Chapter 1

Classification of Stem Cells: Hierarchy, Origin, and Functional Diversity

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Abstract

Stem cells are heterogeneous and undifferentiated cells with the potential to differentiate into several lineages. From past decades to the present time, it has been shown that stem cells have an immense role in the conduction of in vitro studies and modeling of diseases. Different stem cell categories, such as TSCs[1], ESCs[2], and iPSCs,[3] exhibit great potential for differentiation into the embryonic lineages of cells and therapeutic applications. Compared to these cells, multipotent stem cells, like HSCs[4], MSCs[5], and NSCs[6], possess

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1. Totipotent stem cells
2. Embryonic stem cells
3. Induced pluripotent stem cells
4. Hematopoietic stem cells
5. Mesenchymal stem cells
6. Neural stem cells

a limited differentiation capacity but promote tissue repair and homeostasis in adults. Besides, prenatal stem cells like umbilical cord blood and WJ[1] stem cells possess significant immunomodulatory properties. The emergence of sophisticated culture approaches such as organoid technology, CRISPR/Cas9 gene editing, and multi-omics analysis has improved the regenerative properties of stem cells and enabled interventions based on a person's unique characteristics. Here, in this chapter, the taxonomy of stem cells with the application of various philosophical constructs in terms of the hierarchy of development potential, origin, tissue-specific functional diversity, and experimental characteristics will be discussed.

Keywords: Stem cells; Potency Hierarchy, Pluripotency, Multipotency, Regenerative Medicine

1. Introduction

Stem Cells are certain cell types with self-renewal and differentiation properties [1]. The self-renewality is orchestrated by asymmetric or symmetric cell division, while these cells have the potential to differentiate or commit into specialized and functional [2]. It has been thought that these properties make stem cells unique compared to mature cells. Therefore, these features have important key roles in the development, maintenance, and regeneration process. Of note, various types of stem cells have been identified due to breakthrough advances in molecular and developmental biology [3, 4]. Historically, the framework associated with stem cell classification started with the conduction of early embryological research and accelerated with sophisticated technological developments [5]. The identification of totipotent cells was first done in early mammalian embryonic development, followed by the discovery of pluripotent stem

[1]. Wharton's jelly

cells in both mouse and human embryos [3]. In later developmental stages, multipotent stem cells have been detected in various tissues [6, 7].

To be specific, the classifications of stem cells are based on a variety of organizational systems, biological parameters of interest related to development, disease, and regenerative principles [8]. Depending on regenerative potential, stem cells encompass totipotential, pluripotential, multipotential, oligopotent, and unipotential types [9]. In terms of origin, these cells are classified into ESCs[1], adult, perinatal, and induced stem cells [10]. It is also possible that these cells are named based on anatomical source, such as HSCs[2], MSCs[3], NSCs[4], and epithelial stem cells [11]. The existence of stem cells, known as CSCs[5], has also been indicated inside the tumor masses or blood cancers with the potential to advance the metastasis and formation of premetastatic foci [12]. The translational significance of classifying stem cells helps develop disease modeling, drug screening, personalized medicine, and tissue engineering, as a strict scheme of classification becomes paramount at their interface [8]. Therefore, contemporary stem cell classification is based on multiple organizational frameworks, each reflecting distinct biological dimensions relevant to developmental biology, disease modeling, and regenerative medicine.

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1. Embryonic stem cells
2. Hematopoietic stem cells
3. Mesenchymal stem cells
4. Neural stem cells
5. Cancer stem cells

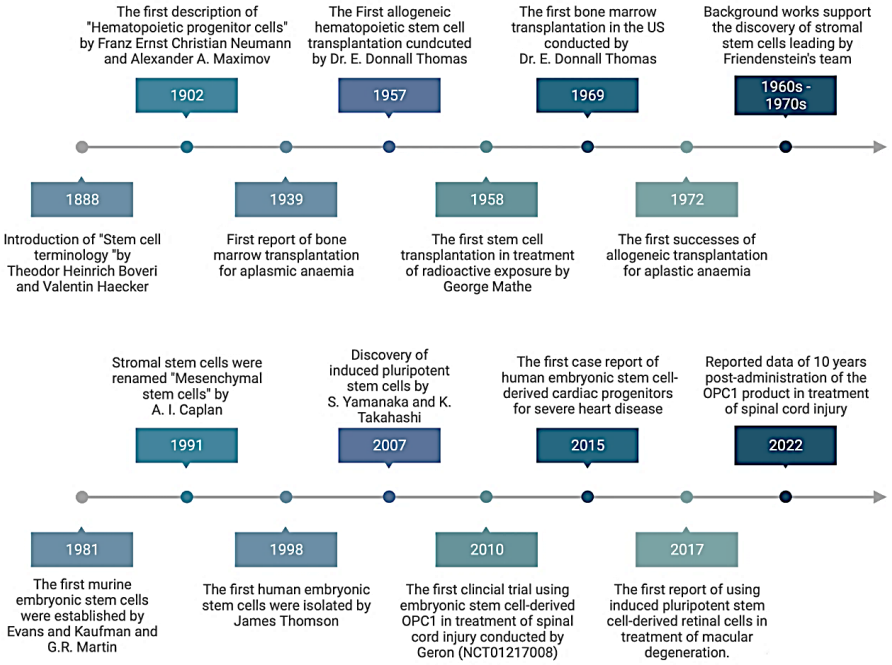

Figure 1. The timeline of discovery and advances in basic research and clinical applications of stem cells. Reproduced with permission. [13]. Signal Transduction and Targeted Therapy. 2022

2. Classification of stem cells based on developmental potential

Development potential is one of the primary tools for stem cell categorization, which includes a hierarchical limitation in terms of differentiation capacity along with embryonic development (**Table 1**) [14]. To be specific, this categorization is related to the potential for commitment into various cell lineages, starting from the highest potential status to generate all cell types [15]. The cell with the highest potential is the TSCs with the putative properties to orient into an entire organism. Besides, these cells exhibit the capacity to be sampled and expanded under laboratory conditions [16]. These can easily mature into all embryonic cells, leading to the development of the fetus and extraembryonic tissues such as trophectoderm, which further produce the placenta and yolk sac. Zygote and blastomere cleavage-stage

embryos are TSCs, which undergo epigenetic changes and transcriptome alterations by advancing embryo development [17, 18]. Monitoring the molecular profile has revealed the existence of developmental circumstances in these cells over time. In the zygote, the cell division initiates before implantation with interconnected cells [19]. Upon 8 to 16 cell stages on day 4 post-fertilization, the compaction phenomenon is initiated, resulting in the generation of a fluid-filled blastocyst composed of trophectoderm and the ICM[1] (**Figure 2**) [20].

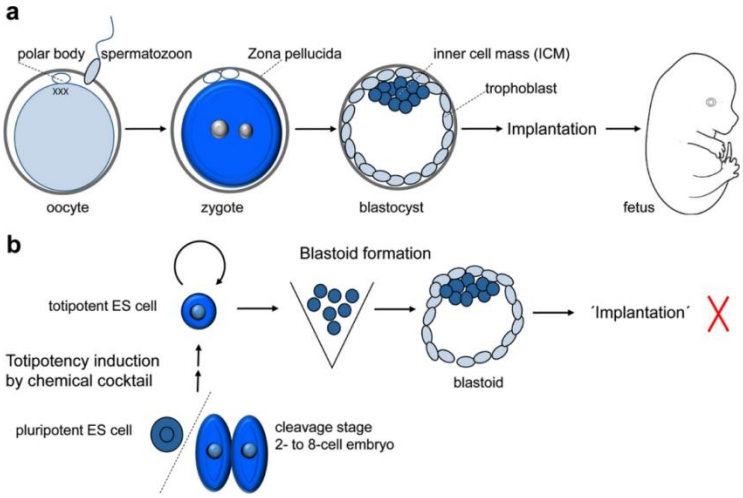

Figure 2. Totipotency in *in vivo* and *in vitro* conditions. Following fertilization leads to the generation of a totipotent zygote with the potential to develop into a fetus. It is suggested that in vivo totipotency is a transient condition in the zygote (**a**). In vitro totipotency (**b**). Totipotency can be stimulated in ESCs and early cleavages using culture medium supplemented with a defined cocktail. Using a 3D culture system, the totipotency can be induced via self-organization into the blastomere-like structures. Reproduced with permission. [21]. Signal Transduction and Targeted Therapy. 2022.

With the progression of the developmental stage, the transition from totipotent to pluripotent state begins, indicated by the loss of differentiation into extraembryonic tissues [3]. Recent data have revealed the eligibility of genetic manipulation approaches, epigenetic modifications, and

[1]. Inner cell mass

reprogramming strategies to generate totipotent-like cells in the laboratory setting via the modulation of certain signaling pathways [22]. These approaches can upregulate selected genes and transcription factors with distinct molecular profiles and functions. For instance, the expression of pluripotency genes, known also as Yamanaka factors, such as Oct4, Sox2, and Klf4, c-Myc increases along with the expression of factors involved in extraembryonic lineage commitment like Cdx2, Eomes, Gata3, and Ascl2 [23]. Like TSCs, PSCs[1] have the potential to generate all cell types belonging to ectoderm, endoderm, and mesoderm layers without the ability to produce extraembryonic tissues [14]. Due to the loss of totipotency in all epiblast layers in the blastocyte stage, ESCs with pluripotency are produced. Under such conditions, the induction of factors such as Oct4, Sox2, and Nanog proteins, along with SSEA4[2], TRA 1-60, and ALP,[3] can help the cells acquire the ESC phenotype [24].

[1]. Pluripotent stem cells
[2]. Stage-specific embryonic antigen-4
[3]. Alkaline phosphatase

Table 1. Comparison of stem cell potency levels: developmental capacity, representative examples, and key markers.

Potency Level	*Developmental Capacity*	*Representative Examples*	*Markers*
Totipotent	All embryonic and extraembryonic cell types	Zygote, early blastomeres (up to 2–4 cell stage), 2-cell-like cells	Oct4, Sox2, Nanog, Cdx2, Eomes
Pluripotent	All three germ layers (embryonic tissues only)	ESCs, iPSCs	Oct4, Sox2, Nanog, SSEA-4, TRA-1-60
Multipotent	Multiple cell types within a restricted lineage or tissue	HSCs, MSCs, and NSCs	CD34, CD90 (HSCs); CD73, CD90, CD105 (MSCs); Nestin, Sox2 (NSCs)
Oligopotent	2–5 related cell types within a tissue	Epidermal stem cells, intestinal crypt stem cells	Integrin α6, CD71 (epidermal); Lgr5, Ascl2 (intestinal)
Unipotent	Single cell type only	Myogenic satellite cells, EPCs	Pax7 (myogenic); CD34, VEGFR2 (endothelial)

Abbreviations: Embryonic stem cells: ESCs, Induced pluripotent stem cells: iPSCs; Endothelial progenitor cells: EPCs; Hematopoietic stem cells: HSCs; Mesenchymal stem cells: MSCs; Neural stem cells: NSCs.

According to recent data, two PSC types, including ESCs and iPSCs,[1] have been identified in the human and animal systems. ESCs are directly isolated from the ICM of blastocysts in 5-to-7-day-old embryos, and these cells can morph into three germ layers in the presence of certain growth factors and cytokines [25]. While iPSC technology is a breakthrough invention in cell biology to manipulate mature cells to reprogram into a pluripotent state [26]. Takahashi and Yamanaka first transferred four transcription factors: Oct4, Sox2, Klf4, and c-Myc, using a retroviral vector to mouse fibroblasts and achieved a pluripotency state in these cells (**Figure 2**). Other approaches have also been used for the induction of pluripotency and iPSC production

[1]. Induced Pluripotent Stem Cells

using viral vectors, plasmids, proteins, RNAs, and small molecules. It is thought that advancing and progressing human iPSC technology facilitates personalized biomedicines, disease modeling, and autologous cell therapies [27, 28].

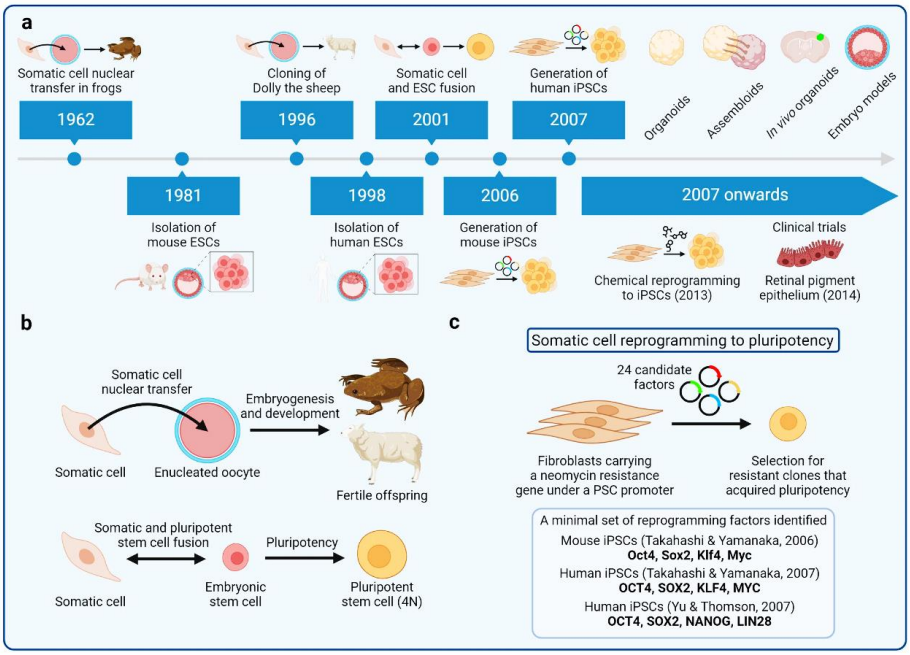

Figure 2. Technology of iPSCs. Timeline associated with advances in iPSCs technology (**a**). The SCNT[1] approach was used by John Gurdon in the African clawed frog (**b**: Top). It was suggested that somatic cells acquire the genetic data required for differentiation into a germline-competent organism. Successful SCNT modality was progressed in mammals by Keith Campbell, Ian Wilmut, and co-workers to clone Dolly the sheep. Masako Tada et al. found that pluripotency features can be induced via the fusion of somatic cells with ESCs, resulting in the formation of hybrid tetraploid cells (Bottom). Fibroblast reprogramming to iPSCs was done by Kazutoshi Takahashi and Shinya Yamanaka. For pluripotency induction, 24 factors were selected and delivered into mouse fibroblasts via viral vectors in various conditions (**c**). Takahashi and Yamanaka found that the combination of Oct4, Sox2, Klf4, and Myc is enough to induce a pluripotency state in mouse fibroblasts. In 2007, Yamanaka and James Thomson did the human fibroblast-to-iPSC reprogramming. Reproduced with permission. [26]. Signal Transduction and Targeted Therapy. 2024.

[1]. Somatic cell nuclear transfer

Both ESCs and iPSCs exhibit pluripotent states in the transcriptional, epigenetic, and signaling profiles. In naive PSCs derived from mouse ESCs and human PSC lines, the expression of specific genes coincides with reduced DNA methylation and histone modifications similar to preimplantation epiblasts. Primed PSCs exhibit features related to post-implantation epiblasts with intermediate DNA methylation and lower transcription of pluripotency factors [29, 30]. Compared to iPSCs and ESCs, multipotent stem cells also possess limited self-renewal and differentiation properties that originate from a single embryonic germ layer or certain tissues. In terms of stemness features, multipotent stem cells are between the USCs[1] and PSCs, with the key role in tissue homeostasis and the healing process following conditions with concomitant epigenetic alteration [31]. HSCs are a typical model of multipotential stem cells that exist in a hemopoietic niche, such as bone marrow, umbilical cord blood, after cytokine stimulation. Owing to self-renewal and long-term proliferation properties, HSCs can mature into different progenitors, followed by the production of all blood lineages like RBCs[2], platelets, neutrophils, lymphocytes, monocytes, and eosinophils. HSCs are identified using LTC-IC[3] assays and xenograft immunodeficient animal models [32, 33]. MSCs, also known as mesenchymal stromal cells, are multipotent stem cells in different tissues such as bone marrow, adipose tissue, umbilical cord tissue, and placenta, etc. [34]. Based on different studies and pre-clinical studies, MSCs exhibit prominent osteogenic (Runx2↑, Osterix↑, and ALP↑), chondrogenic (Wnt/β-catenin↑ and BMP↑), and adipogenic (PPARγ↑ and C/EBPα↑) capacity [1, 35-37]. The existence of significant

[1]. Unipotent stem cells
[2]. Red blood cells
[3]. Long-term culture-initiating cell

immunomodulatory properties and the release of several anti-inflammatory cytokines such as IL-10[1] and TGF-β[2] make MSCs a suitable candidate cell for immunotherapy applications [36, 37]. Likewise, NSCs are other multipotent cells located in the nervous system within the hippocampus, SVZ[3] , and the DG[4]. These cells have the self-renewal potential and produce several cell types, such as excitatory and inhibitory neurons, astrocytes, and oligodendrocytes [38, 39]. These cells are activated in response to external stimuli such as cytokines, such as EGF[5] and b-FGF[6]. To be specific, the integration of NSCs into the neurogenic niches is orchestrated via vascular, immune system, and other neuronal cells [38, 39]. OSCs[7] are tissue-specific progenitors with limited self-renewal and have the potential to give rise to a few cell lineages. For example, epidermal stem cells are in the epidermis' basal layer, and hair follicles can produce cutaneous tissue cells over time [40]. Similarly, $Lgr5^+$ intestinal stem cells produce enterocytes, goblet cells, enteroendocrine cells, as well as Paneth [41]. USCs with less potency scale, and self-renewal properties can mature into a single cell type [42]. Satellite cells are unipotent progenitors in skeletal muscles and have myogenic capacity via direct fusion with existing myofibers. EPCs[8] are another USC with angiogenesis properties and differentiate into vascular cells [43].

3. Classification based on tissue or physiological system

In this classification system, stem cells are categorized based on the origin of tissue. This approach helps in understanding how various stem

1. Interleukin-10
2. Transforming growth factor-β
3. Subventricular zone
4. Dentate gyrus
5. Epidermal growth factor
6. Basic fibroblast growth factor
7. Oligopotent stem cells
8. Endothelial progenitor cell

cell types function in different biological systems to preserve homeostasis with different tissue-specific features [44]. In this regard, HSCs play a key role in the continuous production of blood cells. These cells are in close contact with other cells, such as osteoblasts, adipocytes, endothelial cells, and stromal elements in the hematopoietic microenvironment [45]. In terms of hierarchical organization, HSCs consist of LT-HSCs[1] and ST-HSCs[2] , which are committed into CMPs[3], CLPs[4], and CMPs[5] [46]. In the clinical setting, allogenic HSCs have been used for regenerative purposes in patients with hematologic malignancies, inherited blood disorders, and certain inherited immune deficiencies. Recently, autologous HSCs were manipulated using globin gene therapy[6] and applied to sickle cell disease. In another strategy, cord blood HSCs were treated with nicotinamide[7] to improve recovery in hematology-related diseases [47, 48]. MSCs are heterogeneous cells originating from different tissues with broad applications in human medicine. These cells are immunophenotyped using the existence of cell membrane markers such as CD73, CD90, and CD105 [49]. Among different MSC sources, bone marrow MSCs, while adipose tissue MSCs are also at the center of attention for preclinical and clinical use. Compared to bone marrow MSCs, it has been shown that adipose tissue MSCs can be achieved with less invasive behavior, with comparable stemness features. WJ-MSCs[8] also have less immunogenicity and can be collected with minimal invasion [49]. MSCs are used for regenerative purposes based on the regulation of angiogenesis, inflammation, and

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1. Long-term repopulating hematopoietic stem cells
2. Short-term repopulating hematopoietic stem cells
3. Common multipotent progenitors
4. Common lymphoid progenitors
5. Common myeloid progenitors
6. Lyfgenia
7. Omisirge
8. Wharton's Jelly-derived mesenchymal stem cells

differentiation into the target injured cells [50]. NSCs can orient into neuroblasts via the rostral migratory stream to the olfactory bulb to generate GABAergic interneurons. The neurogenic properties of NSCs contribute to the restoration of spatial learning, memory formation, and cognitive flexibility [51]. During the last decades, NSCs have been used for neurodegenerative conditions such as SCI[1] and ischemic stroke [52]. Of course, iPSC-derived NSCs have been approved by the FDA[2] for the alleviation of pathological conditions in PD[3], SCI, and ALS[4]

4. Stem Cell Lines and Culture

ESC lines, as well as lines of iPSCs, are globally accepted cellular tools with a defined molecular profile for biological studies, drug screening, and tissue engineering purposes [53]. However, for preserving pluripotency in laboratory conditions, it is essential to consider several culture parameters. For example, growth factors such as FGF, Activin/Nodal, etc., along with the regulation of oxygen levels and nutrients, should be controlled [54]. In modern in vitro culture systems, the efficiency of pluripotency and expansion has been increased due to the existence of a feeder layer and the addition of chemically defined components, making this platform suitable for translational medicine [55, 56]. By progressing culture technology and 3D-based environments such as organoids, it is possible to educate stem cells to regulate their behavior and metabolic profile similar to the in vivo-like conditions [57]. The organoid system can be used for ESCs and various tissue stem cells for analyzing the impacts of various components and factors [58]. It has been thought that organoid systems

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1. Spinal cord injury
2. Food and Drug Administration
3. Parkinson's disease
4. Amyotrophic lateral sclerosis

are much more than only a tissue-like niche, and these platforms provide in vivo-like cues for modeling pathological conditions, such as drug screening. Notably, patient-derived organoids induced by real samples and biopsies can increase the data relevance in the laboratory setting to biological conditions in a personalized manner. Besides, recent progress in sophisticated organoid development using various modalities and bioprinting approaches can contribute to significant reproducibility [59, 60]. Using CRISPR/Cas9 systems or other gene editing approaches in ESCs and iPSCs, it is possible to functionally regulate genes for induction and/or mimicking various pathological conditions. This platform enables us to modify specific genes at different levels to correct and modify specific genes. It is thought that the combination of CRISPR/Cas9 systems and iPSC cells helps us to create isogenic control cell lines resembling the real genetic conditions. The concomitant insertion of reporter genes makes it easy to monitor cell development, differentiation, and certain metabolic conditions [56, 61].

5. Conclusions

Stem cell classification is done based on different parameters such as stemness, developmental features, anatomical location, origin, and functional assay. This classification system can help researchers and clinicians in understanding the intrinsic multidimensional natures and their regenerative potential. For a holistic understanding, it is essential to integrate all possible axes. For example, a single population of MSCs is simultaneously designated as multipotent (potency-based classification), adult somatic (origin-based classification), bone marrow-resident (anatomical location-based classification), and having immunomodulatory capacity (functional classification). The main advancements in the classification of various stem cell types can pave the way for further

implications in regenerative medicine, modeling of diseases, and drug development.

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