Tzu Chi Medical Journal 2024; 36 (4): 349-359

Review Article

Unraveling the interplay between inflammation and stem cell mobilization or homing: Implications for tissue repair and therapeutics

*Hsin-Hou Chang, Yu-Shan Liou, Der-Shan Sun**

Department of Molecular Biology and Human Genetics, Tzu Chi University, Hualien, Taiwan

Submission : 19-Apr-2024
Revision : 29-Apr-2024
Acceptance : 14-Jun-2024
Web Publication : 05-Sep-2024

Abstract

Inflammation and stem cell mobilization or homing play pivotal roles in tissue repair and regeneration. This review explores their intricate interplay, elucidating their collaborative role in maintaining tissue homeostasis and responding to injury or disease. While examining the fundamentals of stem cells, we detail the mechanisms underlying inflammation, including immune cell recruitment and inflammatory mediator release, highlighting their self-renewal and differentiation capabilities. Central to our exploration is the modulation of hematopoietic stem cell behavior by inflammatory cues, driving their mobilization from the bone marrow niche into circulation. Key cytokines, chemokines, growth factors, and autophagy, an intracellular catabolic mechanism involved in this process, are discussed alongside their clinical relevance. Furthermore, mesenchymal stem cell homing in response to inflammation contributes to tissue repair processes. In addition, we discuss stem cell resilience in the face of inflammatory challenges. Moreover, we examine the reciprocal influence of stem cells on the inflammatory milieu, shaping immune responses and tissue repair. We underscore the potential of targeting inflammation-induced stem cell mobilization for regenerative therapies through extensive literature analysis and clinical insights. By unraveling the complex interplay between inflammation and stem cells, this review advances our understanding of tissue repair mechanisms and offers promising avenues for clinical translation in regenerative medicine.

Keywords: *Inflammation, Resilience, Stem cell mobilization, Therapeutic interventions, Tissue regeneration*

Introduction

Inflammation in itself is not to be considered as a disease but as a salutary operation consequent to some violence or some disease [1]. It is closely linked with nearly every human ailment [2]. Inflammation serves as a crucial defense mechanism against pathogens and tissue damage, orchestrated by a complex interplay of immune cells, cytokines, and chemokines. It is characterized by a series of events including vasodilation, increased vascular permeability, and leukocyte recruitment to the site of injury or infection [3]. Adult stem cells, on the other hand, possess remarkable self-renewal and differentiation capabilities, contributing to tissue homeostasis, repair, and regeneration [4,5]. The mobilization or homing of stem cells, the process by which stem cells are released from their niche into circulation or injury sites, plays a pivotal role in tissue repair, particularly in response to inflammatory stimuli [6,7].

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_100_24

Inflammation: A fundamental process in the immune system

Inflammation, a conserved process marked by activating immune and nonimmune cells to safeguard the host against bacteria, viruses, toxins, and infections, can be categorized into acute and chronic phases. Acute inflammation is usually rapid and self-limiting, whereas chronic inflammation endures over an extended period, potentially resulting in tissue damage and organ dysfunction [8,9]. Chronic inflammation is associated with numerous diseases, including ischemic heart disease, stroke, cancer, diabetes mellitus, chronic kidney disease, nonalcoholic fatty liver disease, autoimmune

***Address for correspondence:** Prof. Der-Shan Sun, Department of Molecular Biology and Human Genetics, Tzu Chi University, 701, Zhongyang Road, Section 3, Hualien Taiwan. E-mail: dssun@mail.tcu.edu.tw

How to cite this article: Chang HH, Liou YS, Sun DS. Unraveling the interplay between inflammation and stem cell mobilization or homing: Implications for tissue repair and therapeutics. Tzu Chi Med J 2024;36(4):349-59.

disorders, and neurodegenerative conditions [10]. Injury and infection-triggered inflammatory responses can be detected through two distinct modes of recognition [11] [Figure 1]. First, tissue damage leads to the release of intracellular proteins such as heat-shock proteins, the transcription factor high mobility group box 1 (HMGB1), extracellular adenosine triphosphate (eATP), histone, and mitochondrial peptides bearing the N-formyl group characteristic of prokaryotic proteins, eliciting an inflammatory response [12-16]. Second, microbes and their shed or secreted products are sensed through the binding of their conserved molecular constituents to soluble receptors such as complement, mannose-binding protein, and bacterial cell wall components such as lipopolysaccharide, which in turn bind to cell-surface receptors such as toll-like receptor (TLR) family members [17,18]. The inflammatory response recruits various immune cells, including neutrophils, macrophages, and lymphocytes, to the site of inflammation in a tightly regulated manner. Cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (ILs), along with chemokines, orchestrate leukocyte trafficking and activation, aiding in the clearance of pathogens and damaged cells [17,18]. Furthermore, it is now understood that inflammation can occur independently of infection or tissue injury. Cells experiencing senescence or stress, such as endoplasmic reticulum (ER), mitochondrial, or osmotic stress, activate the NOD-like receptor family and pyrin domain-containing 3 (NLRP3) inflammasome and produce inflammatory cytokines [11,19,20]. Furthermore, a key player in the complex landscape of inflammation is the NLRP3 inflammasome, a protein complex that modulates inflammatory responses and has been implicated in various diseases.

NLRP3 inflammasome

Inflammasomes, first proposed by Martinon *et al*., 2002 [21], are protein complexes containing caspase-1 that positively regulate the inflammation and are associated with various diseases such as diabetes, Alzheimer's disease, gout, and atherosclerosis [22-26]. The NLRP3 inflammasome is among the most studied inflammasome members [23,24,26]. It consists of NLRP3, ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain), and pro-caspase-1 [27,28]. Activation of the NLRP3 inflammasome involves two steps: priming and activation. In the priming signal, pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) bind to TLRs, activating the NF-κB pathway. This activation results in increased expression of inflammasome-related molecules such as pro-IL1β, pro-IL-18, and NLRP3 [29,30]. In the activation signal, the NLRP3 inflammasome assembles and activates through three main mechanisms: ion flux (potassium channels, chloride channels, or calcium signaling), mitochondrial dysfunction, and lysosomal disruption [29,30]. After activation, the inflammasome-activated caspase-1 cleaves pro-IL-1β, pro-IL-18, and gasdermin D, leading to the secretion of IL-1β and IL-18 [31,32] and induction of inflammatory programmed cell death-pyroptosis [29] [Figure 2].

Stem cells: Basics and types

In contrast to the intricate regulatory pathways of inflammasomes, stem cells offer a promising avenue in regenerative medicine. Stem cells, characterized by their remarkable plasticity, play pivotal roles in tissue repair and regeneration. Understanding their dynamics and potential

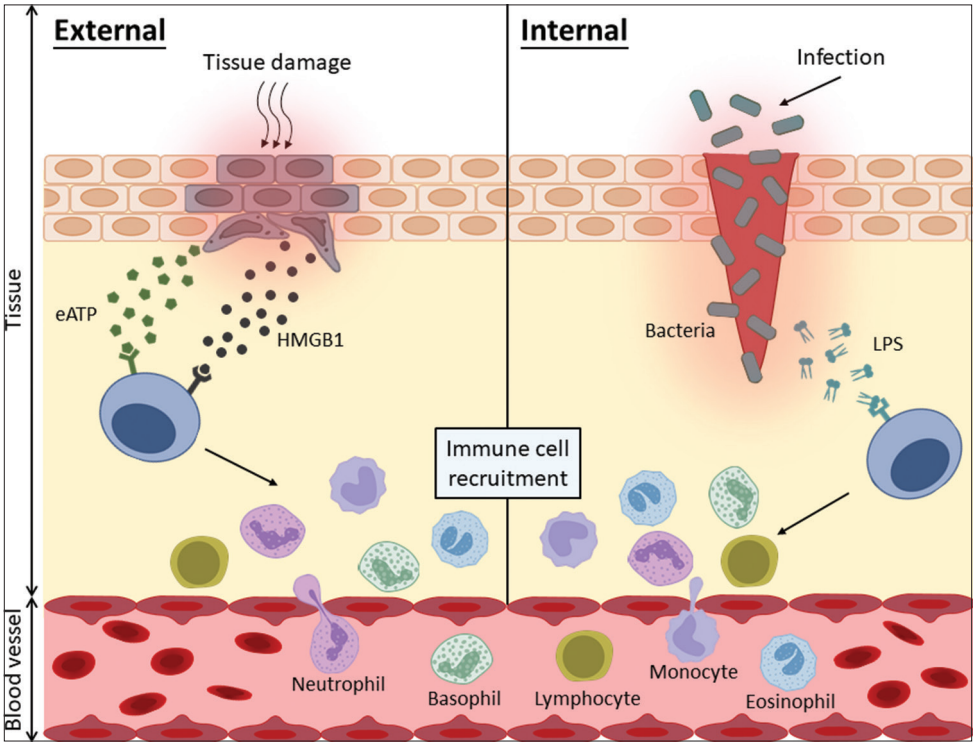

Figure 1: Schematic illustration showing the two types of inflammatory responses: injury-triggered and infection-triggered. Both inflammatory reactions involve recruiting immune cells to clear damaged cells or pathogens

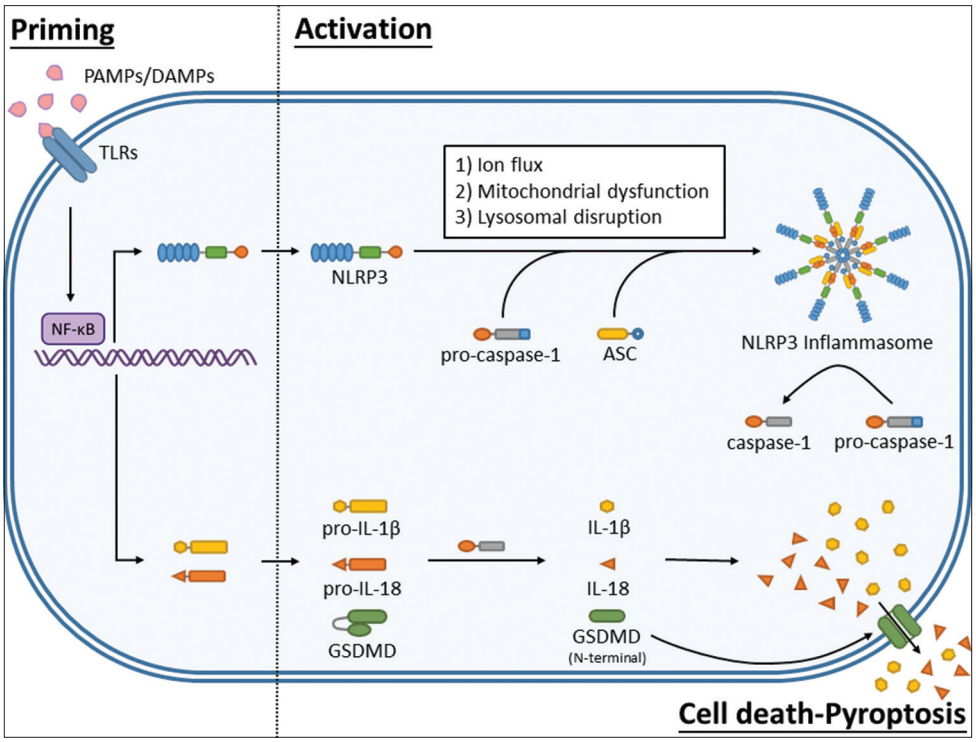

Figure 2: Schematic illustration showing the activation pathway of the NLRP3 inflammasome. The NLRP3 inflammasome, a protein complex crucial for inflammation, involves NLRP3, ASC, and pro-caspase-1. Activation occurs in two steps: priming and activation. Priming involves pathogen-associated molecular patterns or damage-associated molecular patterns binding to toll-like receptors, activating the NF-κB pathway, and increasing pro-interleukin (IL)-1β, pro-IL-18, and NLRP3 expression. Activation involves ion flux, mitochondrial dysfunction, and lysosomal disruption, leading to the assembly of the inflammasome. Activated caspase-1 then cleaves pro-IL-1β, pro-IL-18, and gasdermin D, resulting in IL-1β and IL-18 secretion and pyroptosis

therapeutic applications requires a grasp of their fundamental properties. Stem cells are undifferentiated cells capable of both self-renewal and differentiation into specialized cell types. Hematopoietic stem cells (HSCs) give rise to all blood cell lineages, whereas mesenchymal stem cells (MSCs) have the potential to differentiate into various mesenchymal lineages including adipocytes, osteoblasts, and chondrocytes [33,34]. These multipotent stem cell populations reside in specialized niches within tissues, maintaining tissue homeostasis and responding to injury or inflammation by proliferating and differentiating into required cell types for tissue repair [35] [Table 1].

Hematopoietic stem cells and the bone marrow niche

HSCs reside in the bone marrow niche. The existence of a niche or microenvironment was proposed in 1978 by Schofield [36]. He suggested that stem cells are associated with other tissue-resident cells that prevent stem cell differentiation and maintain self-renewal. Niche is composed of endothelial cells and mesenchymal stromal progenitor cells. The interactions between niche cells and HSCs are associated with adhesion, self-renewal, mobilization, and homing [37,38]. The following ten molecules on the surface of niche cells (N-cadherin, soluble kit ligand, angiopoietin, stromal cell-derived factor 1 [SDF-1, also called CXCL12], vascular cell adhesion molecule-1 [VCAM-1], ICAM-1,2,3, thrombopoietin, osteopontin [OPN], E-selectin, and P-selectin) are responsible for the interaction with the surface receptors (N-cadherin, c-kit, tie2, CXC chemokine receptor-4 [CXCR4], very late antigen-4 [VLA-4], LFA-1, MPL, α and β integrin [CD44], E-selectin ligand-1, and P-selectin glycoprotein ligand-1) on the HSCs, respectively [38]. Niche cells also can provide noncellular ligands such as fibronectin, laminin, collagen, OPN, and hyaluronan for cell adhesion between HSCs and niche cells [39]. Besides endothelial cells and mesenchymal stromal progenitor cells, there are a variety of cells such as macrophages, neutrophils, osteoblasts, and megakaryocytes regulated by sympathetic nerves and complement components that maintain the bone marrow's hemostasis [40,41].

The interplay between inflammation and hematopoietic stem cell mobilization

Inflammation exerts profound effects on stem cell dynamics, influencing their mobilization from the bone marrow into circulation. During inflammation, cytokines and chemokines such as granulocyte colony-stimulating factor (G-CSF, also known as filgrastim), granulocyte-macrophage CSF, and SDF-1 are upregulated, promoting the release of stem cells from the bone marrow niche [42]. In addition, inflammatory signals can directly modulate the behavior of stem cells, enhancing their migratory and homing capacities to sites of injury or inflammation [43]. This orchestrated mobilization of stem cells plays a crucial role in tissue repair and regeneration,

Table 1: Comparison of hematopoietic stem cells and mesenchymal stem cells

Aspect	HSCs	MSCs
Origin and location	Originate in bone marrow	Found in bone marrow and various tissue (e.g., adipose tissue, umbilical cord blood)
Differentiation ability	Give rise to all blood cell types	Differentiate into nonhematopoietic cell types (e.g., bone, cartilage, muscle, and fat)
Function	Primarily involved in blood cell production	Exhibit immunomodulatory properties; contribute to tissue repair and regeneration
Response to inflammation or injury	Mobilize from bone marrow to peripheral blood; participate in tissue repair	Actively respond to inflammation; secrete anti-inflammatory cytokines; promote tissue healing; modulate immune responses
Clinical application	Used in HSCT	Investigated for therapeutic potential in various conditions; enhance HSCT outcomes when combined with HSC infusion

MSCs: Mesenchymal stem cells, HSCs: Hematopoietic stem cells, HSCT: Hematopoietic stem cell transplantation

contributing to the replenishment of damaged cell populations and the restoration of tissue function [44].

Beyond the regulation by circadian rhythms [45], HSCs will mobilize to the peripheral blood in responses to systemic or local inflammation, intensive exercise, hypoxia, and tissue/organ injuries in steady-state conditions [6,46-49]. Accumulated studies revealed that G-CSF or plerixafor (also known as AMD3100) can activate neutrophils in the bone marrow, and then, the activated neutrophils will release some DAMPs such as HMGB1, eATP, DNA, and hyaluronan fragments [50-52]. These DAMPs will be recognized by mannan-binding lectin, which then activates complement system through MBL-associated serine proteinase. The activated complement C5a then lyses erythrocytes and releases sphingosine-1-phosphate into the peripheral blood to attract the HSCs mobilized from the bone marrow [40,50,53,54]. Recent studies have reported that the NLRP3 inflammasome is involved in G-CSF and AMD3100-triggered HSC mobilization in mice. Additionally, the administration of the NLRP3 inflammasome activator nigericin, or the activation mediators IL-1β and IL-18, induces HSC mobilization in mice [55-58]. Mice deficient in caspase-1 and Nlrp3 are poor mobilizers in response to G-CSF and AMD3100 [59]. In clinical settings, proinflammatory cytokine levels (interferon-gamma, IL-22, and TNF-α) correlate positively with G-CSF-triggered HSC mobilization [60]. All these evidence demonstrated that innate immunity plays an important role in HSC mobilization.

Moreover, in addition to influencing stem cell mobilization, inflammatory signals secreted by recruited immune cells also suppress Notch activation in tissue-resident stem cells such as airway stem cells. This process promotes stem cell plasticity and their differentiation into alveolar cells [61,62]. These findings underscore the intricate interplay between inflammation and stem cell dynamics, wherein inflammatory cues mobilize stem cells and shape their fate and function in tissue repair and regeneration processes.

Autophagy and hematopoietic stem cell mobilization

Transitioning to another facet of stem cell regulation, autophagy emerges as a critical intracellular mechanism with implications in immunity and inflammation [63-65]. Recent studies have elucidated a mutual regulation between inflammasomes and autophagy [66-68]. Autophagy is initiated by the formation of a double membrane called autophagosome-sequestered malfunctioning components [69,70]. The autophagosome fuses with lysosome to become the autolysosome and degrades all unwanted cytosolic constituents [69,70]. Autophagy is initiated by the autophagy-related protein 1 (Atg1)-Atg13 protein complex. The class III phosphoinositide 3-kinase-Beclin 1 complex is the key for the nucleation step [71]. Elongation of the isolation membrane is mediated by two ubiquitin-like conjugation systems (coordination by several Atg proteins, such as Atg3 and Atg5-12) [72,73]. Autophagy plays important roles in cell survival, immunity, development, cancer, and adaptation to starvation [74,75]. Evidence also showed that autophagy is important for hematopoietic system and *Atg7*$^{-/-}$ mice developed severe anemia, lymphopenia, and atypical myeloproliferation resembling human myelodysplastic syndrome [72,76,77]. In addition, autophagy also plays an important role in hematopoietic cell differentiation [78,79], including erythroid cell terminal differentiation, especially in reticulocyte maturation [80-83] and megakaryocyte differentiation [84], and is also required for the maintenance of quiescence and stemness of HSCs [85-87]. Notably, G-CSF-induced neutrophil and HSC mobilization is impaired in *Atg7*$^{-/-}$ or *Atg5*$^{-/-}$ mice, suggesting a crucial role for autophagy in this process [88]. Autophagy-related genes also increase expression in both neutrophils and HSCs of mice and humans after G-CSF stimulation [88]. Furthermore, G-CSF has been shown to mobilize regulatory T-cells (Tregs) from the bone marrow to the peripheral blood and induce autophagy for the survival of Tregs [89,90]. These cells are heterogeneous immunosuppressive T-cells that maintain tolerance after HSC transplantation (HSCT) [91]. Understanding autophagy's role in HSC mobilization holds promise for improving HSCT protocols and promoting tolerance of graft-versus-host diseases after HSCT.

Mesenchymal stem cell homing in response to inflammation

Transitioning to another aspect of stem cell behavior, MSCs exhibit remarkable homing capabilities in response to inflammation. MSCs can be isolated from various tissues, including bone marrow [92], adipose tissue [93], umbilical cord tissue [94], placenta [95], umbilical cord [96], peripheral blood [97], and skin [98]. Among these, bone marrow MSCs, adipose-derived MSCs, and umbilical cord MSCs are the most frequently studied. Compared to the other two MSC types, adipose-derived MSCs are readily available and collected noninvasively, making adipose tissue an ideal source for MSCs [99]. For clinical treatments, MSCs can be sourced endogenously or exogenously. Regardless of their origin, MSCs preferentially home to injury or tumor sites under the

influence of inflammatory and chemotactic factors, which promote angiogenesis, regeneration, immunomodulation, anti-inflammatory, and antitumor effects [100-103]. Therapeutic MSC administration can be performed systemically or site specifically; thus, MSC homing can be divided into nonsystemic and systemic [Figure 3]. In nonsystemic homing, MSCs injected locally near the target tissue are recruited to the injury site by sensing chemokines released from injured or inflamed tissue [104]. In systemic homing, MSCs are administered locally or recruited endogenously into the circulation first. They then go home to the injury site akin to leukocytes, following four subsequent steps [101,103,104]. Initially, adhesion molecules such as VLA-4 (also known as α4β1-integrin) on the surface of MSCs bind to VCAM-1 on endothelial cells, promoting adhesion and activating between MSCs and endothelial cells [105,106]. Several reports have demonstrated that damaged tissues or inflammatory sites express various inflammatory cytokines such as IL-1β and IL-6, as well as growth factors such as epidermal growth factor and fibroblast growth factor. These factors bind to receptors on MSC surfaces, facilitating the rolling, capture, and adhesion of MSCs at the target site [107]. For instance, stromal cell-derived factor 1 (SDF-1) significantly increases after cardiac ischemia, and the recruitment of MSCs expressing CXCR4 toward the SDF-1 gradient plays a crucial role in tissue recovery [108]. The SDF-1/CXCR4 interaction between SDF-1 and CXCR4 regulates MSC homing, and strategies have been developed to modify MSCs to express more CXCR4 before transplantation for cardiac repair [109]. Subsequently, matrix metalloproteinases (MMP-9 and MMP-2), released

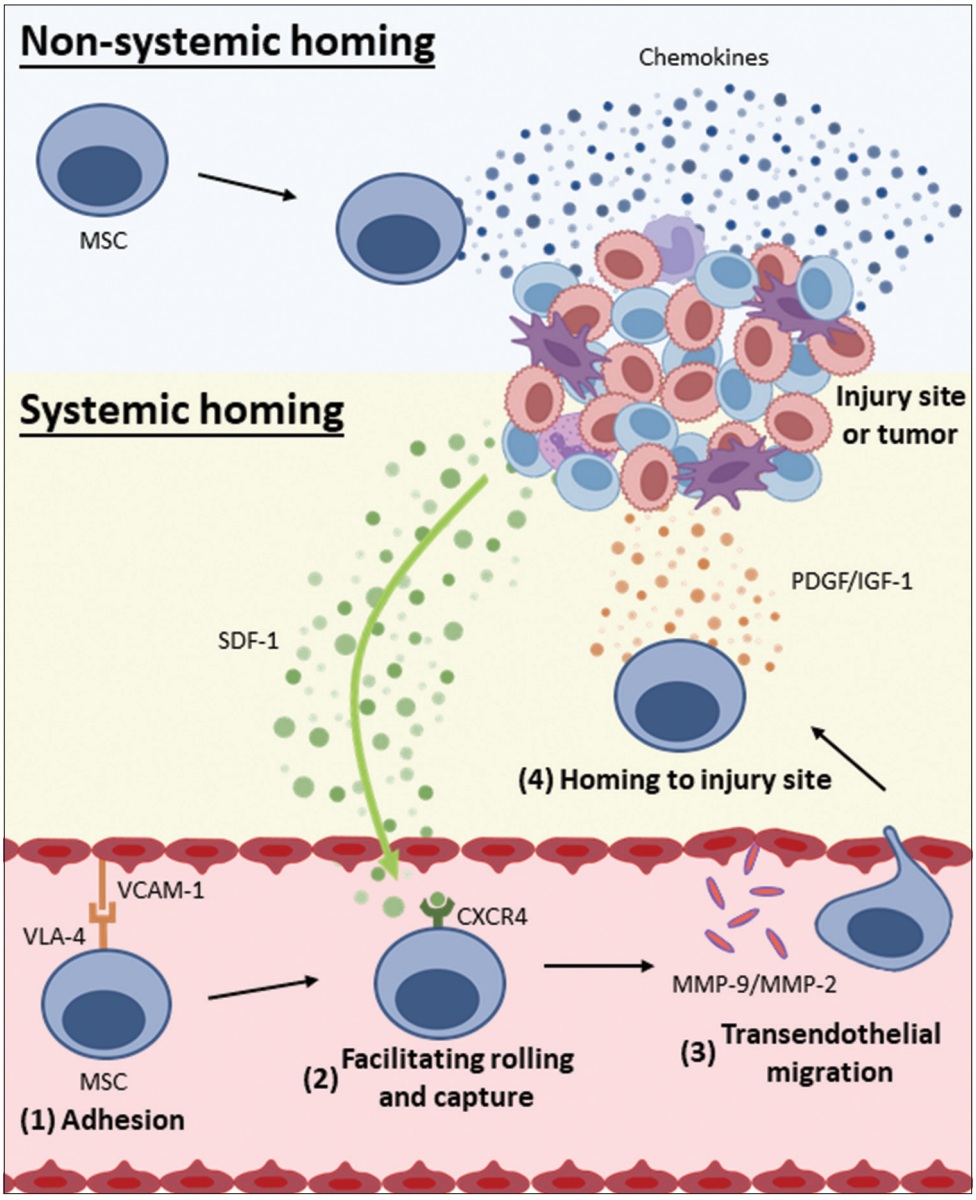

Figure 3: Schematic illustration showcasing mesenchymal stem cell (MSC) homing, depicting two pathways: nonsystemic homing and systemic homing. In nonsystemic homing, MSCs are injected locally near the target tissues. Conversely, MSCs navigate to the injury site or tumor in systemic homing through four subsequent steps: adhesion, facilitating rolling and capture, transendothelial migration, and homing to the injury site. In both modes of MSC homing, recruitment to the injury site is facilitated by the sensing of chemokines

by inflammatory cells or MSCs, degrade the two major components of basement membranes – collagen and gelatin, enabling transendothelial migration of MSCs [110,111]. Finally, chemotactic factors such as platelet-derived growth factors and insulin-like growth factor-1 guide MSCs to the injured or inflamed sites [103]. Several inflammatory mediators (such as TNF-α) or chemokines are produced throughout the homing process, contributing to the formation of a chemotactic gradient that aids in recruiting MSCs to the injury site [101]. Recent studies have reported that MSCs interact with platelets in the blood and are involved in the migration of MSCs both *in vitro* and *in vivo* [107,112-114].

Granulocyte colony-stimulating factor triggered hematopoietic stem cell mobilization

While MSC homing highlights the body's intrinsic repair mechanisms, another vital therapeutic approach involves the mobilization of HSCs. The administration of G-CSF has been widely used clinically to mobilize HSCs for HSCT in the treatment of hematopoietic diseases such as sickle cell anemia, thalassemia, and hematological malignancies [115-122]. In addition, G-CSF, which stimulates the production of granulocytes, has been used since 1988 to treat cytopenia following chemotherapy, as well as neutropenia caused by nonchemotherapy-related idiosyncratic drug reactions or diseases [123,124]. G-CSF also aids in mobilizing granulocytes for transfusions and contributes to treating congenital or acquired bone marrow failure [125]. Furthermore, G-CSF has demonstrated neuroprotective and cardioprotective effects and has been used in numerous clinical trials for the treatment of conditions such as spinal cord injury, carbon monoxide poisoning, nonarteritic anterior ischemic optic neuropathy, and myocardial infarction [126-129]. The administration of G-CSF is associated with a range of side effects, including musculoskeletal pain, bone pain, splenomegaly, thrombocytopenia, and drug hypersensitivity reactions [123,130-132].

Stem cell resilience

In addition to their therapeutic mobilization, stem cell resilience is crucial in understanding their utility. Resilience is the dynamic process by which individuals adapt and maintain their functionality amid various challenges or stressors [133,134]. Stem cells play a crucial role in tissue homeostasis by replenishing damaged or senescent cells, thereby supporting tissue integrity and preserving organ function [135]. Their inherent regenerative potential enables them to participate in tissue repair and regeneration following injury, disease, or physiological stress [136]. Moreover, stem cells exert immunomodulatory effects by regulating inflammatory responses, modulating immune cell function, and promoting tissue repair and regeneration [33]. In addition, they offer neuroprotective effects through diverse mechanisms, including neurotrophic factor secretion, promoting neuronal survival, and modulation of inflammatory reactions. This multifaceted resilience of stem cells underscores their significance in maintaining overall tissue health and function [137]. In clinical trials, MSCs have been used to treat several neurodegenerative diseases, including amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Huntington's disease, and Alzheimer's disease. All MSC treatments have demonstrated safety and early promising signs of efficacy [138-141]. HSCs have also been employed in clinical trials for multiple sclerosis therapy, showing an increase in the percentage of regulatory T-cells and suppression of inflammation [138,142,143].

Clinical implications and therapeutic potential

Dysregulated inflammation and impaired stem cell mobilization or homing are associated with various pathological conditions including cardiovascular diseases, neurodegenerative disorders, and autoimmune diseases [144-147]. Therapeutic strategies to modulate inflammation and enhance stem cell mobilization are promising for treating these conditions. Administering inflammatory factors such as G-CSF has been widely used clinically to mobilize HSCs for HSCT. Beyond neurodegenerative diseases, MSCs have demonstrated effectiveness in alleviating various conditions. They mitigate inflammatory bowel disease by modulating inflammatory cytokines within the inflamed gut in clinical trials [148,149]. Additionally, they ameliorate spinal cord injury by improving motor function in the lower limbs and bladder compliance [150-153]. In addition, MSCs have been shown to safeguard renal function by diminishing serum creatinine and blood urea nitrogen levels, thereby mitigating acute renal injury through various mechanisms such as anti-inflammation, anti-apoptosis, angiogenesis anti-oxidative stress, and anti-fibrosis [154,155]. Furthermore, MSC transplantation has demonstrated improvements in quality of life, functional outcomes, and pain relief for patients with heart failure or knee osteoarthritis [150,156-160] [Table 2]. Moreover, emerging strategies, such as cell-based therapies incorporating MSCs alongside HSCT, aim to enhance hematopoietic reconstitution and address graft-versus-host diseases with ongoing exploration through clinical trials [161]. However, challenges such as optimizing the efficacy and safety of stem cell-based therapies and understanding the long-term consequences of modulating inflammation warrant further investigation.

Conclusion

Inflammation and stem cell mobilization or homing are intricately linked processes essential for tissue homeostasis, repair, and regeneration. Understanding the mechanisms underlying their interplay provides insights into the development of novel therapeutic strategies for a wide range of diseases and conditions. Further research into elucidating the complex crosstalk between inflammation and stem cells will undoubtedly uncover new avenues for therapeutic intervention and enhance our ability to harness the regenerative potential of stem cells.

Table 2: Comparison of clinical implication and disease condition between granulocyte colony-stimulating factor, hematopoietic stem cells, and mesenchymal stem cells

Treatment	Clinical implication	Disease condition	Reference
G-CSF (filgrastim)	Stimulates production of granulocytes	Cytopenia, neutropenia, and cancer	[123-125]
HSCs	Differentiates into various blood cell types	Various hematological disorders (e.g., sickle cell anemia, thalassemia, and hematological malignancies)	[115-122]
MSCs	Immunomodulation, tissue repair, and regeneration	Diverse human diseases (e.g., neurodegenerative diseases, inflammatory bowel disease, acute renal injury, heart failure, and knee osteoarthritis)	[138-141,148-160]

MSCs: Mesenchymal stem cells, HSCs: Hematopoietic stem cells, G-CSF: Granulocyte colony-stimulating factor

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

This work was supported by a research funding from the Ministry of Science and Technology, Taiwan (MOST 103-2320-B-320-006, MOST 103-2321-B-320-001, MOST105-2633-B-320-001, MOST105-2311-B-320-001-MY3, MOST106-2633-B-320-001, MOST108-2311-B-320-001, and MOST109-2311-B-320-001), Buddhist Tzu Chi Medical Foundation (TCMMP104-06, TCMMP108-04, and TCMMP111-01), and Buddhist Tzu Chi General Hospital, Hualien, Taiwan (TCRD106-42, TCRD108-55, TCRD110-61, TCRD111-082, TCRD112-054, and TCRD113-055).

Conflicts of interest

Dr. Hsin-Hou Chang, an editorial board member at the *Tzu Chi Medical Journal*, had no role in the peer review process or the decision to publish this article. The other authors declared no conflicts of interest in writing this article.

References

1. Majno G. The healing hand: Man and wound in the ancient world. Cambridge, Massachusetts: Harvard University Press; 1975.
2. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med 2019;25:1822-32.
3. Serhan CN, Savill J. Resolution of inflammation: The beginning programs the end. Nat Immunol 2005;6:1191-7.
4. de Morree A, Rando TA. Regulation of adult stem cell quiescence and its functions in the maintenance of tissue integrity. Nat Rev Mol Cell Biol 2023;24:334-54.
5. Weissman IL. Stem cells: Units of development, units of regeneration, and units in evolution. Cell 2000;100:157-68.
6. Chang HH, Liou YS, Sun DS. Hematopoietic stem cell mobilization. Tzu Chi Med J 2022;34:270-5.
7. Damon LE, Damon LE. Mobilization of hematopoietic stem cells into the peripheral blood. Expert Rev Hematol 2009;2:717-33.
8. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008;454:428-35.
9. Medzhitov R. Inflammation 2010: New adventures of an old flame. Cell 2010;140:771-6.
10. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736-88.
11. Meizlish ML, Franklin RA, Zhou X, Medzhitov R. Tissue homeostasis and inflammation. Annu Rev Immunol 2021;39:557-81.
12. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature 2002;418:191-5.
13. Basu S, Srivastava PK. Heat shock proteins: The fountainhead of innate and adaptive immune responses. Cell Stress Chaperones 2000;5:443-51.
14. Carp H. Mitochondrial N-formylmethionyl proteins as chemoattractants for neutrophils. J Exp Med 1982;155:264-75.
15. Lai JJ, Cruz FM, Rock KL. Immune sensing of cell death through recognition of histone sequences by c-type lectin-receptor-2d causes inflammation and tissue injury. Immunity 2020;52:123-35.e6.
16. Mariathasan S, Weiss DS, Newton K, McBride J, O'Rourke K, Roose-Girma M, et al. Cryopyrin activates the inflammasome in response to toxins and ATP. Nature 2006;440:228-32.
17. Medzhitov R. The spectrum of inflammatory responses. Science 2021;374:1070-5.
18. Nathan C. Points of control in inflammation. Nature 2002;420:846-52.
19. Lasry A, Ben-Neriah Y. Senescence-associated inflammatory responses: Aging and cancer perspectives. Trends Immunol 2015;36:217-28.
20. Ip WK, Medzhitov R. Macrophages monitor tissue osmolarity and induce inflammatory response through NLRP3 and NLRC4 inflammasome activation. Nat Commun 2015;6:6931.
21. Martinon F, Burns K, Tschopp J. The inflammasome: A molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell 2002;10:417-26.
22. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006;440:237-41.
23. Franchi L, Eigenbrod T, Muñoz-Planillo R, Nuñez G. The inflammasome: A caspase-1-activation platform that regulates immune responses and disease pathogenesis. Nat Immunol 2009;10:241-7.
24. Wen H, Miao EA, Ting JP. Mechanisms of NOD-like receptor-associated inflammasome activation. Immunity 2013;39:432-41.
25. Lien TS, Sun DS, Chang CM, Wu CY, Dai MS, Chan H, et al. Dengue virus and antiplatelet autoantibodies synergistically induce haemorrhage through Nlrp3-inflammasome and FcγRIII. Thromb Haemost 2015;113:1060-70.
26. Mangan MS, Olhava EJ, Roush WR, Seidel HM, Glick GD, Latz E. Targeting the NLRP3 inflammasome in inflammatory diseases. Nat Rev Drug Discov 2018;17:588-606.
27. Inoue M, Shinohara ML. NLRP3 Inflammasome and MS/EAE. Autoimmune Dis 2013;2013:859145.
28. Ito M, Shichita T, Okada M, Komine R, Noguchi Y, Yoshimura A, et al. Bruton's tyrosine kinase is essential for NLRP3 inflammasome activation and contributes to ischaemic brain injury. Nat Commun 2015;6:7360.
29. Huang Y, Xu W, Zhou R. NLRP3 inflammasome activation and cell death. Cell Mol Immunol 2021;18:2114-27.
30. Xu S, Wang D, Tan L, Lu J. The role of NLRP3 inflammasome in type 2 inflammation related diseases. Autoimmunity 2024;57:2310269.
31. Sutterwala FS, Haasken S, Cassel SL. Mechanism of NLRP3 inflammasome activation. Ann N Y Acad Sci 2014;1319:82-95.
32. Zahid A, Li B, Kombe AJ, Jin T, Tao J. Pharmacological inhibitors of the NLRP3 inflammasome. Front Immunol 2019;10:2538.

33. Pittenger MF, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI. Mesenchymal stem cell perspective: Cell biology to clinical progress. NPJ Regen Med 2019;4:22.
34. Hawley RG, Ramezani A, Hawley TS. Hematopoietic stem cells. Methods Enzymol 2006;419:149-79.
35. Morrison SJ, Spradling AC. Stem cells and niches: Mechanisms that promote stem cell maintenance throughout life. Cell 2008;132:598-611.
36. Schofield R. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. Blood Cells 1978;4:7-25.
37. Anthony BA, Link DC. Regulation of hematopoietic stem cells by bone marrow stromal cells. Trends Immunol 2014;35:32-7.
38. Beatriz SA, Antonio LV, Carlos LL. Stem cell transplantation. Ch. 11. Landes Bioscience and Springer Science+Business Media. (Springer); 2012, p. 152-70.
39. Domingues MJ, Cao H, Heazlewood SY, Cao B, Nilsson SK. Niche extracellular matrix components and their influence on HSC. J Cell Biochem 2017;118:1984-93.
40. Tay J, Levesque JP, Winkler IG. Cellular players of hematopoietic stem cell mobilization in the bone marrow niche. Int J Hematol 2017;105:129-40.
41. Mitroulis I, Kalafati L, Bornhäuser M, Hajishengallis G, Chavakis T. Regulation of the bone marrow niche by inflammation. Front Immunol 2020;11:1540.
42. Lévesque JP, Hendy J, Takamatsu Y, Simmons PJ, Bendall LJ. Disruption of the CXCR4/CXCL12 chemotactic interaction during hematopoietic stem cell mobilization induced by GCSF or cyclophosphamide. J Clin Invest 2003;111:187-96.
43. Rüster B, Göttig S, Ludwig RJ, Bistrian R, Müller S, Seifried E, et al. Mesenchymal stem cells display coordinated rolling and adhesion behavior on endothelial cells. Blood 2006;108:3938-44.
44. Lapidot T, Petit I. Current understanding of stem cell mobilization: The roles of chemokines, proteolytic enzymes, adhesion molecules, cytokines, and stromal cells. Exp Hematol 2002;30:973-81.
45. Méndez-Ferrer S, Chow A, Merad M, Frenette PS. Circadian rhythms influence hematopoietic stem cells. Curr Opin Hematol 2009;16:235-42.
46. Wojakowski W, Tendera M, Kucia M, Zuba-Surma E, Paczkowska E, Ciosek J, et al. Mobilization of bone marrow-derived Oct-4+SSEA-4+ very small embryonic-like stem cells in patients with acute myocardial infarction. J Am Coll Cardiol 2009;53:1-9.
47. Möbius-Winkler S, Hilberg T, Menzel K, Golla E, Burman A, Schuler G, et al. Time-dependent mobilization of circulating progenitor cells during strenuous exercise in healthy individuals. J Appl Physiol (1985) 2009;107:1943-50.
48. Massberg S, Schaerli P, Knezevic-Maramica I, Köllnberger M, Tubo N, Moseman EA, et al. Immunosurveillance by hematopoietic progenitor cells trafficking through blood, lymph, and peripheral tissues. Cell 2007;131:994-1008.
49. Luster AD, Alon R, von Andrian UH. Immune cell migration in inflammation: Present and future therapeutic targets. Nat Immunol 2005;6:1182-90.
50. Adamiak M, Ratajczak MZ. Innate immunity and mobilization of hematopoietic stem cells. Curr Stem Cell Rep 2017;3:172-80.
51. Kang JW, Kim SJ, Cho HI, Lee SM. DAMPs activating innate immune responses in sepsis. Ageing Res Rev 2015;24:54-65.
52. Burberry A, Zeng MY, Ding L, Wicks I, Inohara N, Morrison SJ, et al. Infection mobilizes hematopoietic stem cells through cooperative NOD-like receptor and Toll-like receptor signaling. Cell Host Microbe 2014;15:779-91.
53. Bujko K, Rzeszotek S, Hoehlig K, Yan J, Vater A, Ratajczak MZ. Signaling of the complement cleavage product anaphylatoxin C5a through C5aR (CD88) contributes to pharmacological hematopoietic stem cell mobilization. Stem Cell Rev Rep 2017;13:793-800.
54. Ratajczak MZ, Lee H, Wysoczynski M, Wan W, Marlicz W, Laughlin MJ, et al. Novel insight into stem cell mobilization-plasma sphingosine-1-phosphate is a major chemoattractant that directs the egress of hematopoietic stem progenitor cells from the bone marrow and its level in peripheral blood increases during mobilization due to activation of complement cascade/membrane attack complex. Leukemia 2010;24:976-85.
55. Ratajczak MZ, Bujko K, Cymer M, Thapa A, Adamiak M, Ratajczak J, et al. The Nlrp3 inflammasome as a "rising star" in studies of normal and malignant hematopoiesis. Leukemia 2020;34:1512-23.
56. Cymer M, Brzezniakiewicz-Janus K, Bujko K, Thapa A, Ratajczak J, Anusz K, et al. Pannexin-1 channel "fuels" by releasing ATP from bone marrow cells a state of sterile inflammation required for optimal mobilization and homing of hematopoietic stem cells. Purinergic Signal 2020;16:313-25.
57. Ratajczak MZ, Adamiak M, Thapa A, Bujko K, Brzezniakiewicz-Janus K, Lenkiewicz AM. NLRP3 inflammasome couples purinergic signaling with activation of the complement cascade for the optimal release of cells from bone marrow. Leukemia 2019;33:815-25.
58. Lenkiewicz AM, Adamiak M, Thapa A, Bujko K, Pedziwiatr D, Abdel-Latif AK, et al. The Nlrp3 inflammasome orchestrates mobilization of bone marrow-residing stem cells into peripheral blood. Stem Cell Rev Rep 2019;15:391-403.
59. Thapa A, Adamiak M, Bujko K, Ratajczak J, Abdel-Latif AK, Kucia M, et al. Danger-associated molecular pattern molecules take unexpectedly a central stage in Nlrp3 inflammasome-caspase-1-mediated trafficking of hematopoietic stem/progenitor cells. Leukemia 2021;35:2658-71.
60. Wang TF, Liou YS, Chang HH, Yang SH, Li CC, Wang JH, et al. Correlation of body mass index and proinflammatory cytokine levels with hematopoietic stem cell mobilization. J Clin Med 2022;11:4169.
61. Choi J, Jang YJ, Dabrowska C, Iich E, Evans KV, Hall H, et al. Release of notch activity coordinated by IL-1β signalling confers differentiation plasticity of airway progenitors via Fosl2 during alveolar regeneration. Nat Cell Biol 2021;23:953-66.
62. Kathiriya JJ, Peng T. An inflammatory switch for stem cell plasticity. Nat Cell Biol 2021;23:928-9.
63. Bonam SR, Wang F, Muller S. Autophagy: A new concept in autoimmunity regulation and a novel therapeutic option. J Autoimmun 2018;94:16-32.
64. Gan T, Qu S, Zhang H, Zhou XJ. Modulation of the immunity and inflammation by autophagy. MedComm (2020) 2023;4:e311.
65. Mathur A, Ritu, Chandra P, Das A. Autophagy: A necessary evil in cancer and inflammation. 3 Biotech 2024;14:87.
66. Zhao S, Li X, Wang J, Wang H. The role of the effects of autophagy on NLRP3 inflammasome in inflammatory nervous system diseases. Front Cell Dev Biol 2021;9:657478.
67. Lv S, Wang H, Li X. The role of the interplay between autophagy and NLRP3 inflammasome in metabolic disorders. Front Cell Dev Biol 2021;9:634118.
68. Sun Q, Fan J, Billiar TR, Scott MJ. Inflammasome and autophagy regulation – A two-way street. Mol Med 2017;23:188-95.
69. Tooze SA, Yoshimori T. The origin of the autophagosomal membrane. Nat Cell Biol 2010;12:831-5.
70. Mehrpour M, Esclatine A, Beau I, Codogno P. Overview of macroautophagy regulation in mammalian cells. Cell Res 2010;20:748-62.
71. Matsunaga K, Morita E, Saitoh T, Akira S, Ktistakis NT, Izumi T, et al. Autophagy requires endoplasmic reticulum targeting of the PI3-kinase complex via Atg14L. J Cell Biol 2010;190:511-21.
72. Watson AS, Mortensen M, Simon AK. Autophagy in the pathogenesis of myelodysplastic syndrome and acute myeloid leukemia. Cell Cycle 2011;10:1719-25.
73. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell 2008;132:27-42.
74. Gómez-Virgilio L, Silva-Lucero MD, Flores-Morelos DS,

Gallardo-Nieto J, Lopez-Toledo G, Abarca-Fernandez AM, et al. Autophagy: A key regulator of homeostasis and disease: An overview of molecular mechanisms and modulators. Cells 2022;11:2262.

75. Jiang X, Overholtzer M, Thompson CB. Autophagy in cellular metabolism and cancer. J Clin Invest 2015;125:47-54.
76. Mortensen M, Watson AS, Simon AK. Lack of autophagy in the hematopoietic system leads to loss of hematopoietic stem cell function and dysregulated myeloid proliferation. Autophagy 2011;7:1069-70.
77. Mortensen M, Soilleux EJ, Djordjevic G, Tripp R, Lutteropp M, Sadighi-Akha E, et al. The autophagy protein Atg7 is essential for hematopoietic stem cell maintenance. J Exp Med 2011;208:455-67.
78. Hasan KM, Haque MA. Autophagy and its lineage-specific roles in the hematopoietic system. Oxid Med Cell Longev 2023;2023:8257217.
79. Riffelmacher T, Simon AK. Mechanistic roles of autophagy in hematopoietic differentiation. FEBS J 2017;284:1008-20.
80. Zhang J, Wu K, Xiao X, Liao J, Hu Q, Chen H, et al. Autophagy as a regulatory component of erythropoiesis. Int J Mol Sci 2015;16:4083-94.
81. Griffiths RE, Kupzig S, Cogan N, Mankelow TJ, Betin VM, Trakarnsanga K, et al. The ins and outs of human reticulocyte maturation: Autophagy and the endosome/exosome pathway. Autophagy 2012;8:1150-1.
82. Mortensen M, Ferguson DJ, Simon AK. Mitochondrial clearance by autophagy in developing erythrocytes: Clearly important, but just how much so? Cell Cycle 2010;9:1901-6.
83. Zhang J, Ney PA. Autophagy-dependent and -independent mechanisms of mitochondrial clearance during reticulocyte maturation. Autophagy 2009;5:1064-5.
84. Cao Y, Cai J, Zhang S, Yuan N, Li X, Fang Y, et al. Loss of autophagy leads to failure in megakaryopoiesis, megakaryocyte differentiation, and thrombopoiesis in mice. Exp Hematol 2015;43:488-94.
85. Revuelta M, Matheu A. Autophagy in stem cell aging. Aging Cell 2017;16:912-5.
86. Ho TT, Warr MR, Adelman ER, Lansinger OM, Flach J, Verovskaya EV, et al. Autophagy maintains the metabolism and function of young and old stem cells. Nature 2017;543:205-10.
87. Doulatov S, Daley GQ. Autophagy: It's in your blood. Dev Cell 2017;40:518-20.
88. Leveque-El Mouttie L, Vu T, Lineburg KE, Kuns RD, Bagger FO, Teal BE, et al. Autophagy is required for stem cell mobilization by G-CSF. Blood 2015;125:2933-6.
89. Le Texier L, Lineburg KE, MacDonald KP. Harnessing bone marrow resident regulatory T cells to improve allogeneic stem cell transplant outcomes. Int J Hematol 2017;105:153-61.
90. Le Texier L, Lineburg KE, Cao B, McDonald-Hyman C, Leveque-El Mouttie L, Nicholls J, et al. Autophagy-dependent regulatory T cells are critical for the control of graft-versus-host disease. JCI Insight 2016;1:e86850.
91. Beres AJ, Drobyski WR. The role of regulatory T cells in the biology of graft versus host disease. Front Immunol 2013;4:163.
92. Haynesworth SE, Goshima J, Goldberg VM, Caplan AI. Characterization of cells with osteogenic potential from human marrow. Bone 1992;13:81-8.
93. Halvorsen YC, Wilkison WO, Gimble JM. Adipose-derived stromal cells – Their utility and potential in bone formation. Int J Obes Relat Metab Disord 2000; 24(Suppl 4): S41-4.
94. Liau LL, Ruszymah BH, Ng MH, Law JX. Characteristics and clinical applications of Wharton's jelly-derived mesenchymal stromal cells. Curr Res Transl Med 2020;68:5-16.
95. In 't Anker PS, Scherjon SA, Kleijburg-van der Keur C, de Groot-Swings GM, Claas FH, Fibbe WE, et al. Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. Stem Cells 2004;22:1338-45.
96. Zhang X, Hirai M, Cantero S, Ciubotariu R, Dobrila L, Hirsh A, et al. Isolation and characterization of mesenchymal stem cells from human umbilical cord blood: Reevaluation of critical factors for successful isolation and high ability to proliferate and differentiate to chondrocytes as compared to mesenchymal stem cells from bone marrow and adipose tissue. J Cell Biochem 2011;112:1206-18.
97. Potdar PD, D'souza SB. Isolation of Oct4+, Nanog+ and SOX2- mesenchymal cells from peripheral blood of a diabetes mellitus patient. Hum Cell 2011;24:51-5.
98. Potdar P, Subedi R. Defining molecular phenotypes of mesenchymal and hematopoietic stem cells derived from peripheral blood of acute lymphocytic leukemia patients for regenerative stem cell therapy. J Stem Cells Regen Med 2011;7:29-40.
99. Liau LL, Looi QH, Chia WC, Subramaniam T, Ng MH, Law JX. Treatment of spinal cord injury with mesenchymal stem cells. Cell Biosci 2020;10:112.
100. Krueger TE, Thorek DL, Meeker AK, Isaacs JT, Brennen WN. Tumor-infiltrating mesenchymal stem cells: Drivers of the immunosuppressive tumor microenvironment in prostate cancer? Prostate 2019;79:320-30.
101. Liu J, Qi L, Bao S, Yan F, Chen J, Yu S, et al. The acute spinal cord injury microenvironment and its impact on the homing of mesenchymal stem cells. Exp Neurol 2024;373:114682.
102. Gill JK, Rehsia SK, Verma E, Sareen N, Dhingra S. Stem cell therapy for cardiac regeneration: Past, present, and future. Can J Physiol Pharmacol 2024;102:161-79.
103. Ullah M, Liu DD, Thakor AS. Mesenchymal stromal cell homing: Mechanisms and strategies for improvement. IScience 2019;15:421-38.
104. Nitzsche F, Müller C, Lukomska B, Jolkkonen J, Deten A, Boltze J. Concise review: MSC adhesion cascade-insights into homing and transendothelial migration. Stem Cells 2017;35:1446-60.
105. Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: The leukocyte adhesion cascade updated. Nat Rev Immunol 2007;7:678-89.
106. Kumar S, Ponnazhagan S. Bone homing of mesenchymal stem cells by ectopic alpha 4 integrin expression. FASEB J 2007;21:3917-27.
107. Szydlak R. Biological, chemical and mechanical factors regulating migration and homing of mesenchymal stem cells. World J Stem Cells 2021;13:619-31.
108. Fu X, Liu G, Halim A, Ju Y, Luo Q, Song AG. Mesenchymal stem cell migration and tissue repair. Cells 2019;8:784.
109. Jiang Q, Huang K, Lu F, Deng S, Yang Z, Hu S. Modifying strategies for SDF-1/CXCR4 interaction during mesenchymal stem cell transplantation. Gen Thorac Cardiovasc Surg 2022;70:1-10.
110. Steingen C, Brenig F, Baumgartner L, Schmidt J, Schmidt A, Bloch W. Characterization of key mechanisms in transmigration and invasion of mesenchymal stem cells. J Mol Cell Cardiol 2008;44:1072-84.
111. Nagase H, Woessner JF Jr. Matrix metalloproteinases. J Biol Chem 1999;274:21491-4.
112. Teo GS, Yang Z, Carman CV, Karp JM, Lin CP. Intravital imaging of mesenchymal stem cell trafficking and association with platelets and neutrophils. Stem Cells 2015;33:265-77.
113. Jiang L, Song XH, Liu P, Zeng CL, Huang ZS, Zhu LJ, et al. Platelet-mediated mesenchymal stem cells homing to the lung reduces monocrotaline-induced rat pulmonary hypertension. Cell Transplant 2012;21:1463-75.
114. Langer HF, Stellos K, Steingen C, Froihofer A, Schönberger T, Krämer B, et al. Platelet derived bFGF mediates vascular integrative mechanisms of mesenchymal stem cells *in vitro*. J Mol Cell Cardiol 2009;47:315-25.
115. To LB, Levesque JP, Herbert KE. How I treat patients who mobilize hematopoietic stem cells poorly. Blood 2011;118:4530-40.
116. Kumar SK, Callander NS, Hillengass J, Liedtke M, Baljevic M, Campagnaro E, et al. NCCN guidelines insights: Multiple myeloma,

version 1.2020. J Natl Compr Canc Netw 2019;17:1154-65.

117. Copelan EA, Chojecki A, Lazarus HM, Avalos BR. Allogeneic hematopoietic cell transplantation; the current renaissance. Blood Rev 2019;34:34-44.
118. Horwitz SM, Ansell SM, Ai WZ, Barnes J, Barta SK, Choi M, et al. NCCN guidelines insights: T-cell lymphomas, version 2.2018. J Natl Compr Canc Netw 2018;16:123-35.
119. Horwitz SM, Zelenetz AD, Gordon LI, Wierda WG, Abramson JS, Advani RH, et al. NCCN guidelines insights: Non-Hodgkin's lymphomas, version 3.2016. J Natl Compr Canc Netw 2016;14:1067-79.
120. Mehta PA, Faulkner LB. Hematopoietic cell transplantation for thalassemia: A global perspective BMT tandem meeting 2013. Biol Blood Marrow Transplant 2013;19:S70-3.
121. Dalle JH. Hematopoietic stem cell transplantation in SCD. C R Biol 2013;336:148-51.
122. Cheuk DK. Optimal stem cell source for allogeneic stem cell transplantation for hematological malignancies. World J Transplant 2013;3:99-112.
123. Bumbăcea RS, Udrea MR, Ali S, Bojincă VC. Balancing benefits and risks: A literature review on hypersensitivity reactions to human G-CSF (Granulocyte Colony-Stimulating Factor). Int J Mol Sci 2024;25:4807.
124. Pick AM, Nystrom KK. Nonchemotherapy drug-induced neutropenia and agranulocytosis: Could medications be the culprit? J Pharm Pract 2014;27:447-52.
125. Cesaro S, Chinello P, De Silvestro G, Marson P, Picco G, Varotto S, et al. Granulocyte transfusions from G-CSF-stimulated donors for the treatment of severe infections in neutropenic pediatric patients with onco-hematological diseases. Support Care Cancer 2003;11:101-6.
126. Mousavi SR, Mohammadpour AH, Moshiri M, Feizy J, Pourtaji A, Samadi S. A pilot study of neuroprotective effect of granulocyte colony-stimulating factor (G-CSF) in patients with carbon monoxide poisoning: A double-blind, randomized, placebo-controlled trial. Naunyn Schmiedebergs Arch Pharmacol 2023;396:1257-67.
127. Koda M, Hanaoka H, Fujii Y, Hanawa M, Kawasaki Y, Ozawa Y, et al. Randomized trial of granulocyte colony-stimulating factor for spinal cord injury. Brain 2021;144:789-99.
128. Abri Aghdam K, Aghajani A, Ashraf Khorasani M, Soltan Sanjari M, Chaibakhsh S, Habibi A, et al. Intravitreal injection of the granulocyte-colony stimulating factor for the treatment of non-arteritic anterior ischemic optic neuropathy: A pilot study. Semin Ophthalmol 2021;36:649-57.
129. Achilli F, Pontone G, Bassetti B, Squadroni L, Campodonico J, Corrada E, et al. G-CSF for extensive STEMI. Circ Res 2019;125:295-306.
130. Abraham I, Tharmarajah S, MacDonald K. Clinical safety of biosimilar recombinant human granulocyte colony-stimulating factors. Expert Opin Drug Saf 2013;12:235-46.
131. Crawford J, Caserta C, Roila F, ESMO Guidelines Working Group. Hematopoietic growth factors: ESMO clinical practice guidelines for the applications. Ann Oncol 2010; 21(Suppl 5): v248-51.
132. Schriber JR, Negrin RS. Use and toxicity of the colony-stimulating factors. Drug Saf 1993;8:457-68.
133. Masten AS, Barnes AJ. Resilience in children: Developmental perspectives. Children (Basel) 2018;5:98.
134. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: Interdisciplinary perspectives. Eur J Psychotraumatol 2014;5:25338.
135. Watt FM, Huck WT. Role of the extracellular matrix in regulating stem cell fate. Nat Rev Mol Cell Biol 2013;14:467-73.
136. Rando TA. Stem cells, ageing and the quest for immortality. Nature 2006;441:1080-6.
137. Ying C, Zhang J, Zhang H, Gao S, Guo X, Lin J, et al. Stem cells in central nervous system diseases: Promising therapeutic strategies. Exp Neurol 2023;369:114543.
138. Cecerska-Heryć E, Pękała M, Serwin N, Gliźniewicz M, Grygorcewicz B, Michalczyk A, et al. The use of stem cells as a potential treatment method for selected neurodegenerative diseases: Review. Cell Mol Neurobiol 2023;43:2643-73.
139. Petrou P, Kassis I, Ginzberg A, Hallimi M, Karussis D. Effects of mesenchymal stem cell transplantation on cerebrospinal fluid biomarkers in progressive multiple sclerosis. Stem Cells Transl Med 2022;11:55-8.
140. Uccelli A, Laroni A, Ali R, Battaglia MA, Blinkenberg M, Brundin L, et al. Safety, tolerability, and activity of mesenchymal stem cells versus placebo in multiple sclerosis (MESEMS): A phase 2, randomised, double-blind crossover trial. Lancet Neurol 2021;20:917-29.
141. Barczewska M, Maksymowicz S, Zdolińska-Malinowska I, Siwek T, Grudniak M. Umbilical cord mesenchymal stem cells in amyotrophic lateral sclerosis: An original study. Stem Cell Rev Rep 2020;16:922-32.
142. Visweswaran M, Hendrawan K, Massey JC, Khoo ML, Ford CD, Zaunders JJ, et al. Sustained immunotolerance in multiple sclerosis after stem cell transplant. Ann Clin Transl Neurol 2022;9:206-20.
143. Burt RK, Balabanov R, Burman J, Sharrack B, Snowden JA, Oliveira MC, et al. Effect of nonmyeloablative hematopoietic stem cell transplantation versus continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: A randomized clinical trial. JAMA 2019;321:165-74.
144. Sarapultsev A, Gusev E, Komelkova M, Utepova I, Luo S, Hu D. JAK-STAT signaling in inflammation and stress-related diseases: Implications for therapeutic interventions. Mol Biomed 2023;4:40.
145. Buelna-Chontal M, Bansal SS, Barrera-Chimal J, Liberale L. Editorial: Targeting dysregulated inflammation to treat cardiovascular diseases. Front Cell Dev Biol 2022;10:926086.
146. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and age-related diseases: Role of inflammation triggers and cytokines. Front Immunol 2018;9:586.
147. Wojakowski W, Landmesser U, Bachowski R, Jadczyk T, Tendera M. Mobilization of stem and progenitor cells in cardiovascular diseases. Leukemia 2012;26:23-33.
148. Shi L, Chen L, Gao X, Sun X, Jin G, Yang Y, et al. Comparison of different sources of mesenchymal stem cells: Focus on inflammatory bowel disease. Inflammopharmacology 2024;32:1721-42.
149. Tian CM, Zhang Y, Yang MF, Xu HM, Zhu MZ, Yao J, et al. Stem cell therapy in inflammatory bowel disease: A review of achievements and challenges. J Inflamm Res 2023;16:2089-119.
150. Margiana R, Markov A, Zekiy AO, Hamza MU, Al-Dabbagh KA, Al-Zubaidi SH, et al. Clinical application of mesenchymal stem cell in regenerative medicine: A narrative review. Stem Cell Res Ther 2022;13:366.
151. Vaquero J, Zurita M, Rico MA, Aguayo C, Bonilla C, Marin E, et al. Intrathecal administration of autologous mesenchymal stromal cells for spinal cord injury: Safety and efficacy of the 100/3 guideline. Cytotherapy 2018;20:806-19.
152. Vaquero J, Zurita M, Rico MA, Bonilla C, Aguayo C, Fernández C, et al. Repeated subarachnoid administrations of autologous mesenchymal stromal cells supported in autologous plasma improve quality of life in patients suffering incomplete spinal cord injury. Cytotherapy 2017;19:349-59.
153. Mendonça MV, Larocca TF, de Freitas Souza BS, Villarreal CF, Silva LF, Matos AC, et al. Safety and neurological assessments after autologous transplantation of bone marrow mesenchymal stem cells in subjects with chronic spinal cord injury. Stem Cell Res Ther 2014;5:126.
154. Chen F, Chen N, Xia C, Wang H, Shao L, Zhou C, et al. Mesenchymal stem cell therapy in kidney diseases: Potential and challenges. Cell Transplant 2023;32:9636897231164251.
155. Sávio-Silva C, Beyerstedt S, Soinski-Sousa PE, Casaro EB, Balby-Rocha MT, Simplício-Filho A, et al. Mesenchymal stem cell

therapy for diabetic kidney disease: A review of the studies using syngeneic, autologous, allogeneic, and xenogeneic cells. Stem Cells Int 2020;2020:8833725.

156. Mathiasen AB, Qayyum AA, Jørgensen E, Helqvist S, Kofoed KF, Haack-Sørensen M, et al. Bone marrow-derived mesenchymal stromal cell treatment in patients with ischaemic heart failure: Final 4-year follow-up of the MSC-HF trial. Eur J Heart Fail 2020;22:884-92.
157. Matas J, Orrego M, Amenabar D, Infante C, Tapia-Limonchi R, Cadiz MI, et al. Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: Repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial. Stem Cells Transl Med 2019;8:215-24.
158. Lee WS, Kim HJ, Kim KI, Kim GB, Jin W. Intra-articular injection of autologous adipose tissue-derived mesenchymal stem cells for the treatment of knee osteoarthritis: A phase IIb, randomized, placebo-controlled clinical trial. Stem Cells Transl Med 2019;8:504-11.
159. Pers YM, Rackwitz L, Ferreira R, Pullig O, Delfour C, Barry F, et al. Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee: A phase I dose-escalation trial. Stem Cells Transl Med 2016;5:847-56.
160. Gao LR, Chen Y, Zhang NK, Yang XL, Liu HL, Wang ZG, et al. Intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells in acute myocardial infarction: Double-blind, randomized controlled trial. BMC Med 2015;13:162.
161. Lin T, Yang Y, Chen X. A review of the application of mesenchymal stem cells in the field of hematopoietic stem cell transplantation. Eur J Med Res 2023;28:268.