal cells (MSCs) [15,16], mesenchymal stem cells (MSCs) [17-19], tripotent adipochondro-osteoblasts [19], bipotent adipo-fibroblasts [20], and myosatellite cells (myoblasts) [21]. Maintenance cells comprise approximately 40% of all the cells of the body and are located

within specific organs and tissues throughout the body [2].

Healing cells are normally dormant and can be found hibernating within the stromal connective tissues throughout the body [6,21]. Their function is to replace functional cells and maintenance cells lost due to trauma and/or disease. Healing cells are telomerase positive and thus have essentially an unlimited lifespan until they become maintenance cells and functional cells [3,22]. Once healing cells become maintenance cells and/or functional cells they assume the respective lifespans, pre-programming, aging and death of these two groups of cells [2]. Numbers of dormant healing cells remain relatively constant throughout the lifespan of the individual. Examples of healing cells are totipotent stem cells [21,23], pluripotent stem cells [2,24,25], ectodermal stem cells [26], mesodermal stem cells [2,3,26], and endodermal stem cells [26]. Healing cells comprise approximately 10% of all the cells of the body and are ubiquitous throughout all organs and tissues of the body. More specifically, totipotent stem cells comprise approximately 0.1%, pluripotent stem cells approximately 0.9%, and the ectodermal stem cells, mesodermal stem cells, and endodermal stem cells approximately 9% of all cells of the body [2,3].

Multiple laboratories have been analyzing the location, characterization, and activities of endogenous healing cells in bone marrow [27-31], adipose tissue [32], skeletal muscle [21], blood [33], and at least 33 other tissues and organs within the body in multiple species of animals [1,3,34,35]. Animals examined thus far include avians (Chicken, Waddel Crane), amphibians (Ambystoma Salamanders), reptiles (Komodo Dragon), and 12 species of mammals, including humans (i.e., mice, rats, rabbits, dogs, cats, sheep, goats, pigs, cows, Speckled Bear, horses, and humans) [3,36-44]. Healing cells have also been seen in human umbilical cord, amnion, and placenta [45-47]. Pre-clinical animal studies and clinical human studies have shown that the greater the number of healing cells used for replacement therapies the better and quicker the healing response [2,24,48-52].

The majority of current isolation strategies to maximize the number of healing cells for replacement therapies noted that hundreds of dormant healing cells could be isolated from an umbilical cord; thousands of dormant healing cells could be isolated from bone marrow, amnion, or placenta; and hundreds of thousands of dormant healing cells could be isolated from adipose tissue, skeletal muscle, or blood. Current strategies to increase the number of healing cells for replacement therapies have utilized either increasing the amount of tissue for their isolation, expanding their numbers outside the body, or obtaining tissue from allogeneic donors.

My research group has taken an alternative approach to this problem. We discovered that we could increase the number of dormant healing cells inside the body prior to harvest, thus making the individual their own autologous healing cell bio-reactor. We have identified three sets of chemical agents. The first set of chemical agents stimulates an increase in the number of specific

dormant healing cells within the connective tissue stroma. The second set of chemical agents causes a migration of the increased numbers of specific dormant healing cells from the connective tissue stroma into the blood stream. We then harvest the healing cell-enriched blood; separate the healing cells from the hematopoietic cells following FDA-approved minimal manipulative procedures; segregate the healing cells into totipotent stem cells, pluripotent stem cells, and mesodermal stem cells; and then using the third set of chemical agents we activate these previously dormant healing cells. Utilizing this triple stimulatory/migration/activation strategy from a single harvest we can isolate billions of activated healing cells for replacement-regeneration therapies.

We also use the innate characteristics of these particular endogenous healing cells to optimize their regenerative potential. For example, there are distinctive size differences as well as what types of cells these particular healing cells can regenerate. Dormant totipotent stem cells are ultra-small and once activated can form all somatic cell types of the body of ectodermal, mesodermal, and endodermal origin, as well as sperm and ova; dormant pluripotent stem cells are small and once activated can form all somatic cell types of the body of ectodermal, mesodermal, and endodermal origin, but not the sperm nor ova; and dormant mesodermal stem cells are of moderate size and once activated will only form cells of mesodermal origin [2,3,6,21,24].

We have shown in previous pre-clinical studies, both in the culture dish and in animal models, that functional cells and maintenance cells secrete factors (exosomes) that regulate the activities of adjacent cells, including the healing cells. For example, when activated, healing totipotent stem cells and/or healing pluripotent stem cells either incubated with conditioned medium (exosomes) from cultured pancreatic islets or placed next to pancreatic islet tissue in a culture dish, would form functioning glucagon-secreting alpha-cells, insulin-secreting beta-cells, and somatostatin-secreting delta-cells, which are three cell types present within endocrine pancreatic islets [48,50]. Utilizing pre-clinical animal models of Parkinson disease (PD) and myocardial infarction (MI) we showed that placement of activated pluripotent stem cells into regions of damaged tissues within the brain and heart resulted in regeneration of just the damaged tissues and no other cell types. In the PD model previously damaged dopaminergic neurons, interneurons, pyramidal cortical neurons, glial cells, and vasculature were regenerated [49,51,52]. In the MI model previously damaged cardiac myocytes, fibroblastic tissues of the cardiac skeleton, and vasculature were regenerated [2,24].

We have used this pre-clinical knowledge for our human clinical trials. For example, in our Parkinson trial we isolated billions of activated totipotent stem cells. We used their inherently ultra-small size to devise a relatively non-invasive technique for their delivery. This relatively non-invasive technique was in contrast to the very invasive stereotactic surgery that was used for our pre-clinical PD animal studies. We had the subjects rinse the mucus out of their noses with saline and applied the healing activated totipotent stem cells to their olfactory epithelium. Because of their ultra-small

size the healing totipotent stem cells were able to migrate between the olfactory cells, along the nerve rootlets, past the blood-brain barrier, through the cribriform plate of the frontal bone, along the olfactory nerves, into the cisterns surrounding the brain and spinal cord, and then to the sites of tissue damage within the central nervous system (CNS). At one month and two months following a single treatment of healing totipotent stem cells all participants had ceased their downward spiral and started to get better. By seven months after their single treatment 25% had reverted and started to decline, 50% remained stable, and 25% continued to improve. These same results were shown at the 14-month follow-up [49,51,52]. Future studies have begun to optimize the effects of healing cells on chronic diseases and traumatic tissue injuries.

A word of caution for those interested in using allogeneic (non-self) donor tissue to supply healing cells for clinical transplant. It is imperative that all allogeneic donor tissue undergo rigorous Quality Assurance/Quality Control (QA/QC) to protect the recipient. All donor tissue should be screened for infectious agents and genetic diseases. Any allogeneic donor tissue demonstrating either infectious agent(s) or genetic disease(s) should be excluded as a potential transplant tissue. While undifferentiated totipotent and pluripotent stem cells are void of either MHC Class-I and/or HLA-DR-II cell surface markers [2,6] they will demonstrate their respective genomically-programmed markers as they differentiate. Therefore, it is imperative that allogeneic donor tissue and the recipient be matched for ABO or Bombay blood groups. Lastly, long term animal studies have demonstrated that donor female healing cells placed within a male recipient continue to function as female cells and that donor male healing cells placed into a female recipient continue to function as male cells. In some instances, mixed gender transplants will not cause any undue problems, as long as all the transplanted cells remain at their intended target location. However, in other instances where the healing cells migrate to other areas of tissue damage, especially with respect to the expression of secondary sexual characteristics, the results can be devastating. Therefore, it is also imperative that the gender between donor and recipient be matched, i.e., female to female or male to male.

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