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# Effects of cytokines and chemokines on migration of mesenchymal stem cells following spinal cord injury ☆

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## Abstract

We investigated the effects of cytokines and chemokines and their associated signaling pathways on mesenchymal stem cell migration after spinal cord injury, to determine their roles in the curative effects of mesenchymal stem cells. This study reviewed the effects of tumor necrosis factor- $\alpha$ , vascular endothelial growth factor, hepatocyte growth factor, platelet-derived growth factor, basic fibroblast growth factor, insulin like growth factor-1, stromal cell-derived factor and monocyte chemoattractant protein-1, 3 during mesenchymal stem cell migration to damaged sites, and analyzed the signal transduction pathways involved in their effects on mesenchymal stem cell migration. The results confirmed that phosphatidylinositol 3-kinase/serine/threonine protein kinases and nuclear factor- $\kappa$ B play crucial roles in the migration of mesenchymal stem cells induced by cytokines and chemokines.

## Key Words

spinal cord injury; mesenchymal stem cells; migration; cytokine; chemokine; signaling pathway; neural regeneration

## Abbreviations

SCI, spinal cord injury; MSCs, mesenchymal stem cells; PI3K, phosphatidylinositol 3-kinase; NF- $\kappa$ B: nuclear factor- $\kappa$ B; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ ; SDF-1: stromal cell-derived factor-1; VEGF: vascular endothelial growth factor; PDGF: platelet-derived growth factor; HGF: hepatocyte growth factor; bFGF: basic fibroblast growth factor; IGF-1: insulin-like growth factor-1; MCP: monocyte chemoattractant protein

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## INTRODUCTION

Recent studies have focused on mesenchymal stem cells (MSCs) for the treatment of spinal cord injuries (SCIs). However, it is necessary to increase MSC migration to damaged sites and numbers of MSCs at the damaged sites in order to realize the therapeutic effects of MSC transplantation<sup>[1-5]</sup>. A previous study found that the expression levels of various cytokines and chemokines were upregulated after SCI<sup>[6]</sup>. MSCs express cytokine and chemokine receptors that participate in signal transduction pathways during MSC migration<sup>[2]</sup>. However, the

precise relationship between the various cytokines and chemokines and MSC migration remains unclear. The present study reviewed the relationships between cytokines and chemokines and MSC migration, and examined the signal transduction mechanisms activated after SCI, to inform subsequent research into MSC migration mechanisms and SCI treatment.

## EFFECTS OF CYTOKINES ON MSC MIGRATION AFTER SCI

### Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )

TNF- $\alpha$  is an important proinflammatory

factor that is rapidly induced in local regions after SCI<sup>[7]</sup>. TNF- $\alpha$  induces neuronal apoptosis, and early and immediate inhibition of TNF- $\alpha$  expression therefore relieved pathological changes in the spinal cord and improved functional disturbance<sup>[8]</sup>. In contrast, Pan *et al*<sup>[9]</sup> found that TNF- $\alpha$  improved neurological function of the spinal cord, associated with a specific time window of TNF- $\alpha$  upregulation. A study of TNF- $\alpha$  protein and mRNA levels confirmed that human MSCs express TNF- $\alpha$  receptors<sup>[10]</sup>, and that the combination of TNF- $\alpha$  and its receptor enhanced the adhesion of human MSCs and vascular endothelial cells, as well as the targeted-migration ability of human MSCs<sup>[11]</sup>. TNF- $\alpha$  is therefore believed to contribute to the induction of targeted migration of MSCs towards damaged sites in the spinal cord.

Another study<sup>[12]</sup> demonstrated that TNF- $\alpha$  activated the extracellular signal-regulated kinase and p38 pathways in MSCs, accelerated intranuclear genetic transcription and protein synthesis, and promoted MSC migration activity by combining with MSC surface receptors. In addition, TNF- $\alpha$  activated inhibitor protein  $\kappa$ B (I $\kappa$ B) kinase/I $\kappa$ B/nuclear factor- $\kappa$ B (NF- $\kappa$ B), accelerated intranuclear genetic transcription and protein synthesis, and strengthened MSC migration ability<sup>[13]</sup>. CC chemokine receptor expression levels were upregulated and interactions with ligands were reinforced in the presence of TNF- $\alpha$ <sup>[14]</sup>. CXC-chemokine receptor 4 (CXCR4) expression was unaffected by TNF- $\alpha$ , but TNF- $\alpha$  promoted MSC migration by enhancing its sensitivity to stromal cell-derived factor-1 (SDF-1)<sup>[14]</sup>. Further studies are needed to determine if TNF- $\alpha$  enhances MSC migration by directly activating intracellular signal cascade reactions, rather than by enhancing interactions between other factors/receptors.

### Vascular endothelial growth factor (VEGF)

VEGF is a homodimeric glycoprotein that increases MSC transplantation efficiency after ischemic injury<sup>[10]</sup>. Liu *et al*<sup>[15]</sup> found that VEGF-A was highly expressed in ischemic central nervous system, and improved the recovery of spinal cord function. VEGF-A is a highly-active member of the VEGF family, which has been shown to enhance human MSC migration<sup>[16]</sup>. The promotional effects of VEGF-A on the recovery of neurological function of the spinal cord may therefore be associated with stimulation of the migration of MSCs to the damaged region. However, VEGF receptors have not been found on the surface of human MSCs; VEGF and platelet-derived growth factor (PDGF) exert their effects *via* PDGF receptors<sup>[16-17]</sup>. VEGF and PDGF are derived from different branches of the same ancestor, and VEGF can exert its effects after combining with the PDGF receptor<sup>[16]</sup>. Ball *et al*<sup>[16]</sup> indicated that PDGF family

homodimers or heterodimers participate in the VEGF-A/PDGF signaling pathway. Moreover, the combination of PDGF and VEGF was more effective at mediating bone marrow MSC migration compared to either PDGF or VEGF alone<sup>[16]</sup>. Lee *et al*<sup>[18]</sup> reported that VEGF combined with Src stimulated focal adhesion kinase phosphorylation, while focal adhesion kinase also stimulated Src phosphorylation, which finally activated a downstream signaling cascade reaction. The non-receptor tyrosine kinase, Src, regulates cytoskeletal reorganization, cell adhesion, and migration.

### Hepatocyte growth factor (HGF)

Expression levels of HGF and its receptor c-met are upregulated following SCI<sup>[19]</sup>, and contribute to the recovery of spinal cord function<sup>[20]</sup>. An *in vitro* study by Son *et al*<sup>[21]</sup> verified that HGF regulated MSC migration by c-met and exerted chemotactic effects. Upregulated HGF expression therefore contributed to the migration of MSCs to the damaged region.

Royal *et al*<sup>[22]</sup> suggested that the small G-protein Ras-phosphatidylinositol 3-kinase (PI3K) pathway directly controlled Rac and p21-activated kinase and induced cytoskeletal reorganization following HGF-triggered signaling cascade reactions in MSCs. HGF increased Rac1 activity in a Ca<sup>2+</sup>-dependent manner<sup>[23]</sup>, while Rac1 facilitated lamellipodia formation<sup>[24]</sup>, and accelerated MSC migration by stimulating the Wiskott-Aldrich syndrome protein family verprolin-homologous protein. HGF also promoted c-met phosphorylation, and these activated receptors could then activate PI3K/Akt pathway<sup>[25]</sup>, resulting in cell migration. Regulation of the HGF/PI3K/Rac1/ signaling pathway may thus represent a target for enhancing MSC migration and improving its curative effects.

### PDGF

PDGF comprises four subtypes: PDGF-A, -B, -C and -D. PDGF receptor tyrosine kinase contains PDGF-R $\alpha$  and PDGF-R $\beta$ , composed of homodimers or heterodimers. PDGF-A and PDGF-B exist as dimers and exert their effects by combining with their corresponding receptors<sup>[26]</sup>. Wu *et al*<sup>[27]</sup> found that PDGF expression was significantly elevated and exerted neuroprotective effects at 7 days following SCI, consistent with the results of another previously published study<sup>[28]</sup>. Hata *et al*<sup>[29]</sup> verified that upregulation of PDGF-B expression contributed to targeted migration of human MSCs. Upregulated PDGF-B expression could thus induce MSC migration to damaged regions of the spinal cord. Kang *et al*<sup>[30]</sup> thought that PDGF-B activated c-Jun NH<sub>2</sub>-terminal kinases in MSCs, resulting in phosphorylation of the transcription factor c-jun. The

targeted migration ability of human MSCs was strengthened by regulating some genetic transcription processes, but the precise mechanisms were not investigated<sup>[30]</sup>. Ligand-stimulated and activated PDGF receptors could stimulate PI3K and activate small G-protein family Rac<sup>[26]</sup>. The combined effects of Rac1 and Cdc42 led to cytoskeletal changes, and controlled the speed and direction of cell migration<sup>[31]</sup>. The above results may be associated with the activation of actin-related proteins 2/3 and actin polymerization after combination of Cdc42 with Wiskott-Aldrich syndrome protein<sup>[24]</sup>. PDGF may thus induce MSC migration to damaged regions via PDGF-B c-Jun NH<sub>2</sub>-terminal kinases/c-jun and PDGF-PI3K-Rac/Cdc42/Wiskott-Aldrich syndrome protein-actin-related proteins 2/3 pathways.

### Basic fibroblast growth factor (bFGF)

SCI rapidly and significantly increased bFGF expression, activated a cascade reaction<sup>[32-33]</sup>, and promoted the recovery of spinal cord function after SCI<sup>[33-34]</sup>. Schmidt *et al*<sup>[35]</sup> observed significant bFGF-induced human MSC migration, while Liu *et al*<sup>[33]</sup> verified that the number of MSCs highly expressing bFGF after SCI was significantly increased compared to the control group, suggesting that bFGF contributed to the targeted migration of MSCs. Concentration-gradient experiments confirmed that low concentrations of bFGF suppressed MSC migration, while high concentrations promoted MSC migration; when the concentration was continuously increased, the migration activity of human MSCs fell to the initial level<sup>[35]</sup>. bFGF activates FGF receptors, which trigger PI3K/Akt<sup>[36]</sup> signaling and an increase in Akt and phosphoAkt<sup>[35]</sup>. These results indicate that bFGF induces human MSC migration via a FGFR/PI3K/Akt pathway.

### Insulin-like growth factor-1 (IGF-1)

Increased expression of IGF-1 after SCI has been shown to promote the recovery of neurological functions, suppress neuronal apoptosis, and reduce the inflammatory reaction<sup>[37-41]</sup>. Baek *et al*<sup>[40]</sup> reported that IGF-1 mediated MSC migration, which may explain its effect on the recovery of neurological functions. Haider *et al*<sup>[41]</sup> confirmed that transplantation of MSCs expressing high levels of IGF-1 resulted in elevated SDF-1 $\alpha$  and phosphorylated Akt levels. IGF-1 increased the expression levels of CXCR4, strengthened the MSC response to SDF-1 through the PI3K/Akt pathway, and increased cell migration ability<sup>[42]</sup>. Thus although there was no evidence that IGF-1 directly induced MSC migration, it was able to increase SDF-1/CXCR4 chemotaxis and control MSC migration via PI3K/Akt.

## EFFECTS OF CHEMOKINES ON MSC MIGRATION AFTER SCI

### SDF-1

Knerlich-Lukoschus *et al*<sup>[43]</sup> found that SDF-1 and CXCR4 were persistently highly expressed within 2–42 days after SCI. SDF-1 and CXCR4 mediated the migration ability of hematopoietic stem cells and hematopoietic progenitor cells<sup>[44]</sup>. Numerous studies have verified the chemotactic effects of SDF-1/CXCR4 during MSC migration<sup>[2, 45]</sup>. Tysseling *et al*<sup>[46]</sup> demonstrated that SDF-1 induced the migration of CXCR4-positive macrophages to damaged regions following SCI, and several studies have verified that SDF-1/CXCR4 regulates MSC migration to damaged sites in the central nervous system<sup>[47-50]</sup>. These results suggest that SDF-1/CXCR4 can mediate MSC migration to SCI regions. Wynn *et al*<sup>[45]</sup> reported that the CXCR4 response to SDF-1 was concentration-dependent; MSC migration would increase with increasing extracellular SDF-1 concentration or increasing numbers of cell surface receptors. Nevertheless, CXCR4 expression was rare on the surface of MSCs (3.9% of cells), despite the presence of non-activated receptors in 83–98% of MSCs. Thus, mobilization of internal CXCR4 may increase MSC migration ability and improve their therapeutic efficacy. The endothelial nitric oxide synthase/nitric oxide/soluble guanylate cyclase/cyclic guanosine monophosphate pathway upregulated SDF-1 $\alpha$  secretion and CXCR4 expression on the surface of MSCs after SCI<sup>[45]</sup>. Interaction of SDF-1 with CXCR4 resulted in activation of G-protein-coupled phospholipase C and PI3K pathways, as well as the activated protein kinase C pathway<sup>[42, 51]</sup>. SDF-1 chemotaxis is associated with atypical protein kinase C-zeta subtype. However, protein kinase C-zeta is not directly activated by phospholipase C, but is activated indirectly by diacylglycerol and second messengers such as ceramide and phosphatidic acid, or by the PI3K/Akt pathway, leading to activation of downstream signaling molecules<sup>[42]</sup> such as proline-rich tyrosine kinase 2, extracellular signal-regulated kinase<sup>[51]</sup> and the NF- $\kappa$ B pathway<sup>[52]</sup>. In addition, an upstream signaling molecule activated the downstream Janus kinase/signal transducer and activator of transcription and extracellular signal-regulated kinase pathways, and controlled focal adhesion kinase and paxillin activation and expression<sup>[52]</sup>. Interaction between intracellular focal adhesion kinase/Src regulated the downstream cascade reaction<sup>[24]</sup> and promoted human MSC migration.

### Monocyte chemoattractant protein-1 (MCP-1)

MCP-1 belongs to the CC subfamily of chemokines and exerts its effects by binding to CC chemokine receptor 2.

Baek *et al*<sup>[40]</sup> reported that MSCs could express CC chemokine receptor 2 mRNA, but did not express CC chemokine receptor 2 protein because of the lack of an inducer in the medium. Astrocytes in the SCI region have been shown to secrete MCP-1, leading to increased MCP-1 levels in the serum<sup>[53-54]</sup>. Wang *et al*<sup>[55]</sup> reported that MCP-1 contributed to MSC migration to the ischemic region, and CC chemokine receptor 2 is expressed on the surface of MSCs. Upregulated MCP-1 expression thus affected MSC migration by interacting with CC chemokine receptor 2.

Using MSCs transfected with a vector expressing a truncated version of FROUNT (DN-FROUNT), Belema-Bedada *et al*<sup>[56]</sup> reported that binding of activated CC chemokine receptor 2 to FROUNT triggered the PI3K-Rac pathway, induced cytoskeletal changes, produced pseudopodia, and promoted MSC migration after MCP-1 stimulation. When DN-FROUNT competes with endogenous FROUNT for CC chemokine receptor 2 binding and acts as a dominant-negative effector of CC chemokine receptor 2-mediated chemotaxis. The CC chemokine receptor 2/FROUNT/PI3K/Rac pathway could thus promote MSC migration.

### MCP-3

MCP-3 is a member of the CC-chemokine family that exerts various chemotactic effects by binding to its receptors CC chemokine receptors 2, 3 and 5. Ma *et al*<sup>[57]</sup> reported that MCP-3 expression was significantly increased at 1 day after SCI, compared to after 7 days. Interactions between CC chemokine receptors 3 and 5 and their ligand regulated targeted MSC migration<sup>[47]</sup>, but this chemotaxis was weak compared to that stimulated by SDF-1 under similar conditions. Schenk *et al*<sup>[58]</sup> failed to verify the promotion of MSC migration by interactions between MCP-3 and CC chemokine receptor 1 or CC chemokine receptor 2; nevertheless, Belema-Bedada *et al*<sup>[56]</sup> believed that MCP-3 exerted its effects by activating CC chemokine receptor 2. MCP-3 can also act *via* the above-mentioned CC chemokine receptor 2/FROUNT/PI3K/Rac pathway. Further investigations are therefore needed to determine if upregulated MCP-3 exerts chemotaxis by one or two receptors.

## DISCUSSION

In summary, expression levels of various cytokines and chemokines and their corresponding receptors are upregulated after SCI. These factors participate in targeted MSC migration, together with numerous signaling molecules in the *in vivo* microenvironment. All

these factors are interlinked to produce a signaling network able to induce targeted MSC migration *in vivo*. However, few recent studies have reported direct evidence for the promotion of targeted MSC migration by chemokines following SCI.

Current studies addressing the mechanisms of MSC migration have provided theoretical evidence to improve our understanding of the pathological changes and signaling molecule transduction occurring during MSC migration.

TNF- $\alpha$  can mediate MSC migration through its specific receptor. TNF- $\alpha$  binding to its receptors results in receptor activation, activation of NF- $\kappa$ B-inducing kinase *via* an adaptor protein, and triggering of the NIK/I $\kappa$ B kinase/I $\kappa$ B/NF- $\kappa$ B pathway, resulting in I $\kappa$ B complex degradation. Activated NF- $\kappa$ B subsequently enters the nucleus and induces various genes, including genes for cytokines, chemokines and adhesion factors<sup>[13]</sup>. Moreover, interactions between activated TNF receptors and ligands can activate various transcription factors, including c-Jun, NF- $\kappa$ B and ATF-2<sup>[13, 30]</sup> by activating MEKK1-MKK4/7-c-Jun NH<sub>2</sub>-terminal kinases and the MEKK1-MKK3/6-P38 pathway<sup>[25]</sup>, as well as promoting the expression of genes for products such as enzymes and receptors, including CC chemokine receptor 3, CC chemokine receptor 4 and intercellular adhesion molecule 1<sup>[12, 14]</sup> in MSCs, and responding to surrounding inducers. NF- $\kappa$ B plays an important role in signal transduction. TNF- $\alpha$  mediates NF- $\kappa$ B activation and intranuclear transfer<sup>[13]</sup>, and chemotaxis by SDF-1 associated with NF- $\kappa$ B<sup>[52]</sup>. In accordance with the NF- $\kappa$ B activation pathway, NIK caused MEKK1 activation resulting in I $\kappa$ B kinase phosphorylation, thus linking TNF- $\alpha$  downstream signaling molecules. Moreover, the p21-activated kinase, Akt and germinal center kinase pathways could activate MEKK1 and NIK kinases, and induce c-Jun NH<sub>2</sub>-terminal kinases and NF- $\kappa$ B activation. Second, as shown in Figure 1, the chemotaxis induced by many cytokines and chemokines was confirmed by PI3K/Akt pathway experiments. Interactions between ligands and receptors could directly or indirectly trigger PI3K and further activate downstream signaling molecules, including Akt and protein kinase C, as well as the Rho family member Rac, resulting in cascade reactions in the cytoplasm and nucleus, and mediating MSC activity<sup>[18, 22, 25-26, 35-36, 41-42, 52, 56]</sup>. The PI3K/Rac pathway is important<sup>[22, 26, 29, 42, 56]</sup>. The regulation by Rac of the downstream signaling molecules extracellular signal-regulated kinase and protein kinase C and the c-Jun NH<sub>2</sub>-terminal kinase pathway could induce nuclear gene expression and protein synthesis, resulting in MSC migration. It is assumed that the factors that trigger the PI3K/Akt pathway could activate NF- $\kappa$ B and control MSC migration activity.



SDF-1/CXCR4 chemotaxis has been a focus of attention. Previous studies found that SDF-1/CXCR4 mediated MSC migration to the bone marrow<sup>[2, 45]</sup>. Intracellular signaling molecules, such as endothelial nitric oxide synthase/nitric oxide guanylate cyclase/cyclic guanosine monophosphate pathway, adjusted SDF-1/CXCR4 expression on the surface of MSCs. In addition, interaction between SDF-1 and CXCR4 activated PI3K and the phospholipase C pathway, the protein kinase C and Akt pathways, and c-Jun NH<sub>2</sub>-terminal kinases and extracellular signal-regulated kinase signaling molecules, as well as adjusting genetic transcription and protein expression<sup>[24, 42, 51-52]</sup>.

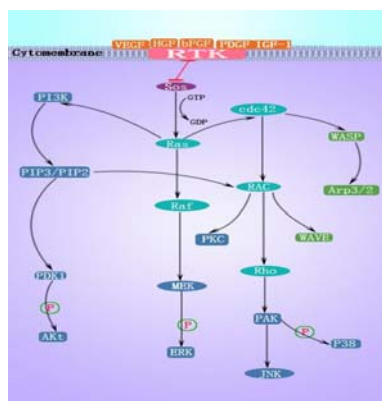


Figure 1 Schematic diagram of cytokine pathways.

Cytokines activated signaling cascade reactions in mesenchymal stem cells (MSCs) via receptor tyrosine kinase, and promoted cell migration.

The combination of cytokines and RTK activated the guanine nucleotide-exchange factor Sos, and further activated the Ras/PI3K/Akt, Ras/MEK/ERK, and Ras/Rac/PAK pathways, activated ERK, JNK and p38 signaling molecules, accelerated gene expression and protein synthesis, and promoted cell migration ability. The signaling cascade reactions were interlinked, and showed complementation and interdependence. Any deletion would thus affect cytokine-mediated MSC migration ability.

PDK: 3-phosphoinositide-dependent protein kinase; ERK: extracellular signal-regulated kinase; JNK: c-Jun NH<sub>2</sub>-terminal kinases; PAK: p21-activated kinase; PI3K: phosphatidylinositol-3 kinase.

SDF-1/CXCR4 could induce MSC migration, but although CXCR4 was expressed in most MSCs, few MSCs demonstrated surface expression of CXCR4<sup>[45]</sup>, thus limiting SDF-1/CXCR4 chemotaxis. Further studies are needed to clarify this issue. Increasing cell surface CXCR4 expression could enhance the effects of cell therapy.

This study reviewed the roles of cytokines and chemokines in MSC migration to damaged regions following SCI, including the signal conduction mechanisms involved in MSC migration. The PI3K pathway, extracellular signal-regulated kinase pathway

and NF- $\kappa$ B in particular, appear to play important roles in cytokine and chemokine-regulated MSC migration following SCI.

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**Conflicts of interest:** None declared.

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