Japanese Dental Science Review (2017) xxx, xxx—xxx

Contents lists available at ScienceDirect

Japanese Dental Science Review

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

Review Article

Two novel mechanisms for maintenance of stemness in mesenchymal stem cells: SCRG1/BST1 axis and cell—cell adhesion through N-cadherin☆

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Received 11 April 2016; received in revised form 12 September 2017; accepted 18 October 2017

KEYWORDS
Mesenchymal stem cells;
Stemness;
CD271/LNGFR;
CD106/VCAM1;
SCRG1/BST1 axis;
N-cadherin

Summary Mesenchymal stem cells (MSCs) retain the ability to self-renew and differentiate into mesenchymal cells. Therefore, human MSCs are suitable candidates for use in regenerative medicine and cell therapies. Upon activation by tissue damage, MSCs contribute to tissue repair through a multitude of processes such as self-renewal, migration, and differentiation. However, loss of self-renewal and multi-lineage differentiation potential occurs at a high rate during cell doubling. Effective MSC therapies require the establishment of new techniques that preserve MSC multipotency after lengthy cell expansions. Here, two novel mechanisms are described for maintenance of stemness in MSCs *via* scrapie responsive gene 1 (SCRG1)/bone marrow stromal cell antigen-1 (BST1) ligand—receptor combination and cell—cell adhesion through N-cadherin. These two mechanisms findings provide a valuable tool for regenerative medicine and cell therapeutic methods that require the *ex vivo* expansion of human MSCs while maintaining native stem cell potential.

☆ Scientific field of dental science: Stem cell biology.

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http://dx.doi.org/10.1016/j.jdsr.2017.10.001

Please cite this article in press as: Chosa N, Ishisaki A. Two novel mechanisms for maintenance of stemness in mesenchymal stem cells: SCRG1/BST1 axis and cell—cell adhesion through N-cadherin. Japanese Dental Science Review (2017), http://dx.doi.org/10.1016/j.jdsr.2017.10.001

Contents

Introduction

Regenerative medicine and cell therapies have garnered attention as innovative methods for the treatment of serious diseases resulting from malfunctions or defects of the body. Cells used in these regenerative therapies include multipotent cells such as adult stem cells and embryonic stem (ES) cells. Recently, the advent of induced pluripotent stem (iPS) cells has contributed further to the development of regenerative medicine by removing ethical and immune barriers.

Mesenchymal stem cells (MSCs) are adult stem cells with the ability to differentiate into mesenchymal cells such as osteoblasts, adipocytes, chondrocytes, and fibroblasts, while retaining self-renewal and migration abilities [1]. In stem cell therapy, human MSCs are expanded *in vitro* and subsequently auto-implanted, eliminating the risk of immune rejection. Upon activation by tissue damage *in vivo*, MSCs contribute to tissue-repair through a multitude of processes such as self-renewal, migration, and differentiation. Human MSCs, first derived from bone marrow, have now been isolated from various tissues such as subcutaneous adipose, articular cartilage, and synovial membrane tissues [2—5]. Isolation of MSCs from a population of various cell types requires the use of cell surface markers. MSCs have been established that fulfill the following criteria: (i) adhering to plastic culture dishes; (ii) being positive for the markers CD73 (ecto-5′-nucleotidase, *NT5E*), CD90 (Thy-1 cell surface antigen, *THY1*), and CD105 (endoglin, ENG); (iii) being negative for the markers CD34, CD45 (leukocyte common antigen, *LCA*), HLA-DR, CD14, CD11b (integrin αM, *ITGAM*), CD79a (immunoglobulin-associated α), and CD19; and (iv) differentiating into osteoblasts, adipocytes, and chondrocytes *in vitro* [6]. In addition to these previously known cell surface markers, useful markers for isolating MSCs and maintaining multipotency have been identified. Recently, Mabuchi et al. reported that human MSCs that are positive for CD271 (low-affinity nerve growth factor receptor, *LNGFR* or p75 neurotrophin receptor, p75NTR) and CD90 and that are highly positive for CD106 (vascular cell adhesion molecule-1, *VCAM1*) retain high propensities for both of self-renewal and multipotency [7]. Thus, the combination marker LNGFR^{+}THY1^{+}VCAM1^{high+} (LTV) can be used to isolate potent human MSCs.

Because of their rarity *in vivo*, MSCs could be used after expansion for therapies in regenerative medicine [8]. *Ex vivo* expanded MSCs have been used for bone regeneration [9]. However, long-term *in vitro* culture of MSCs attenuates their ability for self-renewal and multipotency [10]. After a long period of *ex vivo* expansion, MSCs become large and flat and lose their ability to divide. *In vitro* expansion of MSCs is associated with gradual accumulation of senescent cells [11], telomere erosion [12], and changing phenotypes [13,14]. Thus, *ex vivo* expansion of MSCs seems to degrade multipotency; it is thus important to establish novel MSC expansion techniques that do not sacrifice multipotency even after long-term culture. For regenerative medicine and cell therapeutic purposes, this issue must be addressed. In this review, expression of the cell surface markers CD271 and CD106 and report novel trigger mechanisms for activation of the intracellular signaling pathway that regulates the maintenance of stem-like features, such as migration, self-renewal, and multipotency.

Maintenance of stemness by a novel ligand—receptor combination

Identification of SCRG1 as a novel ligand in MSCs

The gene expression of a cysteine-rich cytokine-like peptide, scrapie responsive gene 1 (*SCRG1*, also known as stimulator of chondrogenesis 1), was found to decrease during osteoblastic differentiation of human bone marrow-derived MSCs by using DNA microarray analysis [15]. Therefore, SCRG1 is expressed only in undifferentiated MSCs. While the function of SCRG1 is unknown, its expression was found to increase in the brains of mice infected with scrapie [16]. Recent studies by Dron et al. have reported that SCRG1 is involved in neurodegeneration and autophagy associated with transmissible spongiform encephalopathy due to scrapie infection [17,18]. SCRG1 is highly conserved in vertebrates and it consists of 98 amino acid residues,

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