Acta Histochemica xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Acta Histochemica

journal homepage: www.elsevier.de/acthis

Review

Bioactive molecules derived from umbilical cord mesenchymal stem cells

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ARTICLE INFO

Article history:
Received 26 July 2016
Received in revised form 5 September 2016
Accepted 19 September 2016
Available online xxx

Keywords:
Umbilical cord mesenchymal stem cell
Cytokine
Immunoregulation
Angiogenesis
Nerve regeneration
Anti-tumor

ABSTRACT

Umbilical cord mesenchymal stem cells (UCMSCs) retain their intrinsic stem cell potential while at the same time displaying high proliferation rates, powerful differentiation capacity, and low immunogenicity. They can also secrete multiple bioactive molecules that exert specific physiological functions. Thus, UCMSCs represent excellent candidates for cell therapy in regenerative medicine and tissue engineering. Abundant preclinical research on different disease models has shown that UCMSCs can accelerate wound or nerve damage recovery and suppress tumor progression. In fact, UCMSCs are thought to possess a higher therapeutic potential than MSCs derived from other tissues. Increasing evidence suggests that the mechanism underlying UCSMCs efficacy depends mostly on cell secretions, in contrast to the early paradigm of cell replacement and differentiation. In this review, we discuss UCMSCs biological characteristics, their secretome-based therapeutic mechanism, and potential applications.

Abbreviations: ACTH, adrenocorticotropic hormone; aFGF, acidic fibroblast growth factor; Akt, activation of protein kinase B; ANG, angiogenin; ASCs, adipose tissue-derived mesenchymal stem cells; B7-H1, B7 homolog 1; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; BMSCs, bone marrow-derived MSCs; CCL, chemokine (C-C motif) ligand; CM, conditioned medium; CSF, colony-stimulating factors; CX3CL, CX3C chemokine ligand; CXCL, chemokine (C-X-C motif) ligand; EGF, epidermal growth factor; EGF-R, epidermal growth factor receptor; ELISA, enzyme-linked immunosorbent assay; DCs, dendritic cells; G-CSF, granulocyte colony stimulating factor; GDNF, glial cell-derived neurotrophic factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GITR, glucocorticoid induced Tnf receptor; GSK, glycogen synthase kinase; HGF, hepatocyte growth factor; ICAM, intercellular adhesion molecule; IDO, indoleamine 2 3-dioxigenase; IFN, interferon; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; IκK, inhibitor of kappa B kinase complex; IκB, inhibitor of kappa B; IL, interleukins; IL-1ra, interleukin-1 receptor antagonist; IP-10, IFN-gamma-inducible protein-10; LIF, leukemia inhibitory factor; LIGHT, homologous to lymphotoxins,inducible competes with HSV glycoprotein D for HVEM expressed by T lymphocyte; LPS, lipopolysaccharide; MCP, monocyte chemotactic protein; MDC, macrophage-derived chemokine; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; MSCs, mesenchymal stem cells; MS/MS, tandem mass spectrometry; MMP, matrix metalloprotease; NFκB, nuclear factor κB; NGF, nerve growth factor; NGFR, nerve growth factor receptor; NT-3, neurotrophin-3; NK, natural killer; PAI, plasminogen activator inhibitor; PDPK1, phosphoinositide dependent protein kinase 1; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; PGF, prostaglandin f; PI3K, phosphatidylinositol 3-kinase; PLGF, lacental growth factor; pSS, primary sicca syndrome; RANTES, regulated upon activation normal T-cell expressed and secreted; SCF, stem cell factor; SDF, stromal cell-derived factor; SLE, systemic lupus erythematosus; sVEGF-R, soluble VEGF receptors; TCF, transcription factors; TGF, transforming growth factor; Tie, tyrosine kinase with immunoglobulin-like and EGF-like domains; TIMP, metalloproteinases; TLR, toll-like receptor; TNF, tumor necrosis factor; TNFR, TNF receptor; TPO, thrombopoietin; TRAIL, Tnf related apoptosis inducing ligand; UCMSCs, umbilical cord mesenchymal stem cells; VEGF, vascular endothelial growth factor.

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http://dx.doi.org/10.1016/j.acthis.2016.09.006
0065-1281/

1. Introduction

Mesenchymal stem cells (MSCs) are multipotent adult stem cells capable of self-renewal that have been isolated from many different tissues, such as bone marrow, adipose tissue, umbilical cord blood, peripheral blood, dermis, liver, skin, and skeletal muscle (Rhee et al., 2015). They are promising tools in cell therapy (Malgieri et al., 2010) and have shown therapeutic efficacy against autoimmune, inflammatory, and degenerative diseases (Maxson et al., 2012; Pati et al., 2010; Shohara et al., 2012; Ullah et al., 2015; van den Akker et al., 2013; Zimmerlin et al., 2013). MSCs have been extensively applied to treat various conditions in animal models (Rastegar et al., 2010), such as rheumatic diseases (Maumus et al., 2013), spinal cord injuries (Dasari, 2014; Ryu et al., 2012), musculoskeletal regeneration (Steinert et al., 2012; Wang et al., 2015), and wound healing (Kim et al., 2013b). Preclinical trials using MSCs have shown encouraging signs for curing a range of otherwise difficult-to-treat diseases. Understanding the molecular and biochemical mechanisms defining MSCs is the key to their therapeutic application. Several studies have demonstrated that multilineage differentiation capacity, immunomodulatory role, homing ability, and strong paracrine capacity of MSCs contribute to tissue repair (Liang et al., 2014). Trans-differentiation into multiple cell lineages, including osteocytes, chondrocytes, adipocytes, cardiomyocytes, islet-like cells, neurocytes, and fibroblasts, enables the replacement of local damaged cells and tissues. MSCs also play an immunomodulatory role when they interact with immune cells and inflammatory factors. Moreover, MSCs display a dramatic homing ability towards tumors and pathological sites. Cultured MSCs secrete valuable factors whose therapeutic effects can be classified into six main categories: immunomodulation, anti-apoptosis, angiogenesis, support for growth and differentiation of local stem and progenitor cells, anti-scarring, and chemoattraction (Meirelles Lda et al., 2009). Primary trophic secretion components include growth factors, chemokines, and anti-inflammatory proteins (Murphy et al., 2013). Regulation of MSC secretions depends on different stimuli, such as hypoxia, pro-inflammatory stimuli, and three-dimensional growth. The most physiologically relevant factors present in MSC conditioned medium (CM) are hepatocyte growth factor (HGF), transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), secreted product of tumor necrosis factor (TNF)-stimulated gene-6, prostaglandin E2 (PGE2), and galectins 1 and 9 (Bigildeev et al., 2015; Madrigal et al., 2014). Depending on their source, MSCs possess different proliferation capacity, as well as transcriptome, proteome, and secretome profiles, which define their regenerative, homing, and immunomodulatory activities (El Omar et al., 2014). Therefore, the purpose of many current studies is to find an optimal cell source for clinical therapy (Barberini et al., 2014; El Omar et al., 2014; Kim et al., 2013a; Troyer and Weiss, 2008). Bone marrow-derived MSCs (BMSCs) are still the most frequently researched cell type and are often considered as the gold standard (Hass et al., 2011). However, they require invasive harvesting procedures (Martins et al., 2014) and their use is limited by the likelihood of viral exposure, possibility of donor morbidity, and significant decrease in cell number and proliferation/differentiation capacity with age (Yoo et al., 2009). Umbilical cord blood-derived MSCs are hampered by very low yields, but present clear advantages associated with their origin from umbilical cord blood such as haematopoietic reconstitution (Secco et al., 2008). Although human adipose tissue-derived mesenchymal stem cells (ASCs) and UCMSCs share considerable similarities in their immunological phenotype and pluripotency, UCMSCs exhibit a more prominent cytokine secretion profile (Hu et al., 2013). This has led to a switch in attention towards UCMSCs (Bongso and Fong, 2012; Fan et al., 2010; Moretti et al., 2009; Taghizadeh et al., 2011), which also benefit from superior proliferation rates, powerful differentiation capacity, and low immunogenicity (Jo et al., 2008).

Here, we will provide an overview of the biological characteristics and secretion properties of UCMSCs as well as discuss their potential applications.

2. Biological properties of UCMSCs

The International Society for Cellular Therapy has proposed a set of minimum criteria that define MSCs: (a) plastic adherence; (b) a specific set of cell surface markers (CD73, CD90, CD105) and concomitant absence of CD14, CD34, CD45, and human leucocyte antigen-DR; and (c) ability to differentiate into adipocytes, chondrocytes, and osteoblasts in vitro (Dominici et al., 2006). UCMSCs, like other MSCs, meet these criteria. Wharton's jelly is the section of the umbilical cord most commonly used to harvest UCMSCs (Hendijani et al., 2014; Lindenmair et al., 2012; Xu et al., 2014). These are isolated mainly by enzymatic digestion and tissue explant (Han et al., 2013). The cells form a monolayer and present homogeneous bipolar spindle-like and whirlpool-like shape; few morphologic changes occur during long-term culturing (Zhuang et al., 2015). MSC yields range from 10,000 cells/mL to 4,700,000 cells/cm of umbilical cord tissue, which is more than for ASCs and BMSCs (Vangsness et al., 2015). UCMSCs present long-term self-renewal, high expandability, and phenotypic stability. Schugar et al. expanded UCMSCs for more than 55 population doublings after 22 passages or 70 days in culture (Schugar et al., 2009). Like BMSCs, UCMSCs can be induced to display morphological and biochemical characteristics of neural, endothelial, and bone tissue adipose cells in vitro (Troyer and Weiss, 2008). The fact that UCMSCs do not express the major histocompatibility complex (MHC-II) or co-stimulatory molecules CD80 and CD86 is advantageous in allogeneic and heterogeneic transplanation. Instead, they produce moderate amounts of MHC-I (Liu et al., 2012), and constitutively express B7 homolog 1 (B7-H1), a negative regulator of T-cell activation (Tipnis et al., 2010). Expression profiles of UCMSCs indicate that genes related to immune tolerance and immunomodulation are positively expressed, whereas those involved in immune response are not (Chen et al., 2012).

3. Secretion by UCMSCs

Cell secretions constitute an extremely complicated pool of molecules and CM contains all the trophic factors secreted by UCMSCs. Tandem mass spectrometry (MS/MS), stable isotype labeling by amino acids combined with liquid chromatography-MS/MS analysis, sodium dodecyl sulfate polyacrylamide gel electrophoresis, immunoblotting, and enzyme-linked immunosorbent assay (ELISA) are used for detecting secretome components (Lavoie and Rosu-Myles, 2013). Wang (2014) analyzed the protein content of UCMSC CM and identified 236 molecules, of which 114 were known and 122 were predicted by the Signal P server. They represented a heterogeneous group that included cytokines, transporters, receptors, and binding proteins. Gene Ontology analysis revealed participation in 15 biological processes and 14 molecular functions involving growth, proliferation, differentiation, and apoptosis. Cytokines are bioactive proteins that play a role in inflammatory responses and maintenance of homeostasis (Stenken and Poschenrieder, 2015). They are clustered into several classes: interleukins (IL), TNF, interferons (IFN), colony-stimulating factors (CSF), TGF, and chemokines (Kruger and Light, 2009). There is a strong clinical interest in detecting cytokines in CM. Amable et al. (Amable et al., 2014) studied the cell supernatant concentration of 49 different cytokines, growth factors, and extracellular matrix-related proteins. UCMSCs were positive for 47 of them

Please cite this article in press as: Bai, L., et al., Bioactive molecules derived from umbilical cord mesenchymal stem cells. Acta Histochemica (2016), http://dx.doi.org/10.1016/j.acthis.2016.09.006