Inflammation and the Migration of Mesenchymal Stem Cell

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Abstract
Mesenchymal stem cells are adult non-hematopoietic stem cells with multilineage proliferation and differentiation capabilities. This type of stem cell has the multipotent ability to differentiate into osteocytes, tenocytes, adipocytes, chondrocytes and bone marrow stromal cells. The migration mechanism of mesenchymal stem cell is not yet fully understood, but based on studies that have been done recently by the researchers worldwide shown that the inflammatory process plays an important role for mesenchymal stem cell migration. A number of chemokine that plays a role in the migration of mesenchymal stem cells such as MCP-1 (CCL2), CXCL8, RANTES (CCL5), LL-37, integrin β1, CD44 receptor, CCR2, CCR3, and tyrosine kinase receptors for the following growth factors: IGF -1, PDGF-bb, HGF and VEGF.
Key words: mesenchymal stem cell, migration, inflammation

Introduction

Stem cells are cells that became the beginning of the growth of other cells that made the whole of the body of an organism. To be classified as a stem cell, a cell must have a number of characteristics such as undifferentiated, self-renewal and able to differentiate into more than one type of cells (multi potent/pluripotent) (Halim *et al*., 2010). Based on the degree of body maturation of the source of its existence, practically stem cell is divided into two types: embryonic stem cells and adult stem cells. Embryonic stem cells are obtained during embryonic stage of individual's development. In the next development stage, these cells will differentiate more mature which has the lower capability of proliferation and differentiation than embryonic stem cells. Embryonic stem cells are classified as pluripotent stem cells which can be used as a treatment for almost all degenerative diseases (Halim *et al*., 2010). Stem cell/progenitor cell can only perform differentiation and proliferation if supported by appropriate microenvironment for its maturation process. Microenvironment (niche) involves a series of supporting cells, cytokines, signaling pathways and cell adhesion molecules. Stem cells migration process requires a substance that can break the bonds between the stem cell with cell adhesion molecules in the matrix (Rettig *et al*., 2012 ; Ratajzak *et al*., 2012).

There are several types of bonds which maintain the stem cell remain in the matrix such as kit with kit ligand, CD44 with hyaluronic acid, CD62 with PSGL, VLA4 with VCAM-1 and CXCR4 with SDF 1. This bond will detach when exposed to cytokines or subcellular protein as a result of the inflammatory process and ischemia such as IL-8 and norepinephrine. Furthermore, the detach stem cells migrate according certain signal found during the process. Some studies have suggested that some molecules can act as chemoattractan such as VEGF, CXCL12, IL-6, MMIF, Integrins and PDGF. With the signals given by a substance that acts as chemoattractan the stem cells/progenitor will mobilize to the location of the source of the chemoattractan and will ultimately perform homing on the site to further develop into cells corresponding to the stimulus it receives (Ratajzak *et al*., 2012 ; Rettig *et al*., 2012). Mesenchymal stem cell is type of adult stem cells which is most widely researched and clinically tested. This type of stem cell has the multipotent ability and able to differentiate into osteocytes, tenocytes, adipocytes, chondrocytes and bone marrow stromal cells. The Mechanism of mesenchymal stem cell's migration/homing is not yet fully understood. However, the inflammatory process is believed to have an important role on the mechanisms of mesenchymal stem cell migration.

Materials and Methods

Data shown in this article refers to a number of worldwide research. Table 1 only provide data about a number of receptors expressed on mesenchymal stem cells which has been known to have implications in cell migration. The selection of this data is used to facilitate a better understanding of the reader regarding the mesenchymal stem cells migration (Spaeth *et al*., 2008).

Results and Discussion

Mesenchymal stem cells are adult non-hematopoeietik stem cells with multilineage proliferation and differentiation capabilities. Mesenchymal stem cells plays a role in the maintenance and regeneration of connective tissue and has the ability to differentiate into osteoblasts, adipocytes, chondrocytes, myocytes, and cardiomyocytes. Marker expressed by mesenchymal stem cells include CD29, CD44, CD51, CD73 (SH3/4), CD105 (SH2), CD166 (Alcam) and stro-1. In order to express a specific marker combination by mesenchymal stem cells is highly dependent on the microenvironment (Spaeth *et al*., 2008 ; Zappia *et al*., 2005). Theoretically, mesenchymal stem cells found in all organs of the human body, more precisely as a part of the population of cells contained in the perivascular region. According to the number of cells, accessibility and previous research, there are three most widely used sources to obtain mesenchymal stem cells: bone marrow, cord blood and adipose tissue (Halim *et al*., 2010).

The number of mesenchymal stem cells present in adipose tissue more than mesenchymal stem cells from two other sources (bone marrow and cord blood). The scientific literature states that the percentage of mesenchymal stem cell isolation from adipose tissue is equal with the bone marrow, which is 100%. Isolation of mesenchymal stem cells from umbilical cord blood is very difficult to do, this condition result in 29-63% success rate of mesenchymal stem cell from this source. Nonetheless, mesenchymal stem cells obtained from umbilical cord blood have much higher proliferation potential than bone marrow (Halim *et al*., 2010).

To date, the absolute characteristics of mesenchymal stem cells is still widely questioned, especially regarding its surface protein molecule. As an example of this discrepancy is the presence of CD29, CD44 and CD166 which are actually also can be found in mesenchymal stem cells. In addition, mesenchymal stem cells isolated from adipose tissue also showed expression of CD34 and CD54 on its surface. In terms of differentiation potential, a number of researchers also reported that mesenchymal stem cells obtained from umbilical cord blood are only able to form in two lines of differentiation: chondrogenic and osteogenic (Halim *et al*., 2010).

In accordance with the consensus issued by the International Society of Cellular Therapy, a cell that categorized as mesenchymal stem cells must have the following characteristics:

- The cells will attach to the surface of the dish when cultured in a plastic culture dish.
- Has a surface protein molecules (Cluster of Differentiation, CD): CD73, CD90, and CD105. In contrast to hematopoietic stem cells, mesenchymal stem cells do not express CD34, CD214, CD45 and HLA-DR.
- Able to differentiate into three main lines of mesenchymal differentiation: the osteogenic (becoming bone cells/osteocytes), chondrogenic (becoming chondrocytes cartilages) and adipogenic (becoming fat cells/adipocytes) (Halim *et al*., 2010).

The bone marrow-derived mesenchymal stem cells has been used in engrafment hematopoietic stem cell transplantation which was performed after chemotherapy to restore the population of bone marrow cells. Mesenchymal stem cells are also has been used to reduce graft-versus-host disease, tissue repair including cerebral injuries, bone fractures, ischemia/myocardial infarction, muscular dystrophy, and also to homing tumor (Spaeth *et al*., 2008; Lopez *et al*., 2007). Mesenchymal stem cells are believed to have chemotactic device similar to other immune cells that provide a response to injury and inflammation location. Inflammation is a cellular response that appears on the condition of cellular injury and the scar tissue. One example of ongoing inflammatory condition is a tumor, and this disease is the target of mesenchymal stem cells. More than two decades ago, Dvorak and colleagues have explained that the tumor act as an 'unheal wound" which produce inflammatory mediators sources continuously (such as cytokine, chemokine and other chemoattractant molecules). The production of these inflammatory mediators (which are constantly occur) will lead to the continuity of maintenance and development mechanisms of tumour microenvironent, this mechanism is the target of mesenchymal stem cells (Spaeth *et al*., 2008).

Inflammatory mediators plays a role in determining the microenvironment conditions, such as its role in regulating the invasion, motility, extracellular matrix interactions through autocrine effects, also in coordinating the movement of cells through paracrine signaling (Spaeth *et al*., 2008). Inflammatory chemokynes produced by a tumour known to have an important role in the infiltration of

leukocytes/macrophages to the tumour. Based on this evidence, it can be speculated that the chemokine-induced inflammation participates in directing migration/mobilization of stem cells, such as mesenchymal stem cells. A number of previous studies have shown the importance of inflammation to the success of the homing mechanism of hematopoietic stem cell infused into the heart tissue, this fact reinforces the idea of inflammatory and chemokine production in mesenchymal stem cell migration (Spaeth *et al*., 2008). Inflammatory conditions has a number of similarities with hypoxia, one of which is the expression of the pro-angiogenic molecules. Induction of transcription factor HIF-1α activates transcription of genes including *vascular endothelial growth factor (VEGF), macrophage migration inhibitory factor, tumor necrosis factor (TNF-α),* a number of proinflammatory cytokines and activation of the transcription factor nuclear factor κB (Spaeth *et al*., 2008; Winner *et al*., 2007).

Nuclear factor κB often activated as a response to inflammatory mediators and it has been proved to induce a number of ckemokines (RANTES (CCL5), MIP-2 (CXCL2), MIP-1α (CCL3), monocyte chemoattractant protein 1 (MCP-1) (CCL2), interleukin-8 (CXCL8)), which are involved in leukocyte migration process (Spaeth *et al*., 2008; Pold *et al*., 2004). Mesenchymal stem cell migration mechanism is not fully understood until now and its still under investigation. However, the factors that are involved in regulating leukocyte migration process has been studied extensively and it seems there are a lot of the same factors that are involved in the regulation of mesenchymal stem cell migration (Spaeth et al., 2008). A number of receptors expressed on mesenchymal stem cells and has been known to have implications in cell migration can be seen in the following table:

Table 1. Mesenchymal stem cells' surface markers and its receptors related to cell migration (Spaeth et al., 2008)

	Cell surface receptors found on MSC	**Ligands**	**Present on other cell types**
Growth hormone receptors	EGFR (ErbB)	EGF	DC, neutrophil
	HGFR (c-met)	HGF	Leukocytes, macrophages
	IGFIR	IGF1	Leukocytes, HSC
	PDGFR (Ra-b)	PDGFa/b	HSC
	VEGFR1	VEGF	HSC, monocytes, neutrophils
	VEGFR2	VEGF	HSC
	FGFR2	FGF2	HSC, leukocytes
	Tie-2	Ang-1	HSC, leukocytes
Chemokine / cytokine receptors	CCR1	CCL3, CCL5, CCL7, CCL13, CCL14, CCL15, CCL16, CCL23	Monocyte, T cell, DC
	CCR2	CCL2, CCL7, CCL8, CCL13, CCL16	Monocyte, T cell, DC
	CCR3	CCL5, CCL7, CCL8, CCL11, CCL13, CCL15, CCL16, CCL24, CCL26, CCL28	T cell, DC
	CCR4	CCL17, CCL22	T cell, macrophage, DC
	CCR5	CCL3, CCL4, CCL5, CCL8, CCL11, CCL14, CCL16	Monocyte, T cell, DC, HSC
	CCR6	CCL20	T cell, B cell, DC
	CCR7	CCL19, CCL21	T cell, DC
	CCR8	CCL1	Monocyte, T cell, DC
	CCR9	CCL25	T cell
	CCR10	CCL27, CCL28	T cell
	CXCR1	CXCL6, CXCL7, CXCL8	Neutrophil, monocyte
	CXCR2	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8	Neutrophil, monocyte
	CXCR3-A/B	CXCL4, CXCL9, CXCL10, CXCL11	T cell, microvascular cells
	CXCR4	CXCL12	T cell, B cell, monocyte, macrophage, DC
	CXCR5	CXCL13	B cell, Th cells, HSC
	CXCR6	CXCL16	CD8 T cells, NK cells, CD4 T cells
	CX3CR1	CX3CL1	Macrophage
	XCR1	XCL1, XCL2	T cell, NK cell
Adhesion	VCAM-1 (VLA-4)	β1 integrin/α4 integrin	Leukocytes

Molecules	ICAM-1/3	LFA-1	Leukocytes, DC
	ALCAM	CD6	Leukocytes
	Endoglin (CD105)	TGF β1/3	Leukocytes, HSC
	TLR1	Lipopeptides	Leukocytes
Innate immune surveillance	TLR2	Peptidoglycans, lipopeptides	Monocytes, DC
	TLR3	dsRNA	DC
	TLR4	LPS	Monocytes, DC
	TLR5	ECM molecules	Monocytes
	TLR6	Peptidoglycans	Epithelium

Activation of mesenchymal stem cells with proinflammatory cytokines (TNF-α) before reinfusion has been proven in vivo able to increase mesenchymal stem cell migration and adhesion capacity (adherence) through the increase of receptor's expression. Existing data stating that the cytokine IL-1β and TNF-α activating adherence devices owned by mesenchymal stem cells include upregulation of adhesion pathway of VCAM-1 VLA-4. Other receptors which undergo upregulation by TNF-α include CCR3 and CCR4; These findings relate to the in vitro observations to the increased migration to RANTES (a CCR3 ligand) and macrophage-derived cytokines (MDC (CCL22)-ligand CCR4) (Spaeth *et al*., 2008; Segers *et al*., 2006; Lopez *et al*., 2007).

Inflammatory chemokine receptor expression in mesenchymal stem cell are affected by the condition of micronvironment. For example, TNF-α causes upregulation chemokine receptors CC- but not on CXC-. The existence of certain chemokine receptor upregulation in response to cellular signals may have a role in tissue-specific homing (Lopez *et al*., 2007; Spaeth *et al.,* 2008).

Conclusions

Mesenchymal stem cell is type of adult stem cells which is most widely researched and clinically tested. This type of stem cell has the multipotent ability and able to differentiate into osteocytes, tenocytes, adipocytes, chondrocytes and bone marrow stromal cells. Marker expressed by mesenchymal stem cells include CD29, CD44, CD51, CD73 (SH3/4), CD105 (SH2), CD166 (Alcam) and stro-1. In order to express a specific marker combination by mesenchymal stem cells is highly dependent on the microenvironment. Mesenchymal stem cells are believed to have chemotactic device similar to other immune cells that provide a response to injury and inflammation location. A number of chemokine that plays a role in the migration of mesenchymal stem cells such as MCP-1 (CCL2), CXCL8, RANTES (CCL5), LL-37, integrin β1, CD44 receptor, CCR2, CCR3, and tyrosine kinase receptors for the following growth factors: IGF -1, PDGF-bb, HGF and VEGF. Further research should be conducted to explore the mechanism of mesenchymal stem cells migration.

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