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Review

Mesenchymal stem cells and acquisition of a bone phenotype: An ion channel overview

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Abstract

Bone remodeling is a physiological process determined by the sequential and coordinated interaction of osteocytes, osteoclasts, osteoblasts and angiogenesis. During bone repair, osteoblastic cells, originated from mesenchymal stem cells (MSCs), are highly regulated to proliferate and to produce an osteogenic matrix, thus forming a new bone. MSCs are multipotential and undifferentiated cells that are present in the adult bone marrow. They serve *in vitro* and *in vivo* as precursors for bone marrow stroma, bone, fat, cartilage, muscle (smooth, cardiac and skeletal) and neural cells. MSCs are usually isolated from adult bone marrow but can also be isolated from several other tissues, such as fetal liver, adult circulating blood, umbilical cord blood, placenta or adipose tissue. In the bone marrow, MSCs give rise to mesenchymal cells residing in the bone (osteogenic, chondrogenic and adipogenic cells) and also support hematopoiesis. Therefore, MSCs regulate both osteogenesis and hematopoiesis, and they are responsible in part for the regenerative capacity of bone tissue. Acquisition of such a phenotype may be also regarded through the modification of the ionic channel expression. This review highlights current status and progresses in the differentiation MSCs along the osteoblastic/osteocytic pathways and the ionic channel expression and evolution during this differentiation.

Key words: Mesenchymal stem cells, osteoblastic differentiation, ionic channels

INTRODUCTION

Stem cells are generally described as clonogenic and undifferentiated cells that are able to self-renew and to differentiate into one or more types of differentiated and committed cells (Reyes-Botella et al., 2000; Jiang et al., 2002). To date, stem cells have been isolated and characterized from tissues of all ages, including embryonic, fetal and adult tissues. Among the general term of adult (postnatal) stem cells, mesenchymal stem cells (MSCs) represent a population of multipotential cells which are currently defined by a combination of morphologic, phenotypic, and functional properties, and which are capable of giving rise to at least mesenchymal-derived tissues, including bone, cartilage, fat, tendon and muscle (Friedenstein et al., 1974; Dazzi et al., 2006). MSCs have been identified into a large number of adult tissues, including the bone marrow where they provide the cellular microenvironment supporting hematopoiesis.

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As a part of the stromal fraction, MSCs also regulate osteogenesis and are responsible, in part, for the regenerative capacity of bone tissue (Friedenstein et al., 1974). Since MSCs differentiate into osteoblasts, the major bone-forming cells, they have been used to develop new clinical therapies to treat or attenuate a number of skeletal disorders. Furthermore, osteoblasts and osteocytes possess ion channels and channels have different functions. It has been reported that K^+ and Ca^{++} channels have roles in proliferation, differentiation and apoptosis (Tao et al., 2008), in the modulation of the progression of the cell cycle and in affecting the proliferation of MSCs (Wang et al., 2008)(Park et al., 2008). There is a variable expression of K^+ channel with cell cycle of MSCs and this way contributes to the cell cycle progression. On the other hand, Ca^{++} channels contribute to the bone renewal and they are different expression during the osteogenic differentiation. Therefore, the purpose of the article is to review the literature on the adult MSC biology and their ion channel profile variations and modifications during the bone phenotype acquisition.

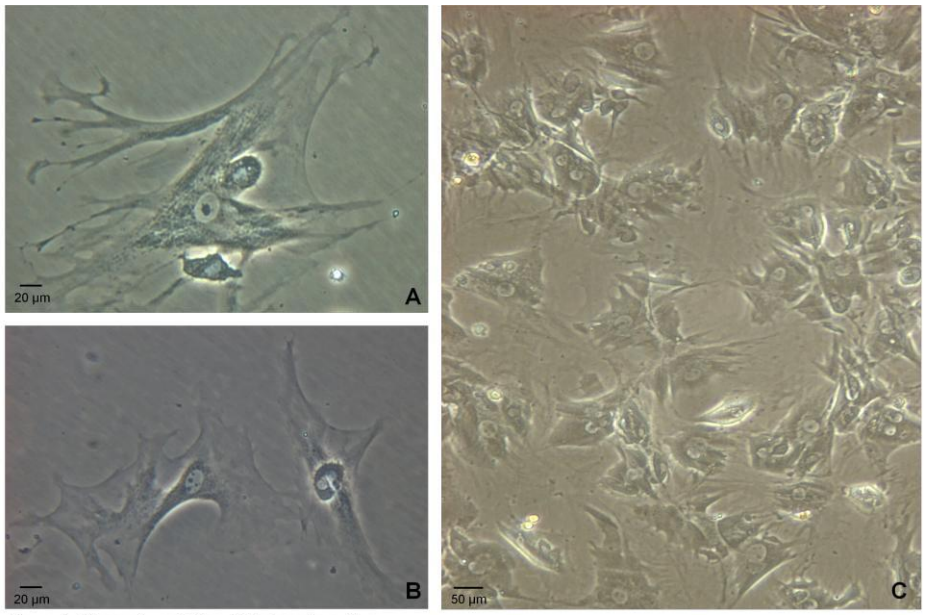

Figure 1: Mesenchymal Stem Cell shape in culture.
Rat mesenchymal stem cells A and B were cultured in DMEM 20% fetal calf serum until sub-confluence (C), before being passaged. These plastic adherent bone marrow cells extract from rat bones are elongated cells that look like fibroblasts and that formed discrete colonies after few days.

Figure 1. Mesenchymal stem cell shape in culture. Rat mesenchymal stem cells (A and B) were cultured in DMEM 20% fetal calf serum until sub-confluence (C), before being passaged. These plastic adherent bone marrow cells extract from rat bones are elongated cells that look like fibroblasts and that formed discrete colonies after few days.

What is a mesenchymal stem cell?

Definition and ontogenesis of a mesenchymal stem cell

MSCs, as the other types of stem cells, own the same characteristics and meet the classic criteria that define a stem cell. One of the defining criteria of stem cells is the self-renewal ability or the ability to generate identical copy of themselves with the same capacities through mitotic division over extended time periods (clonality). In culture, after they have been passed several times, MSCs have self-renewal activity. *In vivo*, cells collected from an initial transplant recipient could rise to a multiple cell type within a secondary recipient (Reyes-Botella et al., 2000; Jiang et al., 2002).

Then, the basic characteristics of stem cells are their multipotenciality where a single cell can differentiate into a variety of lineage cells. MSCs are multipotent stem cells and have the fundamental capacity to differentiate into a limited range of cell lineages (Gronthos et al., 1996; Prockop, 1997). The multilineage differentiation potentials of MSCs are study *in vitro* since their discovery, five decades ago. These studies, *in vitro* and *in vivo*, demonstrated that bone marrow MSCs, from many species, are able to differentiate at a single-cell level into limb-bud mesodermal cell type: osteoblasts, chondroblasts, adipocytes, fibroblasts and skeletal myoblasts. MSCs can also acquire characteristics of non-mesodermal lineages, such as endothelial cells, neural cells and endoderm, *in vitro* and *in vivo* (Pittenger et al., 1999; Schwartz et al., 2002; Verfaillie, 2002; Verfaillie et al., 2002).

Finally, these cells have also, *in vivo*, the capacities to generate a functional reconstitution of a given tissue when they are transplanted in a damage recipient or in the absence of tissue damage (Friedenstein et al., 1974; Latsinik et al., 1986; Haynesworth et al., 1992). Tissue regeneration is a stem cell property that has been partially confirmed for MSCs, especially for bone repair (osteogenesis imperfecta, bone fracture consolidation…). MSCs may also be used in several other diseases because of their large differentiation potential (vascular, cardiac…) (Orlic et al., 2002; Toma et al., 2002; Togel et al., 2005).

Such capacities of differentiation into a variety of connective tissue cells type make them an excellent candidate source for clinical tissue regeneration (Brazelton et al., 2000; Sanchez-Ramos et al., 2000).

The historical identification of mesenchymal stem cells

Alexander Friedenstein and colleagues, in 1974, were the first to identify mesenchymal stem cells (MSC) (Friedenstein et al., 1974; Friedenstein et al., 1974). They noticed, upon the other plastic adherent bone marrow cells extract from rabbit and rodent bones, non phagocytic, elongated cells that look like fibroblasts that formed discrete colonies after few days (Figure 1). Such colony was generated from a single cell and thus was called colony-forming unit-fibroblasts (CFU-F). Thereafter, *in vitro*, clonal cultures derived from individual

CFU-F were introduced into diffusion chambers in experimental models where the formation of bone, cartilage and stromal elements were observed. *In vivo*, when a colony is seeded under the renal capsule of semi-syngeneic animals, cells generated, after few weeks, fibrous tissue, bone and bone-containing bone marrow. Among these chimerical animals, Friedenstein observed that fibrous tissue and bone cells were of donor origin, while marrow hematopoietic cells within the bony spaces were provided by the host. Thus, Friedenstein conjectured that the bone marrow contains a population of progenitor cells able to generate *in vivo* fibrous tissue and bone and that these cells proving the adequate microenvironnement for HSC homing and growth. Friedenstein was the first to consider the existence of stem cell niches within the bone marrow. Few years later, in 1980, Castro-Malaspina showed that the colonies described are of fibroblastic nature by immunologic studies (Castro-Malaspina et al., 1980; Dazzi et al., 2006).

Arnold Caplan, during the 1990s, defined MSCs as cells that could give rise to bone and marrow stroma, but also to cartilage, tendon and muscle (Dennis et al., 1999; Caplan et al., 2006). The development of novel approaches to isolate and purify populations of MSCs has furthered our understanding of MSC biology but has also created several designation and abbreviations for describing these cells (Baksh et al., 2004). In the end of the 1888, Maureen Owen used the term of “Stromal Stem Cells” to show that MSCs take part of the stromal layer of the bone marrow and did not belong to the haematopoietic population (Owen et al., 1988). Teen years later, Darwin Prockop proposed the abbreviation of MSC for “Mesenchymal Stem Cell” or “Marrow stromal cells” because of their ability to differentiate into mesenchymal tissue and to serve also as a niche for other type of stem cells such as HSCs (Prockop, 1997; Kopen et al., 1999). In 1999, James Dennis indicated that this cell type may not represent an authentic category of stem cell but in closer to progenitor cell situated downstream of stem cell compartment and call these cells “Mesenchymal Progenitor Cell” (MPCs) (Dennis et al., 1999). Pamela Gehron Robey and Paolo Bianco used the term of Skeletal Stem Cells, in the early 2000s to show that MSCs were able to give rise to the components of skeletal tissues (Bianco et al., 2000). Catherine’s Verfaillie and colleagues described culture-derived bone marrow-derived progenitor cells that may represent a more primitive cell type with different differentiation potential larger than that of MSCs, and they designated them as MAPCs for “Multipotent Adult Progenitor Cells” and “Mesodermal Progenitor Cells” (Jiang et al., 2002).

Diversity of sources of mesenchymal stem cells

MSCs can be isolated from many different common species. Among all theses species, the human (Pittenger et al., 1999; Zvaifler et al., 2000; Kuznetsov et al., 2001; Covas et al., 2005), the murine (Phinney et al., 1999; Baddoo et al., 2003) and the rat (Santa Maria et al., 2004; Rochefort et al., 2005; Rochefort et al., 2006) MSCs are the best characterized. Next to these three species, MSCs can also be isolated from guinea pigs, cats (Martin et al., 2002), baboons (Devine et al., 2001), sheep (Airey et al., 2004), dogs (Silva et al., 2005), pigs (Moscoso et al., 2005; Bosch et al., 2006), cows (Bosnakovski et al., 2005) and horses (Worster et al., 2000; Ringe et al., 2003).

MSC might be found with a variable proportion in different fetal and adult tissues but these cells often represent a small portion of these tissues.

Usually, they are isolated from the stromal fraction of adult bone marrow. Indeed, the bone marrow source is the most well studied and accessible but MSCs form a rare population of the bone marrow microenvironnement and may represent only 0.01 - 0.0001% of the adult human bone marrow nucleated cells. This is considerably lower than the proportion of hematopoietic stem cells that represent about 1% of the marrow nucleated cells. These cells are obtained by flushing the marrow out of animal bones with culture medium or from human bone marrow aspirates and transferred into a culture dish (Phinney et al., 1999; Pittenger et al., 1999; Santa Maria et al., 2004; Tropel et al., 2004; Zhang et al., 2004; Rochefort et al., 2005; Miao et al., 2006; Rochefort et al., 2006).

Cells with mesenchymal stem cells characteristics were isolated from several adult tissues including spleen, pancreas (da Silva Meirelles et al., 2006; Seeberger et al., 2006), liver (Campagnoli et al., 2001; Dan et al., 2006), kidney (da Silva Meirelles et al., 2006), lung (da Silva Meirelles et al., 2006), smooth muscle (da Silva Meirelles et al., 2006), skeletal muscle (Howell et al., 2003; Barry et al., 2004; Yoshimura et al., 2007), aorta (da Silva Meirelles et al., 2006), vena cava (da Silva Meirelles et al., 2006), brain (da Silva Meirelles et al., 2006), thymus (da Silva Meirelles et al., 2006), dental pulp (Pierdomenico et al., 2005), deciduous teeth (Barry et al., 2004), scalp tissue and hair follicle (Shih et al., 2005), periosteum (Barry et al., 2004; Yoshimura et al., 2007), trabecular bone (Barry et al., 2004), adipose tissue (Barry et al., 2004; Yoshimura et al., 2007) and synovium (Barry et al., 2004; Yoshimura et al., 2007). MSCs have also been isolated from fetal tissues similar to the adult tissues but also, with a variable portion, from several part of the placenta (Igura et al., 2004; Miao et al., 2006) including chorionic vili, amniotic fluid (Tsai et al., 2004), fresh or cryopreserved umbilical cord blood (Erices et al., 2000; Erices et al., 2003) and umbilical cord vein (Covas et al., 2005).

MSCs were also described in the peripheral blood of normal adult and women during and after the pregnancy, from a fetal origin and may persist for at least 60 years (Zvaifler et al., 2000; O'Donoghue et al., 2004; Villaron et al., 2004; Dazzi et al., 2006). Blood samples represent a

particular important source of MSC, more accessible in Human than the bone marrow source. MSCs can be mobilized into the bloodstream after treatment (chemotherapy, cytokine injection) or physiopathological events inducing a physiological release of stem cells from their reservoirs in responses of stress signals such as cytokines like granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF). Recently, scientists show that several physiopathological circumstances, including hypoxia, myocardial infarction or encephalopathy can increase the release of MSCs in blood (Erices et al., 2000; Erices et al., 2003; Romanov et al., 2003; Lee et al., 2004).

The usual phenotype of mesenchymal stem cells

In the past, MSCs were selected by adherence to plastic surface and were considered as a homogeneous population. However, scientists observed differences between the morphology and the differentiation potential of the cultured cells. MSC markers have been identified that are suitable to show heterogeneity of these cells not only with regard to phenotype but also with regard to the differentiation capacity. Scientists bring to the fore distinct primary CSM subsets based on surface markers. Considerable progress has been made about characterizing the cell surface antigenic pattern of MSCs using fluorescence activated cell sorting and magnetic bead sorting techniques. Yet, phenotypic isolation of MSC is not possible because no specific MSC immunophenotyping markers have been identified. However, MSC express a wide variety of antigens presents by many cell types. Thus, their identification is based on an extensive combination of markers building up a pattern of typical surface molecules of MSC, such as differentiation and lineage specific markers, adhesion molecules, extracellular matrix and growth factor factors receptors, and a panel of monoclonal antibodies (Simmons et al., 1991; Simmons et al., 1992; Gronthos et al., 1995, 1996; Dazzi et al., 2006).

An important number of makers have been described that can be suitable for the isolation of MSCs from primary tissues. Currently, the most accepted profile for phenotype MSC is the co-expression of CD105 (SH2) and CD73 (SH3 and SH4). MSCs are positive for CD13, CD 29, CD 44, CD49a and CD49e, CD90, CD106, CD 166, CD349. MSC are negative for the hematopoietic and/or endothelial markers CD14, CD31, CD34, CD45, and CD133. MSCs constitutively express low surface density of MHC class I molecules (HLA-ABC) and are negative for MHC class II (HLA-DR). Therefore, MSCs can be considered as poorly immunologenic (Haynesworth et al., 1992; Pittenger et al., 1999; De Ugarte et al., 2003; Vogel 2003; Barry et al., 2004; Dazzi et al., 2006).

Nevertheless, some molecules, used as markers to identified MSC, are variably expressed during time in culture and depending on the extent of MSC multipotency. Moreover, some antigens appear to be present on cell subsets only. Last markers identified are CD140b, CD271 (bone marrow), SSEA-4 (placenta), the ganglioside GD2, CD146, CD200 and the integrin complex. These markers are very selective for the recognition of MSCs but they lack the ability to discriminate MSC subsets. Very recently, MSCA-1 and CD56 were identified as combination markers suitable to purify and characterize MSC populations from primary bone marrow that show distinct morphological features and differentiation capacities.

Others study that the gene expression pattern of MSC by serial analysis gene expression, restriction fragment differential display and DNA microarray and show the presence of multiple cell lineages as part of their transcription (Silva et al., 2003; Dazzi et al., 2006; Battula et al., 2009; Buhring et al., 2009).

The lineage differentiation abilities of mesenchymal stem cells

An embryo is composed to three layers (ectodermal, endodermal and mesodermal layers) and each layers gives several tissues. The ectodermal tissue gives the peripheral and central nervous systems and also the epithelium that become epidermal tissue, muscles (iris' muscles, the myoepithelial cells of the lacrimal salivary…) (Fuchs et al., 1994; Lo et al., 1997). To concern the mesoderm, it gives also muscles such as skeletal, cardiac, visceral and vascular smooth muscles, bone, cartilage, blood and connective tissue (Baron, 2001). Finally, the endoderm layer gives all the intestinal tissue (Soria, 2001; Gupta, 2002; Wobus et al., 2005).

Mechanism of the lineage differentiation

Stem cell can differentiate into different cells of the tissue in which they reside. They have a multi-lineage differentiation potential of several stem cells types including MSCs (Herzog et al., 2003). MSCs are able to differentiate into limb-bud in different cells like osteoblasts, chondroblasts, fibroblasts, adipocytes and skeletal myoblasts (Friedenstein et al., 1974; Haynesworth et al., 1992; Gronthos et al., 1996; Prockop, 1997; Pittenger et al., 1999). Also, they are able to acquire characteristics of cell lineage outside the limb-bud, such as endothelial cells and neural cells (Brazelton et al., 2000; Reyes-Botella et al., 2000; Sanchez-Ramos et al., 2000; Jiang et al., 2002; Zhao et al., 2004). This differentiation potential has been show in the early 2000s by Markus Loeffler and his team. They described the MSCs differentiation pathway that was reversible and flexible. Therefore, adipocytes became turn into

osteoblasts, chondrocytes into adipocytes, adipocytes into chondrocytes, osteoblasts into chondrocytes, and so on (Loeffler et al., 2002; Baksh et al., 2004; Loeffler et al., 2004; Song et al., 2004). The MSCs express simultaneously the mRNA or protein level of adipocytes, osteoblasts or chondrocytes markers (Baksh et al., 2004). This plasticity is due to the de-differentiation and reprogramming of MSCs lineage by stimulation of different specifics transcription factors.

Plasticity is an important MSCs characteristic because whatever the differentiation level, MSCs are able to give all the cells of his lineage.

The ectodermal differentiation of mesenchymal stem cells

The ectodermal tissue is the covers of the body surface. It forms many tissues, including the central nervous system, cranial bones, ganglia and nerves, epidermis, hair, mammary glands.

The mesenchymal stem cells differentiation into central nervous system cells: The brain development is very crucial, neurons migrate and forms the neural tubes and they differentiate into several cells and satellite cells. In 1992, Reynolds and Weiss isolated for the first time multipotential stem cells from the striatum of adult human brain. Then they induced multipotential stem cells into neural cells *in vitro* (Reynolds et al., 1992). A novel site of mesenchymal stem cell was discovered: the neural stem cells (NSCs). NSCs are present in the brain during life span mammalian and humans (Brazelton et al., 2000; Sanchez-Ramos et al., 2000). These cells are one of the newest and most promising for treating several diseases like neurodegenerative diseases or injuries of central nervous system.

MSCs express neural markers and they could have an *in vitro* neural differentiation into neuron and glial-like cells. It is possible with a NSCs culture with a medium completed by neural factors. Many studies showed different MSCs-NSCs differentiation and MSCs had morphological characteristics, neural markers, electrophysiological properties as a neuron (Deng et al., 2001; Wehner et al., 2003; Kanemura, 2010).

The mesenchymal stem cells differentiation into skin-related cells: Skin is the largest organ of the body. It is composed by three layers: the epidermis, derma and hypoderm and they are several and different functions. The skin has many roles like temperature regulation, vitamin D and melanin synthesis. Also it has an immunity function, it is a barrier against pathogens and it is a sensitive organ.

In vitro, skin MSCs were studied many times. In fact it is a big challenge to understand all the MSCs mechanisms. Today, MSCs are used like a cellular therapy when a burn injury. Bone marrow MSCs ware transplanted and dermis can be regenerate with a scar reduction (Deng et al., 2001; Gharzi et al., 2003; Chunmeng et al., 2004; Bey et al., 2010).

The endodermal differentiation of mesenchymal stem cells

During embryo development, endoderm layer forms a layer inside the gastrula. Endoderm gives many tissues such as digestive tube epithelial lining (except a part of mouth, pharynx and the rectum terminal), all digestive tube glands lining cells (liver and pancreas), tympanic cavity, trachea, bronchi, lung and so on.

The mesenchymal stem cells differentiation into gastrointestinal tract related cells: It is the organ system that takes in food, makes digestion to extract nutrients and energy, and expels waste. The gastro-intestinal tract important functions are digestion and excretion. It is connected with different organs that come from endoderm tissues too including liver which secretes bile, pancreas which secretes bicarbonate and many enzymes (trypsin, lipase, pancreatic amylase, and chymotrypsin).

Gastrointestinal tract measure nearly 6.5 m long (20 feet) in a normal adult male. It is divided into three parts: foregut, midgut and hindgut. The upper gastrointestinal tract including the mouth, pharynx, esophagus and stomach, correspond to foregut except a part of duodenum. The lower gastrointestinal tract are consisting of the intestines and anus that derives from the midgut for the lower duodenum, and are consisting of the transverse colon and upper part of the anal canal from the hindgut.

The mesenchymal stem cells differentiation into Liver cells: It plays an important role in metabolism and many functions in the body like plasma protein synthesis, glycogen storage and drug detoxification. Liver comes from endoderm part of the foregut (hepatic diverticulum). It produces bile and has several functions like carbohydrate metabolism regulation, lipid and cholesterol metabolism and insulin and coagulators factors production. At cellular level, liver is composed to hepatocytes and these cells are able to regenerate themselves, only 25% liver tissue can regenerate all liver.

In fetal and adult liver, many different cells are present: several types of bone marrow-derived stem cells that are able to differentiate into hepatocytes cells with some *in vitro* conditions. A MSCs culture with hepatocytes growth factor (HGF) in medium obtains hepatocytes cells (Oh et al., 2000; Avital et al., 2001; Okumoto et al., 2003; Lange et al., 2005).

In vivo, bone marrow and liver transplantation were used to treat several diseases or in order to reconstitute a liver. Different studies demonstrate that bone marrow-

derived MSCs with some conditions give several types of liver cells such as hepatocytes, oval cells and cholangiocytes (Petersen et al., 1999; Herrera et al., 2006). Recently, MSCs differentiation into hepatocytes lineage was confirmed (Avital et al., 2001; Seo et al., 2005).

The mesenchymal stem cells differentiation into pancreas cells: It is an organ in the digestive and endocrine system which it is both exocrine (secrets pancreatic juice containing digestive enzymes) and endocrine (hormones secretions including insulin, glucagon and somatostatin that are produce by islet of Langerhans). Several diseases could alter pancreas functions including tumors, cancer, cystic fibrosis, diabetes, exocrine pancreatic insufficiency, and so on. Diabetes is responsible to a high morbidity and mortality in many countries caused by a destruction of insulin secreting pancreatic β cells (type 1) or by a relative deficiency due to decreased insulin sensitivity (type 2).

In vitro, MSCs are able to differentiate into insulin, glucagon or somatostatin-secreting cells with some conditions and can differentiate into cells that have the islet pancreatic transcription factors (Nkx-2.2, Nkx-6.1, Pax-4, Pax-6, Isl-1 and Ipf-1) (Hess et al., 2003; Moriscot et al., 2005; Eberhardt et al., 2006; Timper et al., 2006).

The mesenchymal stem cells differentiation into Lung-related cells: It represents the largest surface area, a human adult lung measure nearly 70 m² whereas skin surface area represents only 2 m^2. Lung has an essential function that is respiration; it is able to transport oxygen from the atmosphere into the bloodstream, to excrete carbon dioxide from the bloodstream into the atmosphere.

Lung comes from endoderm epithelium and its development takes place into four chronological stages: the pseudoglandular stage, the canalicular stage, the terminal sac stage and the alveolar stage (Gomi et al., 1994; Yamada et al., 2003).

The mesodermal differentiation of mesenchymal stem cells

The mesoderm layer is forming just in triphoblastic animals during gastrulation. Some cells migrate and contribute a supplementary layer between ectodermal and endodermal layers. Mesoderm formed a coelom that become several tissues including skeleton, dermis of skin, skeletal muscles, connective tissue, heart, blood, and so on.

The mesenchymal stem cells differentiation into adipocytes: Adipocytes are a reserve of energy, they stock lipids and when energy is required, they break down lipids into free fatty acids. They also have other function that is important in control of metabolism by a paracrine secretion end endocrine hormones, thus regulating insulin sensitivity and secretion (Kershaw et al., 2004).

During embryogenesis, a population of MSCs of mesodermal layer migrates in the vascular stroma of adipose tissue. These cells have a multi-step of differentiation process to acquire an adipocytes phenotype (Otto et al., 2005; Rosen et al., 2006). MSCs express also transcription factors such as CCAAT-enhancer-binding protein α (C/EBPα) and peroxisome proliferator-activated receptor γ (PPARγ), these factors promote adipogenesis. Insulin is also a factor of adipocytes differentiation when using low concentrations, more, serums, dexamethasone, indomethacin and 3-isobutyl-1-methylxanthine (IBMX) induce MSCs differentiation into adipocytes.

The mesenchymal stem cells differentiation into osteogenic cells: Bones are rigid organ that form vertebrates skeleton. The most important functions of bone are the organs protection, hold up the body and support muscles. Bones protect the brain, spinal cord, lungs, heart, bone marrow, and so on. Bone permits skeletal muscle movements with the rigid attachment. Red bone marrow in bone is the major producer of blood cells and most of these cells are responsible of immunity. The skeleton has a mineral storage role, it stores calcium and phosphate and release them when the body's needs.

During early development, cells of neural crest give cranio-facial skeleton whereas the axial skeleton comes from sclerotome cells (somites) and the lateral plate of mesoderm gives the appendicular skeletal components (Olsen et al., 2000). But potential MSCs persist in bone marrow and have a role in bone growth, remodeling and bone repair. These MSCs could be differentiate into osteoblasts, *in vitro* osteoblasts derived MSCs can be obtain *in vitro* by medium with different transcription factors in order to induce osteogenic lineage such as transforming growth factor-β (TGF- β), interleukin-6 (IL-6), growth hormone, sortilin, leptin and transglutaminase (Taguchi et al., 1998; Weinreb et al., 1999; Ramoshebi et al., 2002; Canalis et al., 2003; Rawadi et al., 2003; Sykaras et al., 2003). Theirs products can be used to induce osteogenic lineage including prostaglandin E2, 1, 25-dihydroxyvitamin D3 (active form of vitamin D3) L-ascorbic acid (vitamin C), dexamethasone, β-glycerol phosphate, and so on (Raisz et al., 1993; Rogers et al., 1995; Weinreb et al., 1999; Rosa et al., 2003; Sottile et al., 2003).

The mesenchymal stem cells differentiation into chondrogenic cells: Cartilage is a connective tissue that is composed of collagenous fibers and/or elastic fibers and chondrocytes, all embedded in matrix of gel-like ground substance. Cartilage is not vascular and it is localized in many places in body like joints, rib cage,

nose, ear, bronchial tubes and between inter-vascular discs. During embryonic development, cartilage cells precursors (chondroblasts) are enclosed in perichondrium. Perichondrium was replaced by bone or joint cartilage.

Functional differentiation and adaptation of mesenchymal stem cells

MSCs are present into different tissues and during cell differentiation; MSCs are modulating by different conditions (according to the place where MSCs are) like cell stress, bone resorption and bone formation, wound healing, and so on. During differentiation, MSCs membrane has changing in receptors and channels on their surface.

Identification of ion channels into mesenchymal stem cells

Two distinct outward currents, present either alone or in combination, are recorded in MSCs. Most MSCs are demonstrated outward current by K^+ channels blockers but they were not blocked by blockers of Cl^- currents. Therefore, MSCs currents may depend on K^+ channels and not on Cl^- channels.

The most important current present in MSCs is from K+ channels. These channels can be blocked by tetrathylammonium for example: Kv1.1 channels, Kv3 channel family, Kv7.2 channels and BKCa (MaxiK) that are channels voltage Ca^{++} activated K^+ channels of large conductance. There are three criteria to a large conductance Ca^{++} activated K^+ current: 1/ typical electrophysiological properties, 2/ noisy current traces due to large conductance single channel opening, and 3/ BKCa is sensitive to iberiotoxin (a specific BKCa blocker). BKCa channels are sensors of intracellular Ca^{++} that regulate membrane potential in a Ca^{++} dependant manner, and they are modulated by phosphate.

Functional differentiation and adaptation of mesenchymal stem cells into bone cells

MSCs give rise to an osteoblastic lineage: pre-osteoblasts, osteoblasts and osteocytes. Osteoblasts are the cells that produce mineralize matrix to become an osteocyte immured in this mineralize matrix.

During MSCs differentiation, these cells have many changes including forms, functions, phenotypes, and so on. To have osteoblastic lineage in cell culture, medium is constituted to dexamethasone, ascorbic acid and β-glycerophosphate.

Surface marker modifications into mesenchymal stem cells during the bone lineage differentiation: Osteoblasts lineage has different propriety because they have many functions. Osteoblasts lineage express peroxisome proliferator-activated receptor γ (PPAR γ), bone sialoprotein (BSP), osteocalcin, osteopontin, phosphatase alkaline, collagen 1αA and 1α2. But they do not express osterix and lipoprotein lipase (LPL). Also there are modifications about surface markers. MSCs have many markers and during osteoblastic lineage, markers disappear or appear (Table 1).

MSCs, osteoblasts and osteocytes have common markers such as CD29, CD44, CD73 and CD105 and do not expressed CD3, CD4 and CD45. Others markers have a variable expression during MSCs differentiation. CD10, CD13 and HLA-DR are expressed by MSCs and osteoblasts but osteocytes they do not. CD40 is not expressed by MSCs but during their differentiation to osteoblastic lineage, osteoblasts and osteocytes express CD40. Others markers have a very variable expression, MSCs express CDx, osteoblasts do not express this CD and osteocytes express this, and vice versa.

Ion channel evolution into mesenchymal stem cells during the bone lineage differentiation: Like surface markers, ion channels have an evolution during MSCs differentiation to lineage osteoblastic (Table 2 and Figure 2). MSCs, osteoblasts and osteocytes have some common ions channels such as BKca, Kv1.3, Kv2.1, SK1 or SK2. However, a lot of ion channels have a variable expression during MSCs differentiation into osteoblasts and osteocytes. For example, Cav1.1, Cav1.2, Cav1.3, Cav3.1, Kv1.2, Kv3.1 or Kv3.2 are expressed by MSCs but there expression are decreasing in osteoblasts and/or osteocytes. At the opposite, TREK2, TRAAK, Kv1.6 and Kv2.2 are not expressed by MSCs but during their differentiation to osteoblastic lineage, osteoblasts and/or osteocytes express these ion channels. Others markers have a very variable expression, MSCs express some ion channels, osteoblasts do not express these ion channels and osteocytes express this, and vice versa.

Very few specific studies have demonstrated presence or absence during cell differentiation and there are very studies on osteocytes channels, especially only about calcium and sodium channels. Cav are channels that have to activate by a calcium currents in cells. There is one channel in common that is not present in MSCs, osteoblasts and osteocytes and this channel is SK3. Furthermore, osteoblasts and osteocytes possess ion channels and channels have different functions.

K^+ channel has roles in proliferation, differentiation and apoptosis: it has been reported that at least the intermediate-conductance Ca^{++} -activated potassium (IKCa) channel regulates the cell cycle progression and proliferation of mouse MSCs (Tao et al., 2008), whereas Kv channel activity (especially Kv1.2 and Kv2.1 associated with IKDR; Slo and KCNN4 associated with IKCa; and Kv1.4 and Kv4.3 associated with Ito) modulates the progression of the cell cycle and affects the proliferation of MSCs (Wang et al., 2008). A study has also showed that the functional potassium channel

Table 1. Relevant antigens that are strongly, weakly or not expressed in MSCs, osteoblasts and osteocytes.

	MSCs		OSTEOBLASTS		OSTE
	References	**+/- ?**	**References**	**+/- ?**	**Refer**
CD3	(Pittenger et al., 1999; Reyes-Botella et al., 2000; Ahuja et al., 2003; De Ugarte et al., 2003a)	--	(Reyes-Botella et al., 2000)	--	(Ahuja
CD4	(Pittenger et al., 1999; De Ugarte et al., 2003; Katz et al., 2005)	--		?	(Ahuja
CD10	(Battula et al., 2007)	++	(Reyes-Botella et al., 2000; Seshi et al., 2003; Garcia Ruiz et al., 2006)	++	(Tsai e
CD11b	(Katz et al., 2005; Aurich et al., 2007; Parekkadan et al., 2007; Yoshimura et al., 2007)	--	(Reyes-Botella et al., 2000; Marom et al., 2005)	±	(Ahuja 2004)
CD11c	(De Ugarte et al., 2003; Katz et al., 2005)	--		?	(Ahuja
CD13	(Pittenger et al., 1999; De Ugarte et al., 2003b; Aurich et al., 2007; Parekkadan et al., 2007)	++	(Reyes-Botella et al., 2000)	±	(Ahuja
CD14	(Pittenger et al., 1999; Zuk et al., 2001; De Ugarte et al., 2003; Aurich et al., 2007; Parekkadan et al., 2007)	--	(Reyes-Botella et al., 2000)	--	(Ahuja
CD15	(Pittenger et al., 1999; De Ugarte et al.,	--	(Reyes-Botella et al., 2000)	--	
CD19	2003) (Mansilla et al., 2006)	++	(Seshi et al., 2003)	±	
CD29	(Pittenger et al., 1999; De Ugarte et al., 2003)	++	(Jiang et al., 2002)	++	(Tsai e
CD31	(Zuk et al., 2001; De Ugarte et al., 2003; Katz et al.,	--	(Marom et al., 2005)	+	
CD34	2005) (Aurich et al., 2007)	--	(Reyes-Botella et al., 2000)	++	(Jiang
CD38	(Pittenger et al., 1999; De Ugarte et al.,	--	(Reyes-Botella et al., 2000)	++	
CD40	2003) (Weiss et al., 2008)	--	(Ahuja et al., 2003)	++	(Ahuja
CD40L	(Weiss et al., 2008)	--	(Reyes-Botella et al., 2000; Bonewald 2004)	++	(Ahuja
CD44	(Pittenger et al., 1999; Zuk et al., 2001; Silva et al., 2003; Talens-Visconti et al., 2006; Jager et al., 2007)	++	(Noonan et al., 1996; Reyes-Botella et al., 2000; Garcia Ruiz et al., 2006)	++	(Noon 2004;
CD45	(Pittenger et al., 1999; Zuk et al., 2001; Jiang et al., 2002; Silva et al., 2003; Talens-Visconti et al., 2006; Jager et al., 2007)	--	(Brown et al., 1990; Reyes-Botella et al., 2000; Seshi et al., 2003)	--	(Ahuja
CD54	(Pittenger et al., 1999; De Ugarte et al., 2003)	++	(Noonan et al., 1996; Reyes-Botella et al., 2000; Garcia Ruiz et al., 2006)	++	

Table 1. Contd.

CD56	(Brooke et al., 2008)	++	(Reyes-Botella et al., 2000) -- (Marom et al., 2005)	++	±
CD62e	(Pittenger et al., 1999; Zuk et al., 2001; Katz et al., 2005)				
CD68	(Parekkadan et al., 2007; Brooke et al., 2008)	--	(Reyes-Botella et al., 2000)	--	
CD73	(Pittenger et al., 1999)	++	(Brown et al., 1990)	++	
CD79a		?	(Seshi et al., 2003)	±	
CD80	(Pittenger et al., 1999; Katz et al., 2005)	±	(Reyes-Botella et al., 2000; Garcia Ruiz et al., 2006)	++	
CD86	(Weiss et al., 2008; Wang et al., 2009)	--	(Reyes-Botella et al., 2000)	++	(Jiang 2003)
CD90	(Covas et al., 2005; Flores-Figueroa et al., 2005; Mansilla et al., 2006; Kang et al., 2008; Liu et al., 2008; Rose et al., 2008)	++	(Lee et al., 2004)	++	
CD105	(Flores-Figueroa et al., 2005; Mansilla et al., 2006; Battula et al., 2007; Liu et al., 2008; Rose et al., 2008)	++	(Lee et al., 2004)	++	(Jiang
CD117	(Pittenger et al., 1999; Katz et al.,	±		?	(Tsai e
CD265	2005) (Tobon-Arroyave et al., 2005)	++	(McCormick et al., 1988)	++	
HLA-DR	(Panepucci et al., 2004; Ishii et al., 2005; Katz et al., 2005; Aurich et al., 2007)	±	(Reyes-Botella et al., 2000; Garcia Ruiz et al., 2006)	++	(Jiang
CMH II	(Wang et al., 2009)	--		?	(Ahuja 2004)
CMH I	(Kang et al., 2008)	++		?	(Jiang

The attribution concerning the degree of expression of some markers varies between different authors, because of different cultivation media, various a stem cell cultures and different antibodies used.
++: strong expression; ±: weak expression; --: absence of expression; ?: unknown expression.

profiling may depend on the cellular passage of MSCs (Park et al., 2008). There is a variable expression of K^+ channel with cell cycle of MSCs and this way contributes to the cell cycle progression.

Ca^{++} channels contribute to the bone renewal and they are different expression during the osteogenic differentiation. Ca^{++} entry across the plasma membrane is a main pathway for Ca^{++} signal, although it was reported that Ca^{++} release

from intracellula Ca^{++} oscillation cells (Kawano e entry across th operated Ca^{++} c

Table 2. Relevant channels that are strongly, weakly or not expressed in MSCs, osteoblasts and osteocytes.

				MSCs	OSTEOBLASTS	
				References	+/- ?	References
Calcic Channels	IcaL	Cav1.1		(Zahanich et al., 2005)	±	(Zahanich et al., 2005; Bergh et al., 2006)
		Cav1.2		(Zahanich et al., 2005; Balana et al., 2006; Zeng et al., 2011)	+++	(Gu et al., 2001; Zahanich et al., 2005; Bergh et al., 2006)
		Cav1.3		(Zahanich et al., 2005)	±	(Gu et al., 2001; Bergh et al., 2006)
	IcaP/Q	Cav2.1			?	(Zahanich et al., 2005)
	IcaN	Cav2.2			?	(Selim et al., 2006)
	IcaR	Cav2.3			?	(Selim et al., 2006)
	IcaT	Cav3.1		(Zahanich et al., 2005)	+	(Zahanich et al., 2005)
		Cav3.2			?	(Bergh et al., 2006)
		Cav3.3			?	(Gu et al., 2001)
Potassic Channels	2TM	Kir1.x	Kir1.1	(Li et al., 2006)	+	
		Kir2.x	Kir2.1	(Li et al., 2006; Park et al., 2007; Park et al., 2008)	+	
			Kir2.2	(Li et al., 2006; Park et al., 2007)	-	
		Kir6.x	Kir6.1		?	(Gu et al., 2001)
			Kir6.2		?	(Gu et al., 2001)
	4TM	TWIK	TWIK1	(Park et al., 2007)	++	
		TREK	TREK1	(Magra et al., 2007)	++	(Hughes et al., 2006)
			TREK2	(Magra et al., 2007)	--	(Chen et al., 2005; Hughes et al., 2006)
			TRAAK	(Magra et al., 2007)	--	(Wu et al., 2001; Hughes et al., 2006)
	6TM	Kv1.x	Kv1.1	(Heubach et al., 2004; Balana et al., 2006; Park et al., 2007; Bonnet et al., 2008; Park et al., 2008)	++	(Yellowley et al., 1998)
			Kv1.2	(Bonnet et al., 2008; Wang et al., 2008; Wang et al., 2009; Zeng et al., 2011)	++	(Yellowley et al., 1998)
			Kv1.3	(Li et al., 2005; Zeng et al., 2011)	+	(Yellowley et al., 1998)
			Kv1.4	(Wang et al., 2008)	+	
			Kv1.5	(Balana et al., 2006; Bonnet et al., 2008)	+	
			Kv1.6	(Li et al., 2005)	--	(Yellowley et al., 1998)
		Kv2.x	Kv2.1	(Heubach et al., 2004; Bonnet et al., 2008; Wang et al., 2008)	++	(Yellowley et al., 1998)
			Kv2.2	(Li et al., 2005)	--	(Yellowley et al., 1998)

Table 2. Contd.

Sodium Channels	Kv3.x	Kv3.1	(Heubach et al., 2004)	++	(Yellowley et al., 1998)	-
		Kv3.2	(Li et al., 2005)	++	(Yellowley et al., 1998)	-
		Kv3.3		?	(Yellowley et al., 1998) ?	+
		Kv3.4			(Yellowley et al., 1998)	+
	Kv4.x	Kv4.2	(Heubach et al., 2004; Park et al., 2007; Park et al., 2008; Benzhi et al., 2009)	+		?
		Kv4.3	(Heubach et al., 2004; Balana et al., 2006; Wang et al., 2008)	++		?
	Kv7.x	Kv7.1	(Heubach et al., 2004)	--		?
		Kv7.2	(Heubach et al., 2004)	+		?
		Kv7.3	(Heubach et al., 2004)	+		?
	KCNQ	KCNQ2		?	(Yellowley et al., 1998)	+
		KCNQ4		?	(Yellowley et al., 1998)	+
		KCNQ5		?	(Yellowley et al., 1998)	+
	EAG	Eag1	(Li et al., 2006; Park et al., 2008)	++		?
		Eag2	(Li et al., 2006)	--		?
	Slo	BKCa	(Balana et al., 2006; Li et al., 2006; Park et al., 2007; Bonnet et al., 2008; Park et al., 2008; Wang et al., 2008)	++	(Ypey et al., 1992; Yellowley et al., 1998)	+
	SK	SK1		?	(Gu et al., 2001)	+
		SK2		?	(Gu et al., 2001)	+
		SK3	(Li et al., 2006)	--		?
		SK4	(Li et al., 2006)	++	(Yellowley et al., 1998)	+
		Nav1.1	(Li et al., 2006; Mareschi et al., 2009)	++		?
		Nav1.2	(Li et al., 2006; Mareschi et al., 2009)	++		?
		Nav1.3	(Mareschi et al., 2009)	++		
		Nav1.5	(Park et al., 2007)	--		?
		Nav1.6	(Zeng et al., 2011)	++		?
		Nav1.7	(Park et al., 2007)	++		?
		hNE-Na	(Park et al., 2008)	+		?
		EAAT1		?	(Marom et al., 2005)	+

The attribution concerning the degree of expression of some channels varies between different authors, because of different c ultivation media, various ag cultures and different antibodies used.
++: very strong expression; +: positive expression; ±: weak expression; --: absence of expression; ?: unknown expression.

an important role for Ca^{++} entry across the plasma membrane in excitable cells and it is deemed to contribute to cellular differentiation or proliferation. However, it is still not clear which functions voltage-operate excitable cells,

stem cells.

Bone formation depends on proper channels functions: L type $Ca2^{+}$ channels blockers could stimulate alkaline phospholipase activity and mineralization. The channels might come into play at a later stage of differentiation.

Conclusions and future expectation

Mesenchymal Stem Cells differentiation concern the entire organism and during all the organism life. They are defined by different properties like the capacity to differentiate *in vitro* and *in vivo* into many cells include osteoblasts, adipocytes, chondroblasts, like proliferation adherent cells and a defined immunophenotype (markers and channels). MSCs are the most promising cells for the future for therapeutic applications with their capacity to modulate the immune system. It is regarded as a highly interesting topic how different patterns of ion channels diversity may differentially regulate intracellular pathways leading to different physiological responses during mesenchymal stem cell differentiation for its high potential in medical application. It is still unclear how ion channel profiling are differentially expressed during MSC differentiation and how they are decoded, and most importantly, what is the actual relationship between ion channel signals and mesenchymal stem cells differentiation along to the osteogenic differentiation. Further studies are needed to fully clarify this issue.

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