Cellular Immunology 315 (2017) 1–10

Contents lists available at ScienceDirect

Cellular Immunology

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

Review article

Toll-like receptors as a key regulator of mesenchymal stem cell function: An up-to-date review

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ARTICLE INFO

Article history:
Received 23 July 2016
Revised 7 December 2016
Accepted 24 December 2016
Available online 26 December 2016

Keywords:
Toll-like receptor
Mesenchymal stem cell
Mechanism
Therapeutic use
Immunology

ABSTRACT

Understanding the role of toll-like receptors (TLRs) in the immunomodulation potential, differentiation, migration, and survival of mesenchymal stem cells (MSCs) is absolutely vital to fully exploiting their MSC-based therapeutic potential. Furthermore, through recognition of exogenous or endogenous ligands produced upon injury, TLRs have been linked to allograft rejection and maintenance of chronic inflammatory diseases, including Crohn's disease, rheumatoid arthritis. Characterizing the effect of TLRs in biological control of MSCs fate and function could improve our knowledge about the MSC-based cell therapy and immunotherapy. In this paper, we outline the impacts of TLR activation and mechanisms on MSCs immunomodulatory functions, differentiation, migration, and survivability. Moreover, we indicate that the expression patterns of TLRs in MSCs from different sources.

Contents

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http://dx.doi.org/10.1016/j.cellimm.2016.12.005
0008-8749/

1. Introduction

Mesenchymal stem cells (MSCs) are non-hematopoietic stem cells [1]. These cells can be isolated from mesoderm [2] endoderm, and ectoderm, which are three germ layers in the embryo [3]. MSCs approximately constitute 0.01% of bone marrow nucleated cells [1]. MSCs could differentiate into various types of cells, including adipocytes, osteoblasts, chondrocytes, myocytes, β-pancreatic islets cells, marrow stroma, tendon, and, potentially, neuronal cells in standard culture conditions (Fig. 1) [4–6].

In humans, these cells can also be isolated from other sources such as bone marrow [7], adipose tissues [8], synovial membrane [9], dental pulp [10], dermis [11], trabecular bone [12,13], pericytes [14–16], periosteum [9,17], umbilical cord blood [18], placenta [19], fetal liver [20], and amniotic fluid (Fig. 1) [21].

MSCs are powerful therapeutic tools in clinical practices due to their features such as self-renewal and multi-lineage differentiation capacity repair of tissue damage and lack of co-stimulatory molecules such as human leukocyte antigen class-II (HLA-II) CD80 and CD86 [22–24]. MSCs are attractive tools employed in MSC-based therapy for the progressive injuries in bone cartilage tendon skeletal muscle and other mesodermal tissues

The main aims of MSC-based therapy as follows: first, sufficient amount of MSCs (it depends on the type of therapy, but generally, the optimal dosage of MSCs in therapeutic applications is $1.0–2.0 \times 10^6$ MSCs/kg body weight) [25]; second, improving the survivability of MSCs and preventing their apoptosis; third, inducing the differentiation of MSCs into the target tissues; and fourth, repairing injuries via migration of MSCs into injured tissues [1,26]. We require a better understanding of factors and mechanisms influencing on the biological functions of MSCs in order to achieve these aims. One of these factors is the activation and mechanisms of toll-like receptors (TLRs) involved in MSC function. MSCs are then exposed to TLR ligands at the sites of injury or inflammation, resulting in the activation of the receptors. In addition, a number of endogenous ligands (danger signals) such as heat shock protein 70 (HSP-70), fibronectin extra domain A, and intracellular contents produced upon injury can activate the TLRs on the surface of MSCs [22].

Other factors such as cell-to-cell contact and soluble factors secreted by MSCs, for instance, hepatocyte growth factor (HGF), indoleamine 2,3-dioxygenase (IDO), interleukin 10 (IL-10), transforming growth factor-β1 (TGF-β1), and nitric oxide (NO) might modulate MSCs function [27–36].

In vivo utility of MSCs in the treatment of many inflammatory diseases, tissue injury, and allograft rejection necessitates identifying key factors involved in MSCs immune properties, multi-lineage differentiation potential, migration, and survivability in different animal models.

TLRs are type I single-pass transmembrane proteins, either situated in the plasma membrane (such as TLR1, TLR2, TLR4, TLR5, and TLR6) [37], or membranes of endosomes and lysosomes (TLR3, TLR7, TLR9, TLR10, TLR11, TLR12, and TLR13) in different cell types. The Toll gene was first discovered in 1985 by Christiane Nüsslein-Volhard [38] in *Drosophila melanogaster* in relation to their key roles in antifungal immune responses [39] and neural development [40]. *MyD88* (myeloid differentiation primary-response protein 88)-*dependent* (production of inflammatory

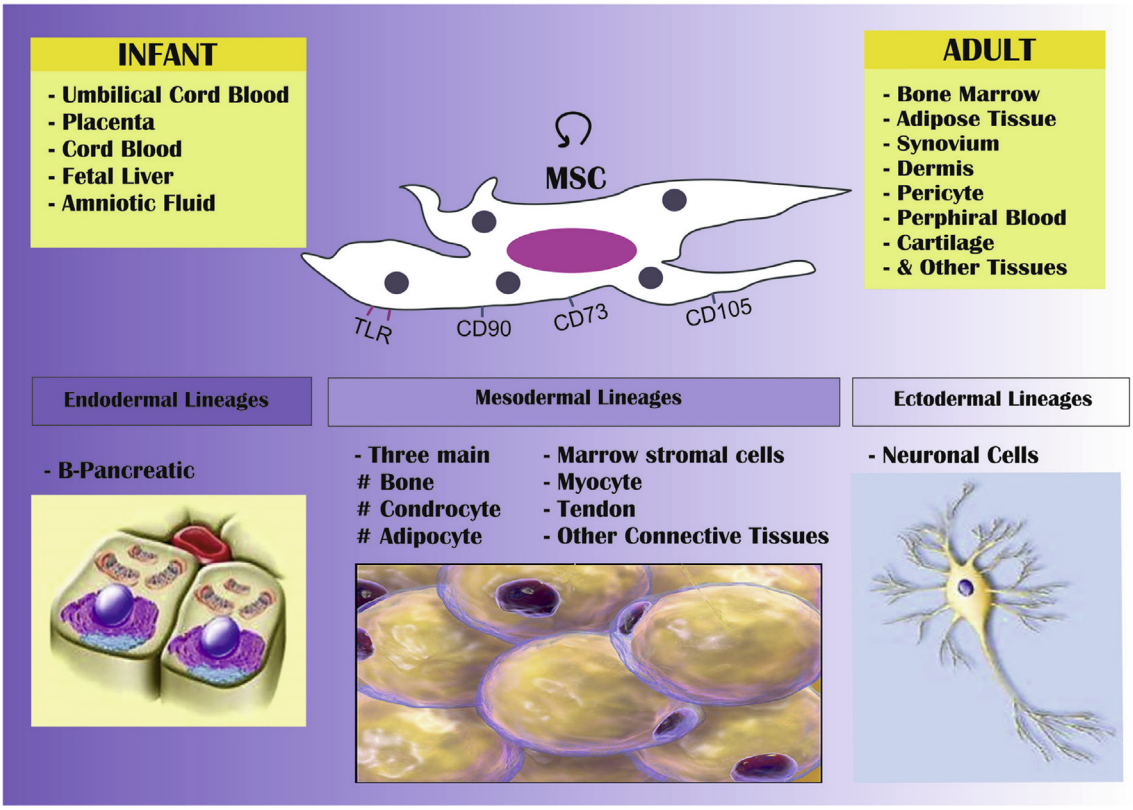

Fig. 1. MSCs can derived from various sources and differentiate into multiple cell lineages. Mesenchymal stem cells (MSCs) can differentiate into various types of cells, including adipocytes, osteoblasts, chondrocytes, myocytes, β-pancreatic islets cells, marrow stroma, tendon, and, potentially, neuronal cells in standard culture condition. In 2006, ISCT proposed the following three main criteria for defining MSCs: first, MSCs must be plastic-adherent; second, they must express markers such as CD105, CD73, and CD90 and lack of expression CD45, CD31, and HLA-DR; and third, they must have a tri-lineage differentiation potential (differentiate into adipocytes, osteoblasts, and chondrocytes as three main mesodermal lineages) [4]. Since 2006, new markers for MSCs have been identified by researchers. However, presently, there are no uniform or specific markers for identifying MSCs isolated from different sources. MSCs can be isolated from various types of tissues in infants and adults, including bone marrow (main source), synovium, adipose, cartilage, peripheral blood, placenta, fetal liver, cord blood, and amniotic fluid.