A concise review on the classification and nomenclature of stem cells

Kök hücrelerinin sınıflandırılması ve isimlendirilmesine ilişkin kısa bir derleme

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Abstract
Stem cell biology and regenerative medicine is a relatively young field. However, in recent years there has been a tremendous interest in stem cells possibly due to their therapeutic potential in disease states. As a classical definition, a stem cell is an undifferentiated cell that can produce daughter cells that can either remain a stem cell in a process called self-renewal, or commit to a specific cell type via the initiation of a differentiation pathway leading to the production of mature progeny cells. Despite this acknowledged definition, the classification of stem cells has been a perplexing notion that may often raise misconception even among stem cell biologists. Therefore, the aim of this brief review is to give a conceptual approach to classifying the stem cells beginning from the early morula stage totipotent embryonic stem cells to the unipotent tissue-resident adult stem cells, also called tissue-specific stem cells. *(Turk J Hematol 2008; 25: 57-9)*
Key words: Stem cells, embryonic stem cells, tissue-specific stem cells, classification, progeny.

Özet
Kök hücresi biyolojisi ve onarımsal tıp görece yeni alanlardır. Buna karşın, son yıllarda çeşitli hastalıklarda tedavi amacıyla kullanılabilme potansiyelleri nedeniyle kök hücrelerine olağanüstü bir ilgi artışı vardır. Klasik tanımıyla kök hücresi, kendini yenileme adı verilen mekanizmayla farklılaşmadan kendini çoğaltan veya bir dizi farklılaşma aşamasından geçerek olgun hücrelere dönüşebilen hücrelerdir. Çok kabul gören bu tanımlamaya karşın, kök hücrelerin sınıflandırması karmaşık olup alanın uzmanlarınca bile çoğu zaman kavram kargaşasına neden olmaktadır. Bu kısa derlemenin amacı, morula aşamasındaki totipotent embriyonik kök hücrelerinden başlayıp dokuda yerleşik olan ve dokuya özgü kök hücresi olarak adlandırılan unipotent hücrelere varan bir yelpazade kök hücrelerini sınıflandırmada kullanılan kriterleri kavramsal olarak özetlemektir. *(Turk J Hematol 2008; 25: 57-9)*
Anahtar kelimeler: Kök hücresi, embriyon kök hücresi, dokuya özgü kök hücresi, sınıflandırma, farklılaşma

Introduction

By definition, a stem cell is capable of self-renewal, differentiation into at least one cell type, and functional reconstitution of the tissue of origin. Almost 35 years ago, murine embryonic stem cells (ESCs) were isolated from the inner cell mass (ICM), a small cluster of cells within murine blastocysts [1]. More recently, similar cells were isolated from human blastocysts [2] and from human primordial germ cells [3]. ESCs can be expanded in an undifferentiated state indefinitely. More importantly, ESCs are pluripotential; they can differentiate into all somatic cell types as well as germ cells when injected into a blastocyst, and form mature progeny of all three embryonic germ layers in vitro [4].

In contrast to ESCs, adult stem cells, also defined as tissue-specific stem cells (TSSCs), present in developmental stages beyond the embryo, can give rise only to progeny restricted to the tissue of origin. The prevailing stem cell con-

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cept has been best evaluated in the hematopoietic system. The hematopoietic system is organized such that multipotent hematopoietic stem cells (HSCs), endowed with self-renewal capacity, are positioned at the origin of a hierarchical tree of branching specificities [5]. This organization facilitates the formation of committed progenitor cells, with more limited self-renewal, followed by lineage-restricted precursor cells, which ultimately give rise to terminally differentiated cells. Consistent with the definition of stem cells, HSCs self-renew in vivo, differentiate at the single cell level into all mature blood elements and functionally repopulate the hematopoietic system of a myeloablated recipient [6].

During the last 10 years, several reports have described that many adult tissues may contain cells with greater potency than previously thought, given that they apparently differentiate in cell types different from their tissue of origin. Indeed, some studies have suggested that certain classes of adult stem cells can unexpectedly differentiate into cell types of all three germ layers, somewhat similar to the differentiation ability of ESCs [7-9].

Classification and nomenclature of stem cells

The terminology used to classify the stem cells is somewat perplexing. If someone uses the term embryonic stem cell (ESC), there is no doubt that he means a group of cells that are derived from the embryo. Thus, one of the most commonly used classifications is based upon their origin or location (Table 1). Depending on their residency, stem cells are classified in two categories: ESCs and adult stem cells, which are also called TSSCs, derived either from a fetus or a postnatal individual (Figure 1).

The second and more functional classification of stem cells is based according to their developmental potential as totipotent, pluripotent, multipotent, and unipotent (Table 1). A totipotent stem cell can give rise to a new individual if provided with appropriate maternal support. Thus, the blastomeres at the morula stage embryo are totipotent because each individual cell can give rise to all embryonic and extraembryonic tissues

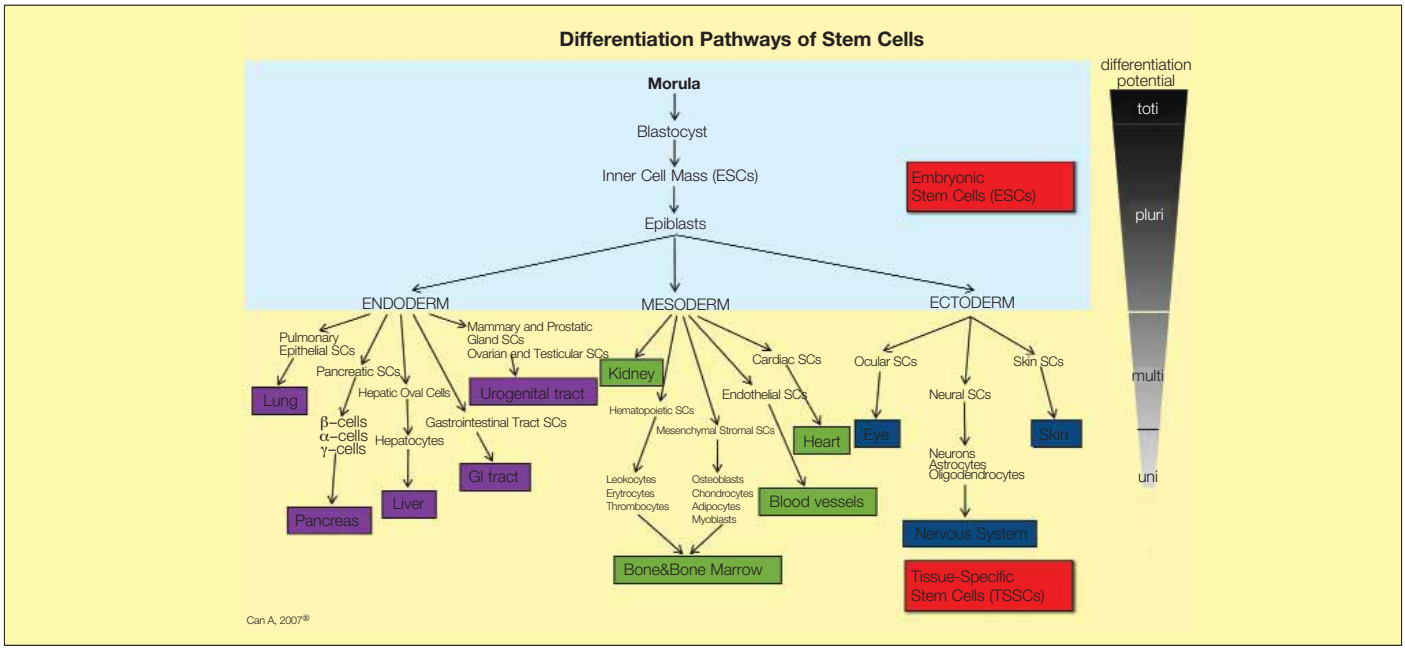

Figure 1. Differentiation pathways of stem cells

Table 1. Stem cell types according to their origin, differentiation potency and progeny.

Name	Cell type (location)	Differentiation potency	Progeny
ESC	Cells at morula stage	Totipotent	Embryonic and extraembryonic tissues ESC
	Cell of inner cell mass at blastocyte stage	Pluripotent	Embriyo proper (all somatic and germ cells)
ESC	Cell of epiblast layer at gasturala stage	Pluripotent	Endoderm, mesoderm and ectoderm
ESC	Cell of ectoderm, endoderm or mesoderm	Pluripotent	All somatic cells
TSSC	Cell of specific tissues	Multipotent	One to several cell types depeding on the residing tissue (e.g. hematopoietic stem cell)
TSSC	Resident cells in a given tissue	Unipotent	Single cell type (e.g. myosatellite cells of muscle

ESc: Embryonic stem cells, TSSc: Tissue-specific stem cells

required for mammalian development [10]. After compaction and blastocyst formation occur, the cells of the ICM are pluripotent because they can give rise to all cell types of the embryo proper, including somatic and germ cells. Embryonic development and the subsequent adult life are viewed as a continuum of decreasing potencies. The term ESC is generally confined to the ICM-derived pluripotent stem cell population. However, cells of the three germ layers are also considered as ESCs.

Human ESCs obtained from the inner mass of blastocysts are characterized by high proliferative index and can give rise not only to all cell types derived from the three germ layers, but also to extraembryonic tissues, such as placenta and umbilical cord [2]. Despite these attractive and promising features, their use in cell therapy for the treatment of various degenerative diseases is limited or avoided because of ethical issues arising from the destruction of human blastocysts when the inner mass is removed. To overcome the problems connected with the use of the ESCs, the research has been focused on TSSCs, which have an almost ubiquitous distribution through the body.

TSSCs are multipotent if they are able to differentiate into multiple cell types of a single tissue. HSCs currently are the best-characterized multipotent stem cells.

They give rise to all the lineages of the blood system [6]. Until recently, it was believed that they were tissue-specific and could not give rise to cells of tissues other than those in the hematopoietic system. However, this notion has been challenged recently. Indeed, with the exception of HSCs and possibly bone marrow stromal stem cells (also called mesenchymal stem cells), little is known about TSSCs in any other tissue. TSSCs are able to differentiate in vitro and in vivo into various cell types not only belonging to the tissue of origin, since this process depends on environmental signals switching on the genes involved in the differentiation programs.

TSSCs have also been isolated from many other organs, including the central nervous system, epidermis, intestine, liver, lung, retina, and others (Table 2). Due to the traditional nomenclature, TSSCs are basically known as pluripotent stem cells of bone marrow, mesenchymal stem cells, neural stem cells and skeletal muscle stem cells. These organ-derived stem cells are undifferentiated but lineage-committed, slowly dividing cells that feed the body's tissue with differentiated progeny. At the final stage of differentiation, one can define as unipotent a cell able to contribute only to one mature cell type. Examples of unipotent, lineage-committed progenitor cells include the myosatellite cells of muscle [11], endothelial progenitor cells, and corneal epithelial cells [12].

Table 2. Sources of tissue specific stem cells

Endodermal Origin
Pulmonary Epithelial SCs
Gastrointestinal Tract SCs
Pancreatic SCs
Hepatic Oval Cells
Mammary and Prostatic Gland SCs
Ovarian and Testicular SCs
Mesodermal Origin
Hematopoietic SCs
Mesenchymal Stroma SCs
(MSCs, MPCs, MAPCs, MIAMI cells, BMSCs, FSSCs, USSCs)
Cardiac SCs
Satellite cells of muscle
Ectodermal Origin
Neural SCs
Skin SCs
Ocular SCs

Bone marrow represents the most employed source of hematopoietic and mesenchymal TSSCs. Nevertheless, the use of TSSCs is limited by some disadvantages: i) very low number in the adult tissues, ii) low proliferative rate, and iii) invasive procedures needed to obtain them, which can lead to morbidity for the donors.

In the last decade, however, there has been an exponential increase in the number of manuscripts on TSSC types, including skin, liver, pancreas, brain, lung, intestine, skeletal muscle, cardiac, Wharton's jelly, and cord blood, etc. Therefore, TSSCs are now acknowledged as a promising pool of undifferentiated cells that are required to renew and repair the tissue microenvironment when needed.

The facts that most organs do contain a population of stem cells that could be harnessed to develop repair strategies and that adult cells may have greater potency than previously thought open up the possibility that they can be used to treat a host of diseases; nevertheless, many studies will be needed to substantiate such claims. More studies will be needed that: characterize cell surface markers that allow positive selection of the stem cell populations; develop standardized culture conditions for the isolation of the cells; and determine whether the many pluripotent stem cells described to date are a culture-mediated dedifferentiation or whether truly pluripotent stem cells persist beyond gastrulation.

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