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ROLE OF CHEMOATTRACTANT CHEMOKINE (SDF-1/CXCR4) IN BONE MARROW NICHE

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INTRODUCTION

Bone marrow is the pioneer for studying stem cells. The basic concept of stem cells obtained by studying hematopoietic stem cells. Although how the interaction of HSCs with the local environment necessary for the maintenance of stem cells can not be fully explained (Compston, 2002; Iwasaki and Suda., 2010)**.** Studies of HSCs aims to study the habits of these cells in a population of cells contained in bone marrow . So far little is known about the interaction of the bone marrow niche. The study was conducted using a culture system that limited done in a sustainable way to prove the interaction of the bone marrow niche. From these results can then be identified subset of osteoblasts (N-Cadherin + CD 45-) that physically attaches to the HSCs in the BM . (Tong Yin , 2006)

Bone marrow consist of hematopoietic cells are wrapped by the bone structure. Hematopoietic cells develop in the bone cavity and retained in the bone marrow until they have matured, then released into the vascular system (Yin and Li , 2006). Most cells of haemopoietic can be found next to the endosteal surface of the bone, which layer is primarily osteoblasts. Osteoblasts is one type of bone cell that serves to reform or bone formation. HSCs are stem cells that are known to differentiate into osteoclasts. Osteoclasts are the cells of bone that serves to bone resorption. Their physical proximity between osteoblasts and which HSCs are parent cells osteoclasts, as well as the identification of N - Cadherin / β - Catenin adherent complex between the two prove their relationship or communication between these cells. Osteoblast cells not only play a role in bone formation, but as osteoblast niche in the bone marrow also, contribute to the maintenance of HSCs that are stem cells osteoclasts (Yin and Li , 2006 ; Tong Yin , 2006).

There are two main types of stem cells are embryonic and adult stem cells . Pluripotent embryonic stem cells derived from the inner cell mass of blastocysts and has the ability to be a three embryonic germ layers , namely ectoderm , endoderm , and mesoderm (Li and Xie , 2005). At birth, adult stem cells including GSCs and SSCs will occupy and live in a special microenvironment, called a niche (Li and Sie., 2005)

Niche is different depending on the type of tissue or organ. Structurally niche supported by the cells and their interactions molecular signals that prepared and provided to form a microenvironment for stem cells. Niche hypothesis has actually been described by Scofield in 1978 (Li and Sie , 2005; Yin and Li , 2006) . Stem cell niche is supported by many signaling and adhesion molecules involved in the interaction of the stem cell niche, accounted diverse characteristics for each niche function (figure 1) that is; SDF -1/CXCR4 , SCF/c - Kit, Jagged/Notch, angiopoietin-1/ Tie2 (Ang-1/Tie2), and Ca2 + - sensing receptor (Yin and Li, 2006). Most studies conducted to know and understand the molecular mechanisms of interaction and behavior of stem cells. Understanding the interaction and behavior of stem cells in the bone marrow niche is very important to understand the events osteoclastogenesis, especially how osteoclast precursor cells can be recruited from niche then mobile until homing (Kollet et al , 2007). Research is usually conducted in diseases associated with the accumulation of osteoclasts or osteoclast progenitor cells that causes pathological osteolysis , such as ; benign bone tumors and bone metastases cancer (Kollet et al , 2007; Jennifer , 2009).

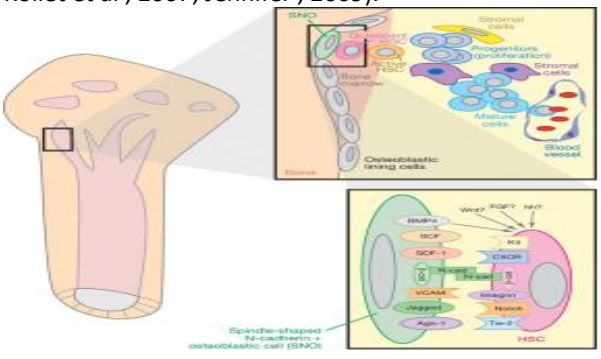

Figure 1. Illustration of Hematopoietic Stem Cell (HSC) niche (Li and Xie , 2005).

Bone Marrow Niche (osteoblastic niche and Haemopoetic/ vascular niche)

Stem cells that are in a particular area in the bone marrow (Iwasaki and Suda., 2010). The researchers tried to explain the contact between cells, such as

hematopoietic stem cells with bone-lining endosteal osteoblasts or stromal cells. The location is situated on the main microenvironment endosteum, between periosteal bone with bone marrow cavity , called bone marrow stem cell niche (Yin and Li , 2006). From the results of the research on bone marrow niche described the existence of endosteal / osteoblast niche and vascular / haemopoietic niche. Endosteal is the inner surface of the bone and bone marrow. In this region of the outer layer is a group of osteoblasts at various stages of differentiation. Osteoblasts have an important role in the maintenance and support of HSCs in the niche are Spindle-shaped N- Cadherin positive Osteblastic Cell (cell SNO) (Yin and Li ,2006; Andrew ,2011). Osteoblasts expressed stromal cell derived factor-1 chemoattractant (SDF-1, also called CXCL12) , which produced very much by endosteal stromal cells. SDF-1 receptor is CXCR4 expressed by hematopoietic stem cells (Kollet , et al , 2007; Jennifer , 2009). N-cadherin/β catenin is a means of communication between osteoblasts and HSC to be attached (Yin and Li , 2006). Another signaling and adhesion molecule involved in the interaction of stem cell niche, accounted diverse characteristics for each function niche, that is; SCF/c - Kit , Jagged / Notch , angiopoietin - 1 / Tie2 (Ang - 1/Tie2) , and Ca2 + - sensing receptor (CAR). WNT , BMP , TPO , IL - 3 , and IL – 6 also known to play a role in the regulation of stem cells. Although at this point it is unclear whether all of the last molecules contained in a niche . (Bianco , et . al, 2000; Li and Sie and 2005 ; Kollet , et .al, 2007).

Hematopoiesis and vascularization occur simultaneously during development. In fact HSCs and endothelial cells derived from progenitor cells of the same (hemangioblas) at the embryonic stage and is closely related to ontogeny of hematopoiesis, occurring in Yolk Sac and adult bone marrow. The research explained that HSCs together using osteoblasts and endothelial cells as a niche in different states. Vascular niche to support proliferation and subsequent differentiation of stem cells (Lianping and Schwarz , 2005; Jennifer , 2009)

Several studies have described that the vascular environment is involved in maintenance of HSCs such as the environment endothelial (wYin and Li , 2006 ; Andrew. , 2011). Bone marrow is rich vascularity, there are medullary arteries , capillaries and sinusoids . Sinusoid is the specific blood vessels have thin walls compiled by the endothelial cells and is the entry and exit of hematopoietic cells. Endothelial cells is an essential component of the HSC niche (Andrew, 2011). The endhotel cells of the vascular niche will express and secrete SDF-1 at the high level to the circulation (figure 2) . The high levels of SDF-1 into circulation can attract HSCs and precursor cells into the circulation . Likewise when the homing process (Yin and Li , 2006) .

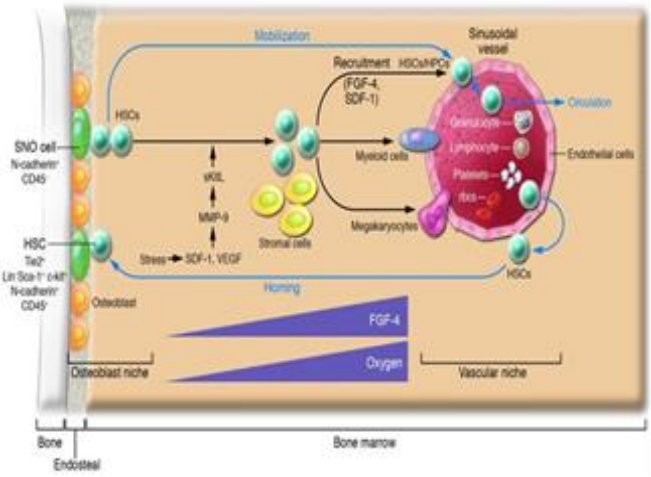

Figure 2. Osteoblastic and vascular niches in BM. (Yin and Li , 2006)

Very slightly primitive progenitor at steady state and stem cells come out into circulation.The function of stem cells in circulation until now has not been fully explained, and mechanisms that mediate physiological homeostasis is not fully understood. Although the level of stem cells in circulation will drastically increase as a response to treatment with mobilizing cytokines , Granulocyte - Colony Stimulating Factor (G - CSF). Other mobilizing other agent showing the effect on the blood HSCs expenditure are ; chemotherapy , irradiation , cytokines (SCF, IL - 8 , CXCR4 - Agonist AMD3100 or sulfated polysacharide) and fucoidan (Juarest , et al ., 2004). SDF - 1 not only regulates cell trafficking but also have implications on the retention of HSCs in the endosteal niche in BM (Juarest, et al., 2004; Gregor and David, 2006)

Chemoattractant chemokine (SDF-1/CXCR4

Chemokines are chemoattractant cytokines that attract inflammatory cells and osteoclast precursor cells. Its name comes from its ability to directly affect chemotaxis in cells , it is called kemotatik kemokine (Juarez , 2004; Green et al 2009).

SDF-1 receptor CXCR4 is expressed by a variety of cell types including the hematopoietic cells , endothelial cells , neurons , microglia and astrocytes (Juarez , 2004). Ties chemokines (SDF-1) on a seven-transmembrane G protein -coupled receptor is required as a regulator for tracffiking and cell adhesion (Teicher and Fricher , 2010) .

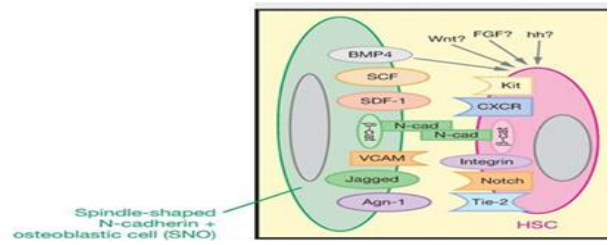

Figure 3. Signal transduction osteoblasts cells and HSC involve chemokines . Some signaling and adhesion molecules involved in the interaction of stem cell niche , accounting for a variety of characteristics for each function niche (Linheng Li and Ting Xie , 2005)

One of the chemokine is SDF - 1 (stromal derived factor - 1) or also known as CXCL12 is secreted by osteoblasts. SDF - 1 receptor is CXCR4 , the SDF - 1 specific receptor that is known to be expressed by leukocytes and stem cells haemopoetik which is the origin of osteoclast precursor cells (Bilezikian , et.al , 2008; Green, et.al , 2009). SDF - 1 is a strongest chemoattractant on stem cells, it is survival of stem cell factor and also the regulator who interact on the attachment of stem cells in the extracellular matrix or stromal cells. The existence of the SDF-1 is believed to be required as a cell signaling system that serves as a guide for the movement of cells (Juarez , 2004; Yu et al , 2003). The statement was based on research results of SDF-1 on the movement of plasma cells , B cells , T cells , and dendritic cells . SDF - 1 is produced by endosteal human or murine osteoblasts , and by stromal cells in BM in both humans and murine (Yu , et al. 2003 , Julius , et al , 2004 , Bilezikian , et.al , 2008; Green , et.al , 2009).

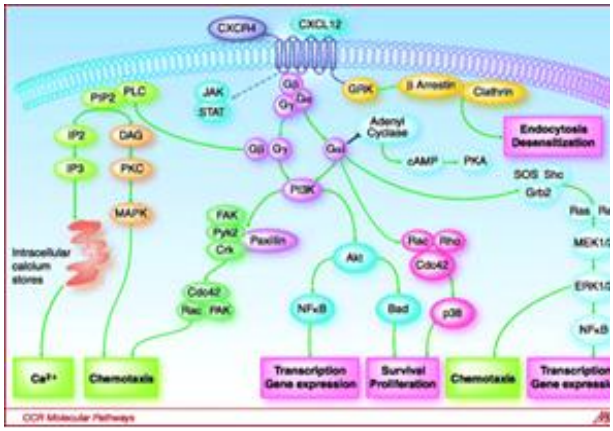

Figure 7. Schematic transduction Intracellular Signaling Pathway of SDF - 1 / CXCR4 (Teicher and Fricher , 2010).

DISCUSSION

It was explained that the circulation of HSCs HSC involve leaving the BM, entry into the vascular system (mobilization) , and returned to the bone marrow (homing). However, the physiological functions that underlie these events is not well understood. Vascular structures in the BM provides a barrier between compartments and hematopoietic peripheral circulation. Physiologically primitive HSCs remained silent in the BM niche, but most HSCs left resting place and begin the process of mobilization. Osteoblastic niche and vascular niche may play an important role in regulating HSC mobilization, includes HSCs leave osteoblastic niche, mobilization to the vascular niche , enter the bloodstream through the endothelial cells, then circulate in the vascular system (Bianco and Robey , 2000; Yin and Li , 2006). Factors niche is one of the factors that play a role in osteoclastogenesis at the time of recruitment of osteoclast precursor stem cells to differentiate into osteoclasts. Multiple signaling includes chemoattractant Chemokines, proteases and adhesion molecule involved in the interaction of stem cell-niche and also donated an assortment of characteristics for each function niche. Molecule signals that have been studied by those involved in the regulation of such niche ; SDF - 1 / CXCR4 , SCF / c - Kit , Jagged / Notch , angiopoientin - 1 / Tie2 (Ang - 1 / Tie 2) and Ca2 + -sensing receptor (Yin and Li, 2006).

Endosteal and vascular niche known to be involved in the regulation of HSC population. Niche supported by the cells and their interactions molecular signals prepared and provided for microenvironment for HSC (Andrew, 2011; Gregor, 2006). The researchers successfully identified a number of intrinsic pathway plays a role in the regulation of HSC is mainly to defend themselves and differentiate. Until now, a lot of research on the BM niche focused on niche Osteoblas and vascular niche suggest that played a key role in regulating HSC mobilization. The process includes leaving osteoblasts HSC niche , mobilization to vascular , and then enter the bloodstream through the endothelial cells and circulating in the vascular system. Next is the HCS homing. HSC homing process is the reverse of the mobilization process , in which the end of the process will return to the HSC niche osteoblasts (Yin and Li , 2006; Magnom , 2010) .

SDF - 1 is a chemoattractant strongest on stem cells, it is survival of stem cell factor and also regulators who interact on the attachment of stem cells in the extracellular matrix or stromal cells (Yu , et al . 2003; Julius , et al ; 2004; Bilezikian , et al . , 2008; Green , et al , 2009). Chemokines will function after binding to its receptor is a superfamily of seven- span transmembrane receptors through G protein coupled heterotrimetric, (Kofuku 2009 ; Teicher and Fricker , 2010). The receptor binds to a G protein called G-Protein-Coupled Receptors (GPCR). is a single polypeptide chain seven transmembran. Protein G consists of three different polypeptide chains that subunit α , β , γ . This receptor activates

mainly by changing the sequence of events resulting in the second messenger cellular response. Some second messenger involved in signal transduction through these receptors are cyclic AMP (cAMP), protein kinase (PKA), Inositol triphosphate (IP3), diasil glycerol (DAG) and calcium Ca ++ (Teicher and Fricker, 2010).

The bond between SDF-1 and CXCR4 signaling causes the activation of intracellular signaling through several different pathways. There are two pathways for GPCR signal transduction pathways that adenylyl cyclase and phospholipase pathway (Figure 4) (Teicher and Fricker , 2010). If there is a GPCR receptor activation through the adenylate cyclase by a ligand, then start a process that begins with the signaling receptor conformational change involving receptor cytoplasmic region, Then the cytoplasmic region of the protein receptors become activated G. Further sub Gα releases GDP and binds GTP, causing conformational changes in the subunit Gα. Gα subunits that are tied to the GDP dissociates from βγ subunits into active subunits, which will activate adenylyl cyclase to produce cAMP. CAMP then will turn on PKA (cAMP - dependent protein kinase) that will catalyze a variety of target proteins. Furthermore initiation signals associated with chemotaxis, survival or proliferation, increased intracellular Ca and gene transcription. The purpose of the various pathway is likely dependent tissues and cell types (Teicher and Fricher , 2010).

Phospholipase pathway activited, initially the same as the adenylate cyclase pathway. But in this pathway are active α subunits would activate the enzyme phospholipase C. Subsequently the enzyme phospholipase C will work outlines phosphatidyl inositol bisphosphate (PIP2) into phosphatidyl inositol triphosphate (PIP3) and diasil glycerol (DAG). Both act as second messengers. IP3 binds to specific receptors on the reticulum endoplasmi associated with Ca ++ channels, thus triggering the release of Ca ++ from the ER to the cytosol (Teicher and Fricker , 2010).

CONCLUTION

Chemoattractant chemokine involved in controlling the migration of cells in the normal process for the development and maintenance of the network. SDF-1 is a strongest chemoattractant chemokine and survival factors in the bone marrow niche, also the regulator who interact on the attachment of stem cells in the extracellular matrix or stroma cells. The existence of the SDF -1 is believed to be required as a cell signaling system that serves as a guide for the movement of cells. Some of the pro-inflammatory chemokine as play a role in the immune response system to recruit immune cells to the area of infection.

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