Advances in Medical Sciences 59 (2014) 273–280

Contents lists available at ScienceDirect

Advances in Medical Sciences

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

Review Article

Very small embryonic-like stem cells as a novel developmental concept and the hierarchy of the stem cell compartment

Mariusz Z. Ratajczak [a,b,*], Krzysztof Marycz [c,d], Agata Poniewierska-Baran [a,b], Katarzyna Fiedorowicz [b], Monika Zbucka-Kretowska [e], Marcin Moniuszko [f,g]

[a] Stem Cell Institute at James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA
[b] Department of Physiology, Pomeranian Medical University, Szczecin, Poland
[c] University of Environmental and Life Sciences, Electron Microscopy Laboratory, Wroclaw, Poland
[d] Wroclaw Research Centre EIT+, Wroclaw, Poland
[e] Department of Reproduction and Gynecological Endocrinology, Medical University of Bialystok, Bialystok, Poland
[f] Department of Regenerative Medicine and Immune Regulation, Medical University of Bialystok, Bialystok, Poland
[g] Department of Allergology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland

ARTICLE INFO

Article history:
Received 30 April 2014
Accepted 4 August 2014
Available online 14 August 2014

Keywords:
Pluripotent stem cells
Multipotent stem cells
Stem cell hierarchy
Development

ABSTRACT

Our current understanding of stem cells suffers from a lack of precision, as the stem cell compartment is a broad continuum between early stages of development and adult postnatal tissues, and it is not fully understood how this transition occurs. The definition of stem cell pluripotency is adapted from embryology and excludes the possibility that some early-development stem cells with pluri- and/or multipotential differentiation potential may reside in postnatal tissues in a dormant state in which they are protected from uncontrolled proliferation and thus do not form teratomas or have the ability to complement blastocyst development. We will discuss the concept that a population of very small embryonic-like stem cells (VSELs) could be a link between early-development stages and adult stem cell compartments and reside in a quiescent state in adult tissues. The epigenetic mechanism identified that changes expression of certain genes involved in insulin/insulin-like growth factor signaling (IIS) in VSELs, on the one hand, keeps these cells quiescent in adult tissues and, on the other hand, provides a novel view of the stem cell compartment, IIS, tissue/organ rejuvenation, aging, and cancerogenesis.

Contents

* Corresponding author at: Stem Cell Institute at James Graham Brown Cancer Center, University of Louisville, 500 South Floyd Street, Rm. 107, Louisville, KY 40202, USA. Tel.: +1 502 852 1788; fax: +1 502 852 3032.
E-mail address: mzrata01@louisville.edu (M.Z. Ratajczak).

http://dx.doi.org/10.1016/j.advms.2014.08.001
1896-1126/

1. Introduction

Stem cell research and regenerative medicine, perhaps more than any other topics in current biology and medicine, generate controversy beyond the bounds of scientific inquiry. The causes of these controversies are patent disputes stemming from the financial interests of biotech companies, religious beliefs, and political issues. However, scientists should remain open to new ideas, and science should stay free of these collateral problems and dogmas that, in many cases, have slowed progress in uncovering scientific truth.

In this review, we will discuss the accumulating evidence that the stem cell compartment in adult tissues is a continuum of embryonic development, and some early-development stem cells with multi-tissue differentiation potential may survive into adulthood [1–11]. Such cells have been described by many investigators and, depending on the methods for how they were isolated, assigned different names, for example, spore-like stem cells, multipotent adult stem cells (MASCs) [12], mesenchymal stem cells (MSCs) [13–15], multilineage-differentiating stress-enduring (Muse) cells [16–18], multipotent adult progenitor cells (MAPCs) [19,20], unrestricted somatic stem cells (USSCs) [21], marrow-isolated adult multilineage-inducible (MIAMI) cells, multipotent progenitor cells (MPCs) [12,23] and, as described by us a decade ago, very small embryonic-like stem cells (VSELs) [24–27]. This has created a kind of nomenclatural chaos, and probably several of these stem cells described as separate entities are in fact overlapping populations of similar cells. Furthermore, we envision that VSELs are on the top of hierarchy of all these various overlapping populations of stem cells endowed with pluti/multipotent differentiation potential [1].

In this review, we will discuss the concept that adult tissues contain cells from the early-development stem cell compartment and that in adult tissues there is a developmental continuum including stem cells with characteristics of pluripotent stem cells (PSCs) or multipotent stem cells (MultiSCs). These cells coexist in a dormant state together with already differentiated tissue-committed stem cells (TCSCs).

It is logical that such early-development PSCs and MultiSCs are protected from uncontrolled proliferation, because otherwise they would form teratomas. We have demonstrated that one of the mechanisms that keep most-primitive stem cells quiescent in adult tissues is based on epigenetic modification of somatically imprinted genes that govern pathways related to development and insulin/insulin-like growth factor signaling (IIS) [28–30]. This mechanism, known very well to regulate the quiescence of primordial germ cells (PGCs) [31–33], was also reported by us for the first time to operate in stem cells isolated from adult tissues, as seen in case of VSELs [34,35]. This original report has been supported by recent papers showing that early-development stem cells residing in adult tissues are also regulated by epigenetic modification of the imprinted genes involved in IIS [36].

Identification of early-development stem cells in adult tissues raises several questions, such as: (i) Are these cells functional and do they play a role in tissue/organ rejuvenation? (ii) Are they involved in regulating life span of the individual? (iii) Are they involved in regeneration of damaged tissues? (iv) If regulatory mechanisms fail, could these cells give rise to malignancies?

We will try to address these questions in this review as well as to address whether these cells could be a potential target for manipulations such as pharmacological, dietary and physical exercise approaches to extending our quality of life and life span.

2. Review

2.1. Definitions of stem cell pluripotency and multipotency

A pluripotent stem cell (PSC) is a stem cell endowed with the ability to differentiate into cells from all three germ layers (meso-, ecto-, and endoderm) as well as into germline cells. Based on research with embryonic stem cells (ESCs), several in vitro and in vivo criteria to classify a given stem cell as pluripotent have been proposed. According to the proposed definition, PSCs display undifferentiated morphology, undifferentiated euchromatin, a high nuclear/cytoplasm ratio, PSC markers (e.g., Oct-4, Nanog, SSEA), and bivalent domains reviewed in our recent publications [37,38]. Moreover, female PSCs reactivate the X chromosome and, as mentioned above, all PSCs must be able to differentiate into cells from all three germ layers (meso-, ecto- and endoderm) as a sign of their multilineage differentiation potential. Finally, based on research with ESCs isolated from embryos, special emphasis has been put on in vivo criteria, such as the ability of these cells to complement blastocyst development and to grow teratomas after inoculation into immunodeficient mice.

We would like to point out that these in vivo criteria proposed by embryologists do not take into consideration that at a certain point in development, PSCs may undergo epigenetic modifications and, despite the fact that they express several markers of PSCs, may be kept quiescent, with their pluripotency locked to reduce the risk of teratoma and tumor formation [39,40]. However, the most important question here is whether this quiescent state is fully reversible and whether such cells could regain pluripotency to comply with the definition proposed by embryologists.

It is well known that even normal somatic cells can be made to revert to a state of pluripotency, as seen in the case of induced pluripotent stem cells (iPSCs), which are generated in vitro by appropriate genetic manipulations. It is obvious that the requirements for unlocking the mechanism that enables PSCs to reside in adult tissues in a dormant state should be much simpler to achieve than in the case of iPSCs and should not affect genomic stability, as seen in the case of iPSCs generated by transduction with retroviruses encoding a cocktail of genes. In support of this expectation, primordial germ cells (PGCs), which due to epigenetic changes based on erasure of regulatory regions in some parentally imprinted genes are locked in a dormant state, can revert to full pluripotency after coculture on murine fetal fibroblasts in the presence of recombinant kit ligand (KL), leukemia inhibitory factor (LIF), and basic fibroblast growth factor (bFGF-2) [41,42]. This interesting phenomenon will be discussed latter in this review. Furthermore, the definitions of in vitro and in vivo criteria of pluripotency are somewhat vague, as demonstrated in the case of epiblast-generated, embryo-derived pluripotent stem cell lines. In many cases, depending on the developmental stage of the embryo, such cells can give rise to all three germ layers in vitro but neither complete blastocyst development nor grow tertomas in experimental animals [31–34,37,43].

In contrast to PSCs, multipotent stem cells (MultSCs) are already more committed in development and are able to give rise not to three germ layers as for PSCs but to cells from two germ layers only. As already mentioned, evidence has accumulated that cells with broader pluripotent or multipotent differentiation potential can be isolated from adult tissues, and their potential origin will be discussed below. These cells are precursors of TCSCs and example of cells that are already committed to one developmental lineage are hematopoietic stem cells (HSCs), skeletal muscle satellite stem cells or epidermal stem cells [1].