Cell Calcium 59 (2016) 57–66

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

Review

Physiology of Ca^{2+} signalling in stem cells of different origins and differentiation stages

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ARTICLE INFO

Article history:
Received 12 January 2016
Received in revised form 28 January 2016
Accepted 2 February 2016
Available online 17 February 2016

Keywords:
Stem cells
Ca^{2+} channels
Ca^{2+} signalling
Spontaneous Ca^{2+} oscillations
Intracellular $[Ca^{2+}]_i$ stores
Inositol trisphosphate
Ryanodine receptors
Glutamate
Purinergic receptors
Vasopressin
Oxytocin
Human embryonic stem cells
Neural precursors
Bone marrow mesenchymal stromal cells
Adipose tissue derived mesenchymal stromal stem cells
Human induced pluripotent stem cells
Cell differentiation
Neurodegeneration
Cell therapy
Transplantation

ABSTRACT

Stem cells (SCs) of different origins have brought hope as potential tools for the treatment of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Amyotrophic Lateral Sclerosis. Calcium signalling plays a key role in SC differentiation and proliferation, and dysregulation of Ca^{2+} homeostasis may instigate pathological scenarios. Currently, the role of ion channels and receptors in SCs is not fully understood. In the recent years, we found that (i) the pre-differentiation of human embryonic SCs (hESCs) led to the activation of Ca^{2+} signalling cascades and enhanced the functional activities of these cells, (ii) the Ca^{2+} homeostasis and the physiological properties of hESC-derived neural precursors (NPs) changed during long term propagation *in vitro*, (iii) differentiation of NPs derived from human induced pluripotent SCs affects the expression of ion channels and receptors, (iv) these neuronal precursors exhibited spontaneous activity, indicating that their electrophysiological and Ca^{2+} handling properties are similar to those of mature neurones, and (v) in mesenchymal SCs isolated from the adipose tissue and bone marrow of rats the expression profile of ion channels and receptors depends not only on the differentiation conditions but also on the source from which the cells were isolated, indicating that the fate and functional properties of the differentiated cells are driven by intrinsic mechanisms. Together, identification and assignment of a unique ion channel and a Ca^{2+} handling footprint for each cell type would be necessary to qualify them as physiologically suitable for medical research, drug screening, and cell therapy.

Abbreviations: AMSCs, adipose mesenchymal stem/stromal cells; AVP, arginine vasopressin; ATP, adenosine-5′-triphosphate; BM, bone marrow; BMSCs, bone marrow stem/stromal cells; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; CNS, central nervous system; CPA, cyclopiazonic acid; EC, embryonal carcinoma; ER, endoplasmic reticulum; ESCs, embryonic stem cells; GABA, *gamma*-aminobutyric acid; HVA, high voltage-activated; hESCs, human embryonic SCs; hESC-NPs, hESC-derived neural precursors; iPSCs, induced pluripotent stem cells; $InsP_3R$, inositol-1,4,5-trisphosphate receptor; LVA, low voltage activated; MSCs, mesenchymal stem/stromal cells; NCX, Na^+/Ca^{2+} exchanger; NGF, nerve growth factor; OT, oxytocin; pAMSCs, pre-differentiated AMSCs; pBMSCs, pre-differentiated BMSCs; PLC, Phospolipase-C; PMCAs, plasmamembrane-Ca^{2+}-ATPase; rMSCs, rat mesenchymal stem/stromal cells; ROCC, receptor-operated Ca^{2+} channels; RyR, ryanodine receptor; SCs, stem cells; SERCA, sarcoendoplasmic reticulum Ca^{2+}-ATPase; SOCs, store-operated Ca^{2+} channels; uAMSCs, undifferentiated AMSCs; uBMSCs, undifferentiated BMSCs; uSCs, undifferentiated SCs; LVA, voltage-activated; VEGF, vascular endothelial growth factor; VGCC, voltage-gated Ca^{2+} channels.

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http://dx.doi.org/10.1016/j.ceca.2016.02.001
0143-4160/

1. Introduction

Public and professional interest in stem cells (SCs) has risen markedly over the last few decades. Two Nobel Prizes in Physiology and Medicine, in 2007 and 2012, were awarded for research in this field. There are many reasons why SCs capture the imagination of so many researches. Firstly, understanding the unique properties of stem cells provides a deeper insight into cell biology and embryology. Secondly, SCs represent the basis for cell replacement therapies in a multitude of degenerative and traumatic diseases. Finally, SCs can serve as an *in vitro* model of various diseases as well as a tool for drug development. SCs of different origin display many differences in molecular phenotype, growth rate, cell marker expression, and the ability to differentiate. The mechanisms underlying these differences remain poorly understood. In particular, the repertoire, major properties and the role of ion channels and receptors in SCs are the subject of intense examination. In this review, we emphasize the notion that the type of SCs used in cell replacement therapies should be carefully chosen based not only on gene expression, morphological features, or cell surface markers, but also on their origin and functional properties correlated with the type of application. Furthermore, identifying the physiological profile of stem cells is essential for assessing the suitability of these cells for their potential use.

2. Historic remarks

"Generatio spontanea"—a theory of spontaneous life generation from nonliving things pronounced by ancient Greeks existed throughout many centuries when in 17th century Francesco Redi and later in 19th century Louis Pasteur by their experiments finally disapproved it and demonstrated that life cannot emerge spontaneously but only from pre-existing life—"*Omne vivum ex vivo*" [1]. This formula was further elaborated by Rudolf Virchow to: "*Omnis cellula e cellula*" [2], which proclaimed that all cells in the organism derive from pre-existing cells. Indeed, all the cells in multicellular organisms (including humans) arise from the fertilized egg, which effectively is the "totipotent" stem cell. The term "stem cell" or "*Stammzelle*" was introduced in 1868 by Ernst Haeckel [3], by which he meant the common cellular ancestor of all living forms. Somewhat later Haekel also applied this term to a fertilized egg [4] (see also Refs. [5,6]). By the beginning of the twentieth century, the notion of SCs had been firmly established, although they were not considered a specific cell population, but rather cells that were transiently formed during development as precursors for differentiated cells. Another meaning of the term 'stem cell' was introduced in 1896 by Arthur Pappenheim to describe the precursor cell of the red and white blood cells lineage [7]. Similar ideas of the common precursor for all blood cells were proposed by Alexandr Maximov, who appointed the lymphocyte to this role [8]. These discoveries not only founded the concept of haematopoietic lineages, but also described the existence of other types of SCs in the organism [5].

The simultaneous capacity of SCs to self-renew and to generate different cell types led to the development of two highly different lines of research. The first resulted as a continuation of work on the characterization and isolation of "true" haematopoietic SCs. The presence of mesenchymal progenitor cells in bone marrow has been documented since the late nineteenth century [9,10]. Goujon was the first to show the osteogenic potential of bone marrow [10]. In 1973, Friedenstein and colleagues showed that the osteogenic potential was a feature of a specific subgroup of cells termed colony-forming unit fibroblastic (CFU-f) cells representing a heterogeneous population of stem and progenitor cells [11,12]. All these experiments provided the theoretical basis for bone marrow transplant studies and started mesenchymal stem/stromal cells (MSCs) research.

The second line of research focused on pluripotent SCs and began in the 1950s from the studies of teratocarcinomas, the latter being malignant germ cells tumours composed of undifferentiated embryonal carcinoma (EC) cells that can include all three germ layers [13]. Subsequently, the EC cells were shown to be capable of both unlimited self-renewal and multilineage differentiation [14], providing a ground for the further generation of embryonic stem cells (ESCs). Isolation and maintenance of mouse ESCs *in vitro* was, for the first time, reported independently by Sir Martin Evans together with Matthew H. Kaufman [15] and by Gail Martin [16]. Somewhat later, in 1998, Thomson and colleagues generated ESCs from human blastocyst [17]. In 2007 Mario J. Capecci, Martin J. Evans and Oliver Smithies shared a Nobel Prize for the "discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells". The establishment of human embryonic stem cells (hESCs) stimulated the rapid rise of stem cell research as well as worldwide debates about the ethical issues of using human embryos, which waned after the discovery of induced pluripotency [18]. The newly generated induced pluripotent stem cells (iPSCs) were produced by reprogramming mature somatic cells to a pluripotent state by gene transfer and possessed properties similar to ESCs. Similar to MSCs, iPSCs can be generated from a patient's cells, allowing "personalized medicine". At the same time, due to their pluripotency, the iPSCs have broader differentiation potential and therapeutic applications compared to MSCs. The importance of this research was recognized by the Nobel Prize committee, who later awarded the 2012 Nobel Prize in Medicine and Physiology to Sir John B. Gurdon and to Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent".

3. Definition and fundamental properties of SCs

Stem cells are defined as undifferentiated, karyotypically normal cells that have the capacity of self-renewal as well as the ability to generate differentiated cells [19]. Self-renewal is the ability to generate at least one identical copy of the mother cell, and is the most important criterion of "stemness". The ability of cells to differentiate into other cell types is known as cell potency. Characteristic SCs are classified as totipotent, pluripotent and multipotent. Totipotent cells can give rise to all cell types, including cells of the trophectoderm lineage. In mammals, only zygote and early blastomeres (up to 8-cell stage) are totipotent. Pluripotent cells can generate the cells of all three germ layers as well as germline, but not the extraembryonic trophoblast. Multipotent cells can give rise to a restricted subset of tissue-specific cell types (within one germ layer). Based on the time of appearance, SCs can be further sub-classified into ESCs, which occur during embryogenesis, and somatic or adult-derived stem cells, that are present in different tissues in postnatal life. Correspondingly, SCs can be isolated from embryonic, foetal or adult tissues.

The SC lines have been characterized by their developmental potential, transcriptional and epigenetic profiles, cell-surface markers and teratomas formation in nude (*i.e.* immunosuppressed) mice. The criteria for these assessments include the expression of surface markers and transcription factors associated with the undifferentiated state. In addition proliferative capacity, pluripotency and euploid karyotype as well as epigenetic status are being assessed [20]. Several approaches have been used to characterize SCs, but the most widespread are analyses of the cell surface-antigen phenotype, often by flow cytofluorimetry, and gene expression studies, commonly assessed by RT-PCR or by microarray analyses. These methods are the first, and very often