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Decoding Mesenchymal Stem Cell Homing to Inflamed Organs: A Cross-Organ Systematic Review of Cytokine Gradients, Chemokines, and Surface Receptors

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Abstract | Chronic inflammatory diseases contribute substantially to global mortality and demand cell-based therapeutic strategies that are not only immunomodulatory but also capable of precise, stable, and sustained homing to target organs, while mechanistic evidence across organs remains fragmented. This study aimed to synthesize empirical evidence on the mechanisms by which mesenchymal stem cells (MSCs) sense inflammatory signals, the key cytokines/chemokines involved, and the surface receptors that regulate homing to inflamed organs. A systematic literature review was conducted using a Population, Intervention, Comparison, Outcome (PICO) framework using Scopus, Web of Science, and ScienceDirect databases, with standardised keywords. Study selection was facilitated by Parsif.al, applying predefined inclusion–exclusion criteria and methodological quality assessment using the Mixed Methods Appraisal Tool (MMAT 2018), followed by structured data extraction and narrative thematic synthesis. From 168 records, 57 experimental studies were included. These indicate that MSC homing is predominantly governed by the SDF-1/CXCL12–CXCR4 axis, which is potentiated by hypoxic and inflammatory conditions, alongside the roles of IL-1, IL-6, TNF-α, IFN-γ, IL-10, TGF-β, CCL2, chemerin, and CCL5, and the secretion of VEGF, HGF, TSG-6, and MMPs for tissue repair and matrix remodelling. Receptors including CXCR4, CXCR7, CCR2, CXCR1, CCR1, ChemR23, integrins, ICAM-1, VCAM-1, CD44/HCELL, PDGFR, and c-Met shape an organ-specific "homing signature". The concept of MSC "homing competence" supports the design of preconditioning strategies, route selection, and receptor engineering to achieve safer, more effective, clinically translatable and personalised therapies for inflammatory diseases.

Keywords | Mesenchymal stem cells, Homing, Cytokines, Chemokines, Surface receptors

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INTRODUCTION

Chronic inflammatory diseases are now recognised as the cause of more than 50% of deaths worldwide and are a major driver of the burden of non-communicable diseases (Furman *et al*., 2019). A global burden of disease analysis of seven immune-mediated inflammatory diseases (IMIDs) including asthma, psoriasis, rheumatoid arthritis, and inflammatory bowel disease (IBD) showed that their incidence and prevalence increased steadily from 1990 to 2021, with projections indicating a continued rise until 2046 (Zhu *et al*., 2025). Mesenchymal stem cells (MSCs) have emerged as candidate therapies for a variety of inflammatory and autoimmune diseases because of their immunomodulatory capacity and regenerative potential (Han *et al*., 2025).

Conventional therapeutic options, including corticosteroids, immunomodulators, and anti-TNF or anti-integrin biologic agents, are currently utilized in clinical practice, with clinical responses often remaining incomplete and being accompanied by loss of response, serious adverse events, and substantial treatment costs (Zaidi *et al*., 2025). Therapeutic strategies that not only suppress inflammation but also specifically and durably target structurally damaged organs are required. An in-depth understanding of how MSCs sense inflammatory signals and home to target organs is regarded as crucial for improving therapeutic success.

Multiple experimental studies have shown that MSC homing to inflamed organs is regulated by a combination of cytokine/chemokine gradients (e.g. SDF-1/CXCL12, CCL2), surface receptors such as CXCR4, CCR2, and adhesion molecules (ICAM-1, VCAM-1), as well as the route of administration (intravenous, intraperitoneal, anal, intranodal) (Ullah *et al*., 2019). *In vivo* studies in models of liver injury, acute kidney injury, and colitis have demonstrated that manipulation of the SDF-1/CXCR4 axis, choice of injection route, and the inflammatory microenvironment can alter the biodistribution and accumulation of MSCs in target organs (Ling *et al*., 2016; Moustafa *et al*., 2016; Wang *et al*., 2016; López-Santalla *et al*., 2018; Zheng *et al*., 2019; Ding *et al*., 2023). However, most of these studies have focused on a single organ, a single chemokine axis, or a single route of administration, and there is still no systematic cross-organ synthesis that specifically addresses: (1) how MSCs recognise inflammatory signals, (2) which key cytokines and chemokines guide MSC homing, and (3) which MSC surface receptors determine the specificity of homing to inflamed organs. This research gap underpins the research questions in this systematic literature review (SLR).

This study aimed to conduct a SLR of empirical evidence regarding: (1) the mechanisms by which MSCs recognise inflammatory signals, (2) the key cytokines and chemokines that direct MSC homing to inflamed organs, and (3) the surface receptors that play pivotal roles in cross-organ homing. By synthesising findings from various animal models and experimental studies, this SLR is expected to generate a "homing competence" framework that links cytokine/chemokine profiles, receptor expression, and routes of MSC administration. Accordingly, this study is important for bridging the gap between mechanistic evidence and the design of more precise, organ-targeted MSC therapies for inflammatory diseases.

MATERIALS AND METHODS

This study employed a Systematic Literature Review (SLR) approach to identify and critically appraise research on the mechanisms by which mesenchymal stem cells (MSCs) recognise inflammatory signals, the key cytokines and chemokines involved in MSC homing to inflammatory sites, and the surface receptors that are crucial for MSC homing to inflamed organs. The SLR approach was chosen because it enables a comprehensive, structured, and unbiased appraisal of the literature and provides a robust empirical basis for formulating evidence-based recommendations.

The review framework was structured using the Population, Intervention, Comparison, Outcome (PICO) approach derived from the following research questions (Stark and Woods, 2022): How do MSCs recognize inflammatory

signals? Which key cytokines and chemokines are involved in MSC homing to inflammatory sites? Which MSC surface receptors are important for homing to inflamed organs? Based on these questions, the PICO elements were defined as follows: Population (P): inflamed organs; Intervention (I): mesenchymal stem cells; Comparison (C): factors influencing MSC homing; Outcome (O): molecular mechanisms involved in stem-cell homing in the recognition of inflammation.

Search strategy and literature selection

Literature searching was carried out in three major academic databases Scopus, Web of Science, and Science Direct using the following combination of keywords: (Mesenchimal Stem Cells" OR "Mesenchymal stromal cells) AND (Peritoneal Injection Mesenchimal stem cells) AND (inflammation organ) AND (Homing Process) AND (Distribution of Mesenchimal stem cells).

The article selection process was conducted systematically with the assistance of the Parsif.al platform, which facilitated reference management, duplicate identification, and efficient implementation of the inclusion and exclusion criteria.

Quality assessment: MMAT 2018

Methodological quality was assessed using the Mixed Methods Appraisal Tool (MMAT) version 2018, in accordance with the guidelines of Hong *et al.* (2018). This process comprised: Screening Questions (S1–S2), which evaluate the clarity of the research questions and the adequacy of the data to address them; Identification of Study Design, whereby each article was classified into one of the five MMAT study designs (qualitative, quantitative descriptive, quantitative non-randomised, randomised controlled trial, or mixed methods); and Appraisal of the Five Core Criteria, in which design-specific criteria were applied to evaluate the methodological rigour of each study.

RESULTS AND DISCUSSION

Literature identification

The PRISMA flow diagram (Figure 1) illustrates the systematic study selection process, beginning with the identification of 168 records from two databases, namely Scopus (n= 83) and Web of Science (n= 85). After removal of duplicates (n= 5), 163 records were screened at the title and abstract level, and several were excluded for not meeting the initial criteria, namely publication before 2014 (n= 70), non-English language (n= 4), review articles (n= 13), book chapters (n= 2), book abstracts (n= 1), and conference proceedings (n= 1); all of these are indicated by right-pointing arrows as records excluded from selection. Of the remaining records, 72 full-text reports were sought, but 5 could not be retrieved, leaving 67 reports to be assessed for eligibility. At this stage, 10 full-text articles were excluded because their topics were not aligned with the review focus (full-text out of focus), also indicated by right-pointing arrows. Ultimately, 57 studies met the inclusion criteria and were incorporated into this systematic review.

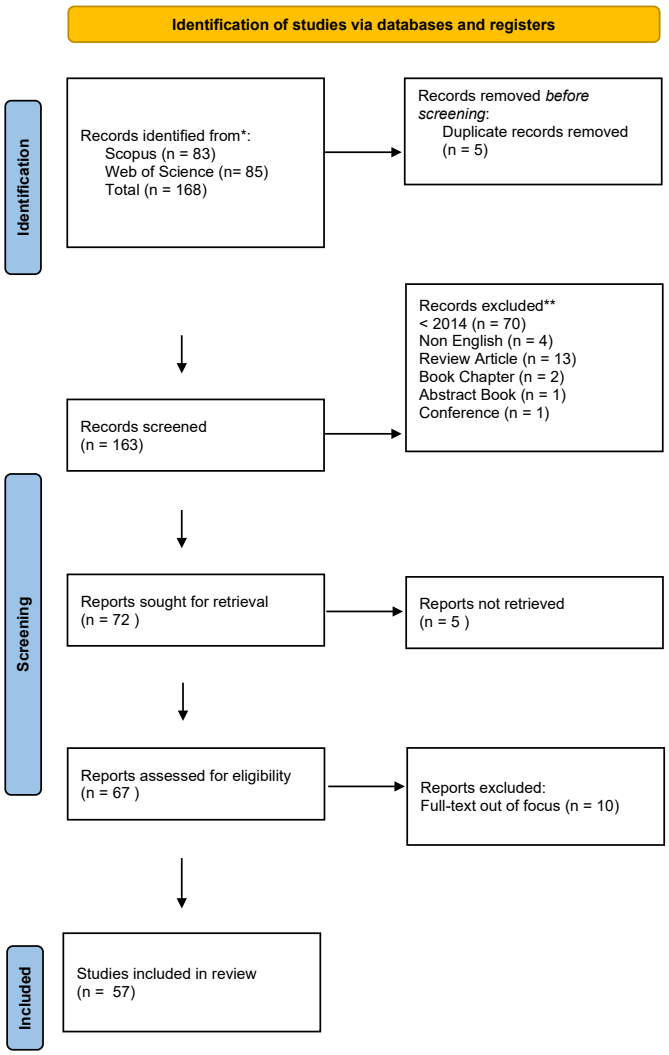

Figure 1: PRISMA flow diagram of study selection process from three databases (Scopus, Web of Science, ScienceDirect).

Mechanisms of mesenchymal stem cells (MSCs) recognise inflammatory signals

The synthesis of the included articles indicates that MSC homing is a coordinated sequence of events that begins at the onset of tissue injury and culminates in cell colonisation of the target organ. Injury and inflammation trigger the release of cytokines, chemokines, and growth factors that establish a chemical gradient from the damaged tissue toward the adjacent blood vessels. MSCs expressing chemokine receptors and adhesion molecules respond to this gradient by rolling along the endothelium, firmly adhering, transmigrating across the vascular wall, and ultimately migrating into the inflamed stromal tissue. This process does not depend on a single signalling axis

but involves an interconnected network of CXCL12/SDF-1–CXCR4, other receptors, adhesion molecules, and intracellular signals that regulate cell motility.

More specifically, the synthesis of the literature from multiple articles shows that the CXCL12/SDF-1–CXCR4 axis is the core mechanism guiding MSC homing in various organ models, including liver, kidney, brain, lung, colon, and wound tissue (Deng *et al*., 2014; Nan *et al*., 2018; Wang *et al*., 2014; Xu *et al*., 2024). Tissue injury upregulates SDF-1 expression through activation of factors such as HIF-1, thereby generating a chemokine gradient that attracts CXCR4-positive MSCs. Binding of SDF-1 to CXCR4 activates the Rho-ROCK, Rac, and Cdc42 pathways, which orchestrate cytoskeletal reorganisation and directional movement (Park *et al*., 2017). Several studies have reported that CXCR4 expression decreases during prolonged in vitro culture, and different strategies have been used to counteract this, including cytokine pretreatment, hypoxic culture, small molecules (e.g. DMOG, muscone), genetic engineering, and physical stimulation such as ultrasound-microbubble exposure (Chen *et al*., 2014; Costa *et al*., 2021; Gu *et al*., 2015).

MSCs recognise inflammatory signals through a combination of danger signals, chemokine gradients, and changes in the microenvironment of injured tissue. Tissue damage leads to the release of damage-associated molecular patterns (DAMPs), pro-inflammatory cytokines, and chemokines, which are sensed by pattern-recognition receptors such as Toll-like receptors (TLRs) on the MSC surface (Zhou *et al*., 2017). TLR activation regulates MSC viability, proliferation, cytokine secretion, migration, and immunomodulatory capacity and can be manipulated to enhance MSC biodistribution to sites of injury (Zhou *et al*., 2017).

Hypoxic and inflammatory conditions increase the expression of homing factors such as SDF-1/CXCL12 in damaged tissues, mainly through HIF-1 activation (Ciullo *et al*., 2018; Hu, 2021). The SDF-1 gradient formed from the centre of injury toward the blood vessels functions as a major chemotactic signal for CXCR4-positive MSCs (Deng *et al*., 2014; Nan *et al*., 2018). The interaction between SDF-1 and CXCR4 activates the Rho-ROCK, Rac, and Cdc42 pathways, which govern cytoskeletal reorganisation and directional migration from the vessel lumen into the inflamed stroma (Park *et al*., 2017).

Several studies have shown that CXCR4 expression declines during *in vitro* expansion, thereby reducing MSC sensitivity to homing signals (Chen *et al*., 2014; Nan *et al*., 2018). To address this, various approaches have been explored, including genetic engineering to overexpress CXCR4, cytokine pretreatment, hypoxic preconditioning, small molecules such as DMOG, and physical stimulation such as ultrasound-microbubble exposure (Wang *et al*., 2014; Costa *et al*., 2021; Gu *et al*., 2015). Nano-engineering strategies that induce mild oxidative stress can also activate Nrf2 and enhance CXCR4 expression and the Gα13–Rho pathway, thereby strengthening homing capacity to tumour tissues (Prabha *et al*., 2023).

These mechanisms support the concept that MSC homing is a multistep adaptive response that begins with danger sensing through TLRs and cytokines, followed by guidance via chemokine gradients and culminating in docking on the endothelium and inflamed stromal tissue (Xu *et al*., 2024; Bai *et al*., 2017). Thus, the success of MSC therapy is highly dependent on the cells' "homing competence", which is influenced by culture conditions, preconditioning strategies, and the inflammatory context of the target tissue.

Key cytokines and chemokines involved in MSC homing to inflammatory sites

A range of cytokines and chemokines play crucial roles in directing MSC homing to inflamed tissues by establishing chemotactic gradients, activating the endothelium, and increasing the expression of adhesion molecules that facilitate MSC migration and extravasation into target organs. The key mediators, together with their biological functions and primary target organs, are summarised in Table 1.

The synthesis of the included articles reveals a strong consensus that the SDF-1/CXCL12–CXCR4 axis is the principal chemokine pathway in MSC homing (Yu *et al*., 2024; Alicka *et al*., 2020; Song *et al*., 2019; Harbringer *et al*., 2018; Hewet *et al*., 2017). SDF-1 expression is upregulated in tissues subjected to injury, hypoxia, or inflammation, including infarcted myocardium, ischaemic brain, liver, kidney, and colonic mucosa in IBD (Deng *et al*., 2014; Nan *et al*., 2018; Ciullo *et al*., 2018). SDF-1 acts as a potent chemoattractant for CXCR4-positive MSCs and directs their migration toward areas of highest concentration, thus enhancing MSC engraftment at the lesion site (Zhang *et al*., 2019; Hu *et al*., 2021).

Pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-γ have dual roles in this process. On the one hand, they initiate and maintain inflammatory responses in tissues; on the other, they modulate the expression of adhesion molecules and homing receptors on both MSCs and the endothelium (Deng *et al*., 2014; Bai, 2017). TNF-α enhances NF-κB activation and stimulates CXCR4 expression in MSCs, thereby boosting migration to inflamed tissues (Bai, 2017). IL-1 and TNF-α also increase the expression of selectins and other adhesion molecules in the microvasculature, which are critical for MSC rolling and firm adhesion prior to transmigration (Chen *et al*., 2021; Dykstra *et al*., 2016).

Table 1: Key cytokines and chemokines that are implicated in the homing of MSCs to sites of inflammation.

Cytokine / Chemokine	Context / Primary source	Role in MSC homing to inflamed sites	References
SDF-1 / CXCL12	Ischaemic / inflamed tissues (myocardium, brain, liver, kidney, colon)	A key chemokine that is highly expressed in injured tissues; a concentration gradient is established to attract CXCR4-positive MSCs and to enhance engraftment at lesion sites.	(Deng, 2014; Nan, 2018; Ciullo, 2018; Zhang, 2019; Hu, 2021; Alicka, 2020; Song, 2019; Hu, 2019; Li, 2019; Wang, 2018; Xiao, 2016)
IL-1	Inflamed or wounded tissues	A pro-inflammatory cytokine by which endothelial activation and expression of adhesion molecules/selectins are upregulated, thereby facilitating MSC rolling and adhesion in vessels within inflamed areas.	(Deng, 2014; Chen, 2021; Bai, 2017)
IL-6	Serum and inflammatory microenvironment	An inflammatory cytokine that is involved in the acute-phase response and by which the microenvironment is modulated so that recruitment and functions of MSCs at injured sites are supported.	(Deng, 2014; Bai, 2017; Khasawneh, 2022)
TNF-α	Inflammatory serum, injured vasculature	TNF-α-mediated activation of NF-κB is increased and expression of CXCR4 on MSCs as well as endothelial selectins is stimulated; MSC migration and adhesion to inflamed tissues are thereby strengthened.	(Deng, 2014; Bai, 2017; Zhao, 2021)
IFN-γ	Tumour-conditioned media / chronic inflammatory milieu	A component of the pro-inflammatory milieu by which MSC secretory and migratory profiles are altered, contributing to chemotaxis and modulation of immune responses at lesion sites.	(Smith, 2015; Wang, 2014)
VEGF	Activated MSCs in injured tissues	A pro-angiogenic factor that is secreted by MSCs after homing; tissue repair and neovascularisation are supported and a microenvironment that further attracts MSCs is reinforced.	(Liu, 2014; Bai, 2017; Costa, 2021; Jiang, 2022; Tu, 2016)
HGF	Liver and other injured tissues	A growth factor that binds c-Met; tissue regeneration is promoted and recruitment and retention of MSCs in damaged organs may be facilitated.	(Bai, 2017; Wang, 2024; Bang, 2017)
BMP-7	Renal injury	Secreted by MSCs as a renoprotective factor; tissue repair after MSC homing to inflamed kidneys is supported.	(Liu, 2014)
IL-10	Inflammation-resolution milieu	An anti-inflammatory cytokine that is secreted by MSCs to suppress excessive inflammation after homing; local immune homeostasis is restored.	(Wang, 2014; Liu, 2014; Li, 2024)
TSG-6	MSC under hypoxic / 3D conditions	An anti-inflammatory and matrix-modulating molecule whose expression is increased in preconditioned MSCs and which contributes to protective effects after homing.	(Costa, 2021)
MMP-2 / MMP-9	Pretreated / inflamed MSCs	Matrix metalloproteinases that facilitate matrix remodelling and penetration of MSCs across tissue barriers; transmigration into organ parenchyma is critically supported.	(Bidkhori, 2016; Costa, 2021; Li, 2024)
Chemerin	Liver, lung, inflamed tissues	A chemotactic protein that binds ChemR23; migration of cells (including MSCs and immune cells) towards injured sites is directed.	(Kim, 2021)
CCL5 (RANTES)	Tumours / cancer microenvironment	A chemokine by which MSC chemotaxis is induced through receptors such as CCR1; MSC migration into the tumour microenvironment is enhanced.	(Melen, 2015)

MSCs modulate the inflammatory milieu via paracrine secretion. Several studies report increased secretion of VEGF, HGF, BMP-7, IL-10, TSG-6, and MMP-2 by MSCs under conditions of renal, hepatic, and vascular injury (Liu *et al.*, 2014; Bai *et al.*, 2017; Costa *et al.*, 2021). VEGF and HGF accelerate angiogenesis and tissue regeneration, whereas IL-10 and TSG-6 suppress excessive inflammation and the recruitment of pro-inflammatory effector cells (Wang *et al.*, 2014; Li *et al.*, 2024). MMP-2 and MMP-9 contribute to extracellular matrix remodelling and facilitate MSC penetration into the organ parenchyma (Bidkhori *et al.*, 2016; Costa *et al.*, 2021).

The chemokines, such as chemerin and CCL5, also participate in recruiting MSCs and immune cells to sites of injury or tumour growth. Chemerin binds to the ChemR23 receptor and directs cell migration to inflamed tissues (Kim *et al*., 2021). CCL5, together with SDF-1, has been shown to induce MSC chemotaxis in an oncolytic virus carrier model for neuroblastoma (Melen *et al*., 2015). Conversely, in a stroke model, CXCR4-rich MSC membranes have been used as "nanodecoys" to bind CXCL12 and prevent the recruitment of neutrophils and monocytes to the lesion, thereby reducing secondary inflammation (Shi, 2021). These findings suggest that understanding cytokine and chemokine networks can be exploited not only to enhance MSC homing but also to limit the homing of pro-inflammatory immune cells.

Surface receptors on MSCs that are critical for homing to inflamed organs

MSC homing is determined by the expression of various surface receptors that sense chemotactic signals, interact with vascular adhesion molecules, and mediate attachment and translocation of MSCs across the endothelium into inflamed tissues. The main receptors involved in directing MSC migration and organ specificity are summarised in Table 2.

The synthesis of the included studies underscores that the MSC surface receptor profile is a key determinant of successful homing to inflamed organs. CXCR4 emerges as the principal and most extensively studied homing receptor. High CXCR4 expression correlates with enhanced MSC migration along the SDF-1 gradient and increased accumulation in inflamed colon, ischaemic brain,

Table 2: Surface receptors on MSCs that are considered critical for homing to inflamed organs.

Receptor / surface molecule	Ligand/ Primary signal	Primary role in MSC homing	Organ	References
CXCR4 (chemokine receptor)	SDF-1 / CXCL12	A key receptor for MSC chemotaxis along SDF-1 gradients; migration towards ischaemic / inflamed tissues is directed.	Colon in IBD, infarcted myocardium, ischaemic brain, liver, kidney, lung	Chen, 2014; Nan, 2018; Wang, 2014; Zhang, 2019; Ichiseki, 2023; Yu, 2024; Alicka, 2020; Song, 2019; Hu 2019; Xiao, 2016
CXCR7	SDF-1 / CXCL12	An alternative receptor for SDF-1; homing is regulated at the endothelial level and SDF-1 availability is modulated.	Bone marrow, inflamed tissues	Bidkhori, 2016; Park, 2017
CCR2	CCL2 (MCP-1)	Migration of MSCs towards tissues with high CCL2 expression is regulated; associations with pulmonary and other tissue inflammation have been reported.	Inflamed lung, other injured tissues	Bidkhori, 2016; Li, 2024
CXCR1 / CCR1	IL-8, CCL5	An increased tropism of MSCs for the tumour microenvironment is conferred; high expression has been associated with better clinical responses.	Solid tumours (neuroblastoma, etc.)	Melen, 2015
ChemR23	Chemerin	Migration of cells towards tissues that produce chemerin under injury or inflammatory conditions is directed.	Liver, lung, inflamed tissues	Kim, 2021
ICAM-1 (adhesion molecule)	LFA-1 (on endothelium/ immune cells)	Adhesion and attachment of MSCs to host tissues after transplantation are facilitated; retention at injured sites is rendered critical.	Heart, blood vessels, inflamed tissues	Zhao, 2021; Khasawneh, 2022
Integrin α2, α5, α6, β1	Collagen, fibronectin, laminin	Interactions of MSCs with extracellular matrix and endothelium are regulated; firm adhesion and transmigration are enabled.	Bone, blood vessels, biomaterial scaffolds	Andersen, 2015; Dollet, 2020; Smith, 2015
CD44 / HCELL	Hyaluronan, E-selectin (via sLeX)	An important ligand for E-selectin; glyco-engineering of HCELL has been shown to enhance tethering, rolling, and MSC homing to bone marrow / bone. One of the CD44 isoform is CD44v6, which is considered as a homing receptor.	Bone, bone marrow	Dykstra, 2016; Chen, 2021; Nabizadeh, 2022
JAM-A	JAM ligands / integrins	Chemotaxis, migration, and the number of MSCs homing to wound surfaces are increased and secretory activity is enhanced.	Skin wounds / wound healing	Wu, 2015

PDGFR-α / PDGFR-β	PDGF	Growth factor receptors by which MSC chemotaxis towards fracture sites and areas of bone remodelling is regulated.	Bone, fractures, skeletal regeneration	Andersen, 2015; Smith, 2015
c-Met	HGF	Migration of MSCs towards tissues with high HGF levels is directed; homing to injured liver and post-stroke brain is mediated.	Failing liver, post-stroke brain	Bang, 2017; Wang, 2024
"Targeted coating" anti-KIM-1 (antibody on MSC surface)	KIM-1 (in injured kidneys)	Not an endogenous MSC receptor, but an antibody coated onto the MSC surface to increase the selectivity of homing to ischaemic kidneys.	Ischaemic / stenotic kidney	Zou, 2018

infarcted myocardium, lung, and kidney (Chen *et al*., 2014; Nan *et al*., 2018; Wang *et al*., 2014; Zhang *et al*., 2019). Overexpression of CXCR4 through genetic engineering or preconditioning improves MSC homing and therapeutic effects, whereas CXCR4 knockdown reduces their migratory ability toward injured tissues (Ichiseki *et al*., 2023; Zhao *et al*., 2019).

The MSC homing receptor profile is more complex than CXCR. CXCR7, CCR2, CXCR1, CCR1, and ChemR23 also participate in directing MSCs to inflammatory and tumour microenvironments (Bidkhori *et al*., 2016; Melen *et al*., 2015; Kim *et al*., 2021). CXCR7 functions as an alternative receptor for SDF-1 and plays an important regulatory role at the endothelial level, whereas CCR2 responds to CCL2 in models of lung and other tissue injury (Bidkhori *et al*., 2016; Li *et al*., 2024). ChemR23 binds chemerin and guides migration to damaged tissues (Kim *et al*., 2021). Better clinical responses in CELYVIR therapy have been observed in association with higher CXCR1/CCR1 expression in MSCs in experimental clinical studies, thereby underscoring the functional relevance of these receptors in tumour homing (Melen *et al*., 2015).

Adhesion molecules and selectin ligands add an important layer to homing mechanisms. ICAM-1 and VCAM-1 mediate firm adhesion of MSCs to the endothelium, while various integrin subunits (α2, α5, α6, β1) regulate interactions with the extracellular matrix and transmigration (Khasawneh, 2022; Dollet *et al*., 2020). CD44 and its glyco-engineered form HCELL act as ligands for E-selectin on inflamed endothelium, and exofucosylation of MSCs using fucosyltransferase has been shown to enhance tethering and rolling on the endothelium and to direct homing to bone (Dykstra, 2016). PDGFR-α/β and c-Met link homing signals to chemotaxis and tissue regeneration in bone fracture and liver failure models (Andersen *et al*., 2015; Wang *et al*., 2024; Bang *et al*., 2017). Antibody coating of MSCs with specificity for KIM-1 has also been shown to increase selective homing to ischaemic kidneys compared with other organs (Zou *et al*., 2018).

The notion that each organ and type of injury possesses a distinct "homing signature," determined by specific combinations of chemokine receptors, adhesion molecules, and growth factor receptors, is supported by this evidence (Teo *et al*., 2020; Smith, 2015; Toraih *et al*., 2016). On this basis, the development of "homing competence" indicators derived from MSC surface receptor profiles is proposed as a means of defining quality and potency criteria for cell-therapy products in both human and veterinary medicine.

CONCLUSION

This systematic review confirms that MSC homing to inflamed organs is a multistep process guided by cytokine and chemokine gradients particularly IL-1, IL-6, TNF-α, IFN-γ, IL-10, TGF-β, and the SDF-1/CXCL12–CXCR4 and CCL2 axes which, together with adhesion molecules and surface receptors, determine the direction of migration and cell retention. The review clarifies cross-organ homing patterns, reinforces the concept of "homing competence", and highlights the potential to optimise preconditioning, administration routes, and receptor engineering to enhance therapeutic efficacy. Practically, these findings support the design of more targeted MSC therapies for inflammatory diseases in both humans and animals.

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NOVELTY STATEMENT

This is the first cross-organ systematic review that consolidates cytokine / chemokine receptor, homing signatures of MSCs to guide targeted and route-optimized cell therapy.

AUTHOR'S CONTRIBUTION

WP: Conceptualization, methodology, writing- reviewing

and editing, visualization; investigation. FAR, AA, LTS, HP, ES, ISY, BS: Supervision, conceptualization, methodology.

Generative AI and AI-assisted technology statement

Generative AI tools were used to improve language clarity and grammar and/or to assist in drafting non-substantive text. All scientific content, interpretations, and references were produced, verified, and approved by the authors.

Conflict of interest

The authors have declared no conflict of interest.

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