Best Practice & Research Clinical Obstetrics and Gynaecology 31 (2016) 82–87

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

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

5

Human Foetal Mesenchymal Stem Cells

Cecilia Götherström, PhD *

Division of Obstetrics and Gynaecology and Centre for Haematology and Regenerative Medicine, Karolinska Institutet, Stockholm, Sweden

Keywords:
mesenchymal stem cells
multipotent mesenchymal stromal cells
foetal stem cells
perinatal stem cells
osteogenesis imperfecta

Finding suitable cell sources is one of the main challenges in regenerative medicine. In addition to improving the dysfunctional tissue requiring reconstruction, low immunogenicity is beneficial. Mesenchymal stem cells (MSCs) are immune-privileged multipotent stromal cells that can easily multiply and differentiate along many lineages with a minimal oncogenic risk. MSCs derived from foetal tissues present characteristics that suggest an even stronger cell therapeutic potential in comparison to adult MSCs. Due to these characteristics, they have been and are currently being tested in clinical trials for a diverse variety of disorders.

Mesenchymal stem cells

Human mesenchymal stem cells (MSCs) represent a mesodermal-derived population of multipotent stromal cells. Friedenstein first described the MSCs in the 1960s observing that non-haematopoietic cells which adhered to plastic could be isolated from adult bone marrow [1,2], but they were not fully characterised until 1999 where strict culture techniques demonstrated their expansion and multilineage potential in culture [3]. Adult bone-marrow-derived MSCs remain the best characterised source of human MSCs to date, but considerable research has also been performed on MSCs isolated from other sources and developmental stages, many of which are described in this book.

* Division of Obstetrics and Gynaecology, K57 Karolinska University Hospital Huddinge, SE-141 86 Stockholm, Sweden. Tel.: +46 8 585 811 61; Fax: +46 8 585 811 67.
E-mail address: Cecilia.Gotherstrom@ki.se.

http://dx.doi.org/10.1016/j.bpobgyn.2015.11.010
1521-6934/

MSC during the development

MSCs make up only a minor fraction of tissues and are, for example, about 10-fold less abundant than haematopoietic stem cells (HSCs) in the bone marrow, but they are easily isolated and propagated in vitro. The prevalence of MSCs declines with advancing age: In the marrow of a newborn, one MSC is found among 10,000 nucleated bone marrow cells, compared with one MSC per 250,000 nucleated cells in adult bone marrow and one per 2×10^6 in that of an 80-year-old [4]. By contrast, the foetus is relatively rich in MSCs. It has been shown that the first-trimester foetal blood contains one MSC among every 3000 nucleated cells and the second-trimester foetal bone marrow one MSC among every 400 cells [5,6]. Human foetal MSCs are present in the foetal circulation from early gestation and then progressively decline in frequency in foetal blood during the late first trimester, suggesting that they may play an important role in establishing foetal haematopoiesis. One hypothesis is that foetal MSCs migrate to the definitive site of haematopoiesis in the bone marrow where they adhere and act as stromal support to the HSCs. This function by the MSCs is supported by the detection of maximal numbers of fibroblast colony-forming units in murine foetal liver, spleen and bone marrow at the time haematopoiesis begins at each site, suggesting the existence of a stromal stem cell population migration on which HSCs are seeded [7]. Foetal MSCs have been demonstrated to localise within haematopoietic sites throughout ontogeny, consistent with parallel and coordinated development of the haematopoietic and mesodermal systems [8]. In line with this, it has been determined that foetal MSCs support haematopoiesis in long-term cultures and maintain expansion of umbilical cord blood-derived HSC in vitro [5,9], and animal studies show that foetal MSCs support and enhance engraftment of HSC [6,9]. These data indicate that the foetal MSCs are implicated in the establishment of haematopoiesis.

Phenotype of MSC

Foetal MSCs have similar characteristics as adult bone marrow-derived MSCs; they grow as spindle-shaped fibroblastic cells displaying colony-forming capacity in low-density cultures [3,10]. In 2006, the International Society for Cellular Therapy stated the minimal criteria for MSCs as follows: adherence to plastic; positive for cluster of differentiation (CD)105, CD73 and CD90 and negative for haematopoietic and endothelial markers and co-stimulatory molecules CD45, CD34, CD14 or CD11b, CD79a or CD19 and human leucocyte antigen (HLA-DR); and ability of tri-lineage differentiation into bone, fat and cartilage [11]. There is no identified specific surface marker for MSC, but the cells are positive for a wide range of surface markers such as CD29, CD44, CD146, CD166 and CD271 [3,5,9,12]. MSCs also express a variety of cell adhesion molecules as integrins α1, α2, α3, α4, α5, α6, αv, β1, β3, β4 and β5 [13–15] Further characterisation shows expression of ligands for surface proteins present on cells of the haematopoietic lineage, including intercellular adhesion molecule (ICAM)-1, ICAM-2, vascular cell adhesion molecule (VCAM)-1, lymphocyte function-associated antigen (LFA3), CD72 and C-X-C chemokine receptor type 4 (CXCR4) [3,13–17], molecules important in cell binding and homing interactions. Several extracellular matrix molecules such as collagen, fibronectin, laminin and proteoglycans are also secreted by MSCs, suggesting that they may play a central role in the organisation of the extracellular matrix [3,5,18]. In addition, MSC constitutively secrete an extensive array of factors and micro vesicles that may act in a paracrine fashion in vivo [19–21].

Stem cell properties of MSCs

MSCs are defined as multipotent cells, which means that they are capable of differentiating into mesodermally derived tissues such as bone, cartilage, tendon, bone marrow stroma and adipose tissue. Single-cell clones of expanded foetal and adult MSCs retain their multilineage potential [3,5,22], and the single-cell colonies co-express gene characteristics for osteoblastic, chondrocytic, adipocytic, myoblast, haematopoiesis-supporting stromal, endothelial, epithelial and neuronal lineages [23]. Furthermore, in immunocompetent allogeneic/xenogeneic animal models, it has been shown that when infused intravenously, MSCs engraft widely in multiple tissues and demonstrate site-specific differentiation [24–27].