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REVIEW

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The regenerative journey: exploring stem cell roles from injury detection to tissue repair

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Abstract

The intricate process of tissue regeneration, driven by endogenous mechanisms, represents a sophisticated interplay of biological events from injury detection to functional recovery. This review discusses the multifaceted journey of stem cells in response to physiological and pathological cues. Beginning with detecting tissue damage through biochemical signals, the subsequent acute inflammatory response activates stem cells residing in specialized niches. These cells are then recruited to the injury site via chemotactic gradients of growth factors and cytokines. Once localized, stem cells proliferate and differentiate, influenced by the local microenvironment, which provides essential cues for their fate decisions. Integrating newly formed cells into the tissue matrix, supported by modulation of inflammation, angiogenesis, and extracellular matrix remodelling, is crucial for restoring tissue architecture and function. By exploring these biological details and leveraging advancements in medical technology, this review aims to enhance the understanding of regenerative therapies, offering new avenues for effective tissue repair and recovery.

Introduction

The human body exhibits a remarkable capacity for tissue repair and regeneration in the face of injury, disease, or age-related degeneration. At the heart of this restorative ability lie stem cells, which function as key components of the body's intrinsic repair network. These cells possess the distinctive capability to differentiate into multiple cell types, making them essential for preserving tissue integrity and promoting repair [119]. The regenerative process driven by stem cells is orchestrated through a dynamic and tightly regulated sequence, beginning with normal function.

This review outlines the multifaceted mechanisms that underpin tissue regeneration. The regenerative cascade is initiated by biochemical distress signals emitted from injured or dying cells [12, 40, 58, 101]. These signals elicit an acute inflammatory response that not only limits damage but also mobilizes stem cells from their niches, whether tissue-resident or bone marrow-derived [33].

Following activation, a range of stem cell types, such as hematopoietic stem cells, mesenchymal stem cells, and endothelial progenitor cells, are recruited to the injury site in response to gradients of cytokines and growth factors [81]. Their migration is guided by chemotactic cues and shaped by complex interactions with the surrounding microenvironment [109]. Once localized to the damaged area, these stem cells must determine whether to self-renew or undergo differentiation into specific cell lineages required for repair, an outcome heavily influenced by local factors such as oxygen availability, nutrient levels, and cell–cell interactions [28].

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Differentiation is governed by both chemical and physical cues from the microenvironment [28]. Within the injury milieu, stem cells may either directly transdifferentiate or contribute indirectly by secreting trophic factors that support regeneration [9]. In either case, this phase involves not just cell fate transitions but also modulation of inflammation, stimulation of new blood vessel formation, and remodeling of the extracellular matrix [64].

Successful regeneration depends on the integration of newly formed cells into the preexisting tissue architecture. This step requires finely tuned communication between newly differentiated cells and the host environment to ensure the reestablishment of structural and functional homeostasis [42].

The novelty of this review lies in its integrative framework that connects injury sensing, immune-stem cell crosstalk, and tissue-specific regenerative cascades into a unified biological narrative. Unlike prior reviews that examine isolated components of regeneration, this work emphasizes the sequential and cooperative nature of endogenous repair processes, highlighting how immune signalling, stem cell activation, microenvironmental cues, and tissue remodelling function in concert.

In this review, we discussed the detailed cellular and molecular steps involved in stem cell-mediated tissue regeneration from injury detection to functional tissue reconstitution. By dissecting these processes and incorporating recent technological advancements, we aim to offer insights that can enhance therapeutic strategies for tissue repair in degenerative or traumatic conditions.

The regenerative process in response to injury or disease typically unfolds in the following stages:

(1) Injury Detection and mechanisms
(2) Recruitment of Stem cell
(3) Activation and Proliferation of Stem Cells
(4) Differentiation into Functional Lineages
(5) Integration and Tissue Remodeling

Each stage is governed by tightly regulated signaling networks that ensure precise cell fate decisions and continuous incorporation into the damaged tissue, restoring structural and functional integrity.

Injury detection and mechanisms:

The initial recognition of tissue injury is a fundamental step in the complex process of tissue repair and regeneration. This step initiates a cascade of tightly regulated cellular and molecular responses that serve as an internal alert or guard system, identifying damage and activating the body's healing mechanisms (Fig. 1).

Under normal physiological conditions, stem cells reside in specialized microenvironments called niches. These niches help maintain stem cell dormancy or slow cycling and deliver essential cues that balance self-renewal and prevent premature differentiation [93]. However, upon tissue injury, the niche environment undergoes significant disruption, altering local signals and triggering stem cell activation. This shift prompts previously quiescent stem cells to initiate regenerative activities [83].

Cells detect tissue damage through multiple pathways, one of which involves the release of Damage-Associated Molecular Patterns (DAMPs) from injured or necrotic cells. These molecules, such as ATP, fragmented DNA, and reactive oxygen species (ROS), escape into the extracellular environment where they function as distress signals [48]. Once released, DAMPs interact with pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and the receptor for advanced glycation end-products (RAGE), located on nearby cells [19]. This receptor binding activates intracellular signalling pathways, most notably the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) cascade [57] (Fig. 1).

The NF-κB pathway plays a central role in mediating the inflammatory response. Under resting conditions, it is retained in the cytoplasm by its inhibitor, IκB. When DAMPs trigger PRR activation, IκB becomes phosphorylated and subsequently degraded, releasing NF-κB to translocate into the nucleus [57]. Once inside, it promotes the expression of genes encoding inflammatory mediators such as cytokines and chemokines, which are crucial for coordinating the subsequent repair and healing process [54].

Moreover, the role of immune cells like macrophages and mast cells becomes prominent as they respond to the injury. Macrophages phagocytose debris and release cytokines and chemokines that amplify the inflammatory response [69]. Mast cells contribute by releasing histamine and other mediators that increase vascular permeability, facilitating the influx of more immune cells to the injury site [7]. This interaction and feedback between different cell types, including the recruitment and activation of stem cells via cytokines and chemotactic signals like the chemokine stromal cell derived factor 1 (SDF-1), are crucial for initiating the tissue repair processes. This chemokine, binding to the CXCR4 receptor on stem cells, effectively guides them to the site of injury, ensuring that repair processes commence promptly. [43].

This orchestrated response involving various cell types and signalling pathways leads to the activation and recruitment of stem cells, setting the stage for efficient tissue repair and regeneration. The cascades ensure that stem cells are directed precisely where they are needed,

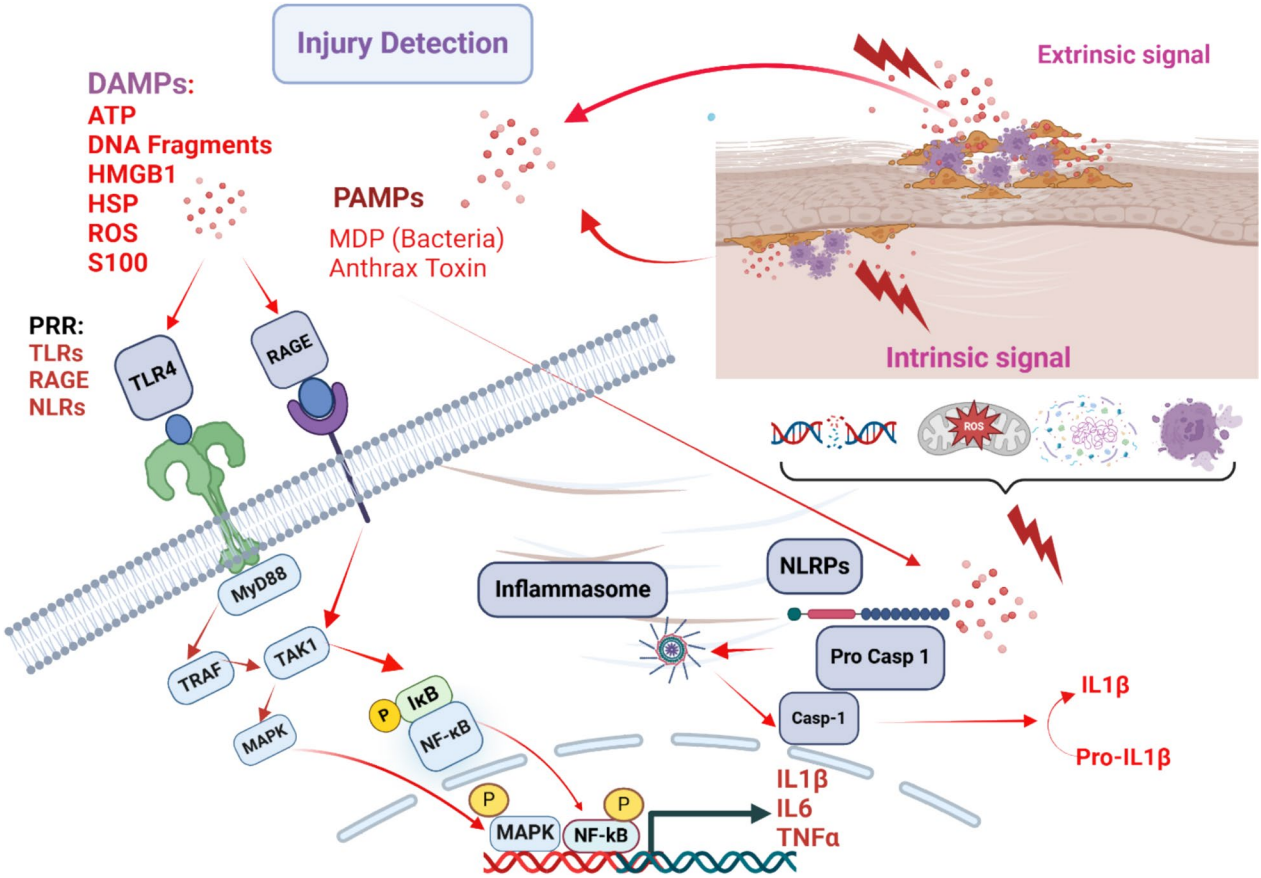

Fig. 1 Cellular mechanisms involved in injury detection. This figure depicts injury detection and immune activation via intrinsic and extrinsic signals. Damage-associated molecular patterns (DAMPs) like ATP, DNA fragments, HMGB1, and ROS, alongside pathogen-associated molecular patterns (PAMPs) such as muramyl dipeptide, are recognized by pattern recognition receptors (PRRs) including TLRs, RAGE, and NLRs. Activation of TLR4 triggers MyD88-dependent signaling, leading to MAPK activation, IκB degradation, and NF-κB translocation. Concurrently, intracellular stress activates NLRPs, forming inflammasomes that activate caspase-1 to cleave pro-IL-1β into IL-1β. NF-κB promotes transcription of IL-1β, IL-6, and TNF-α, amplifying inflammation. While crucial for defense, these pathways also drive pathological inflammation in autoimmune and chronic diseases, guiding therapeutic interventions

enabling effective healing and restoration of function (Fig. 2).

Damage-associated molecular patterns (DAMPs) and injury detection

Overview of DAMPs

DAMPs and their role in immune activation and inflammation DAMPs are endogenous molecules released into the extracellular space following cellular stress, injury, or necrosis, where they act as danger signals to initiate immune responses [82]. Unlike pathogen-associated molecular patterns (PAMPs), which are exclusively microbial and signal infection, DAMPs reflect tissue damage and cellular disruption [59, 82]. Both DAMPs and PAMPs are recognized by pattern recognition receptors (PRRs), including TLRs, the RAGE, and NLRs, which activate downstream inflammatory cascades [11, 73].

Key DAMPs include high-mobility group box 1 (HMGB1), heat shock proteins (HSPs), ATP, extracellular DNA/RNA, uric acid crystals, S100 proteins, and reactive oxygen species (ROS). Upon binding to PRRs, these molecules activate intracellular signaling pathways such as NF-κB and MAPK, resulting in the transcription of pro-inflammatory cytokines and chemokines [71, 73]. Notably, the NF-κB pathway, especially through HMGB1–TLR4 interaction, plays a central role in modulating inflammation. This signaling mechanism is experimentally validated in hepatic injury models, where HMGB1 and histones activate TLRs and RAGE, leading to NF-κB activation and sterile inflammation [27].

In addition to endogenous sources, exogenous DAMPs, also termed DAMP mimics, are derived from non-microbial environmental stimuli such as air pollutants (e.g., diesel exhaust, PM2.5), cigarette smoke,

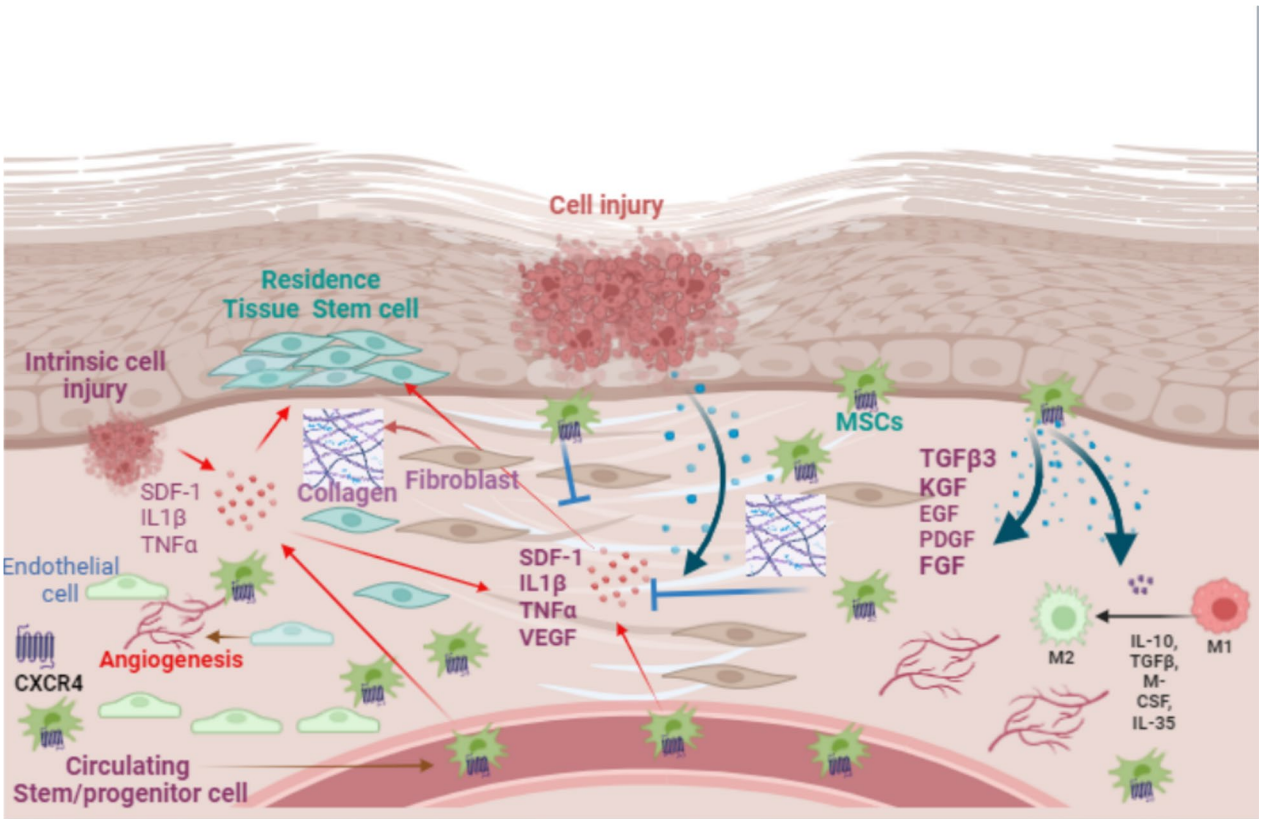

Fig. 2 Cellular Responses to Tissue Injury and Regeneration: This diagram illustrates the coordinated cellular responses to tissue injury, highlighting the roles of resident tissue stem cells, MSCs, fibroblasts, and immune cells in repair and regeneration. Injury triggers the release of pro-inflammatory cytokines (e.g., SDF-1, IL-1β, TNF-α) from intrinsic cells, which recruit and activate MSCs and progenitor cells via CXCR4. Resident and circulating MSCs migrate to the injury site, differentiate into fibroblasts and other reparative cells, and secrete growth factors (TGF-β3, KGF, EGF, PDGF, FGF) that promote collagen synthesis, ECM remodelling, and tissue regeneration. Activated fibroblasts rebuild the tissue matrix, while angiogenesis restores blood supply. Macrophages polarize into M1 and M2 phenotypes, balancing inflammation and repair. These integrated actions restore tissue integrity and function

advanced glycation end-products (AGEs), radiation, and nanoparticles. These exogenous factors activate similar PRR-mediated pathways, contributing to chronic inflammation, fibrosis, and disease progression [59].

PAMPs, by contrast, are derived from pathogens such as bacteria, viruses, fungi, and parasites. They can exist in both intracellular (e.g., viral RNA, bacterial DNA) and extracellular forms, activating immune responses upon recognition by PRRs [98]. Additionally, extrinsic stressors like radiation or toxins can indirectly induce the release of endogenous DAMPs, compounding inflammatory responses [73].

Understanding the complex interplay among endogenous, exogenous, and extrinsic DAMPs, alongside PAMPs, is critical for elucidating mechanisms of sterile inflammation, autoimmunity, fibrosis, and chronic inflammatory diseases. Targeting DAMP-associated signaling pathways offers promising therapeutic potential for controlling pathological inflammation and restoring tissue homeostasis.

While PAMPs are exclusively derived from microbial sources such as bacteria, viruses, fungi, and parasites, they can also exist in both intracellular and extracellular compartments. For instance, viral RNA in the cytoplasm or bacterial DNA within phagosomes act as intracellular PAMPs, whereas extracellular PAMPs are released upon pathogen lysis, triggering immune recognition [98]. Meanwhile, extrinsic DAMPs refer to external environmental stressors, such as pollutants, toxins, and radiation, which indirectly induce the release of endogenous DAMPs, further amplifying inflammation [73].

Understanding the interplay between endogenous, exogenous, or extrinsic DAMPs and PAMPs is essential for studying sterile inflammation, autoimmunity, fibrosis, and chronic disease pathology. Targeting DAMP-related signaling holds promise for therapeutic interventions in inflammatory and fibrotic diseases.

Recruitment of stem cells

The recruitment of bone marrow-derived stem cell populations, including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and endothelial progenitor cells (EPCs), is a crucial process in tissue repair and regeneration following injury. This process, while most thoroughly characterized in HSCs, involves a complex and coordinated network of signalling pathways that are likely similar across different stem cell types. The recruitment of these cells involves several key stages: mobilization from the bone marrow into circulation, homing to the site of injury, vascular rolling and adhesion, endothelial transmigration, and migration within the extracellular matrix toward the injured tissue Liesveld et al. [56].

One of the most well-defined mechanisms governing stem cell mobilization and homing is the interaction between SDF-1 and its receptor CXCR4 on stem cells. SDF-1 plays a pivotal role in maintaining stem cells within their bone marrow niches under normal conditions. It achieves this by interacting with CXCR4 on stem cells, supported by a tightly regulated network of chemokines, cytokines, growth factors, and adhesion molecules [51, 97]. This interaction not only retains stem cells in the bone marrow but also regulates their release and mobilization when injury occurs.

Upon tissue injury, a shift in the local microenvironment triggers the release of cytokines and growth factors from endothelial cells, platelets, and other local cells. This disrupts the homeostasis of stem cells in the bone marrow, initiating their mobilization into the bloodstream [116]. SDF-1, which is regulated by the transcription factor HIF-1α, plays a central role in this process. Following injury, SDF-1 levels increase significantly in hypoxic regions of the bone marrow and at the injury site, creating a chemokine gradient that directs CXCR4-expressing stem cells to migrate toward the damaged tissue [16, 44]. Once in circulation, the chemokine gradient of SDF-1 continues to guide the stem cells to the injury site, where they undergo a series of interactions that facilitate their adhesion to the vascular endothelium, transmigration across the endothelium, and subsequent migration within the extracellular matrix [103]. The upregulation of SDF-1 in injured tissues is critical for this process, as it enhances the binding capacity of CXCR4 on stem cells, promoting their adhesion to endothelial cells and localization at the injury site [97]. SDF-1 binds to the CXCR4 receptor on stem cells, triggering signalling cascades that not only guide the cells to the site of injury but also promote their activation and entry into the cell cycle [16, 112].

Notably, research has demonstrated that disrupting the SDF-1/CXCR4 axis, either by blocking SDF-1 or inhibiting CXCR4, significantly impairs the recruitment of EPCs and other stem cells, while enhancing SDF-1 expression can improve the recruitment and regenerative potential of these cells [16, 97].

Beyond the SDF-1/CXCR4 axis, other molecules play crucial roles in stem cell recruitment. Nitric oxide (NO) is one such molecule that has gained attention for its involvement in this process. NO, produced by endothelial nitric oxide synthase (eNOS), can upregulate SDF-1 expression via a cGMP-dependent pathway, thus enhancing the mobilization and homing of stem cells [4, 53, 106]. A recent study in a bone regeneration model, Xiao et al. (2025) showed that an acid-responsive hydrogel system facilitated injury-triggered release of SDF-1, which recruited endogenous MSCs to the site of injury. These MSCs, in turn, secreted NO, which further amplified SDF-1 production via activation of the cGMP pathway. This creates a positive loop that strengthens the SDF-1/CXCR4 system and improves healing.

Additionally, NO has been shown to facilitate the adhesion of progenitor cells to the endothelium, further supporting their recruitment to injury sites [47, 106]. The interaction between NO and SDF-1/CXCR4 signaling is synergistic. NO not only enhances SDF-1 expression but also increases the responsiveness of MSCs to SDF-1 by promoting the activation of the CXCR4 receptor on MSCs. This increased sensitivity further aids in the efficient homing and engraftment of MSCs at sites where tissue repair and regeneration are needed [106].

The Notch signalling pathway is another critical regulator of stem cell recruitment and function. Notch interactions, particularly between Notch1 and its ligand Jagged, are essential for the recruitment of BM-MSCs and EPCs during tissue regeneration [81, 108]. The Notch pathway influences CXCR4 expression, thereby modulating the responsiveness of stem cells to SDF-1 and enhancing their recruitment to damaged tissues. Knockout models that disrupt Notch signalling show significant impairments in stem cell recruitment and subsequent tissue repair, highlighting the importance of this pathway [104, 108].

Monocyte chemoattractant protein-1 (MCP-1) and its receptor CCR2 also contribute to the recruitment of bone marrow-derived stem cells. While MCP-1 is primarily recognized for its role in recruiting monocytes, it also plays a role in the homing and engraftment of MSCs and HSCs [92]. The MCP-1/CCR2 axis promotes chemotaxis by stimulating the formation of lamellipodia, which facilitate cell migration. Although this pathway is not as universally involved as the SDF-1/CXCR4 axis, it remains significant for specific stem cell populations, particularly in the context of inflammation and tissue repair [92].

Growth factors such as VEGF and G-CSF are also crucial in mobilizing and recruiting stem cells to injury sites. VEGF, which is upregulated following ischemic injuries,

has a dual role depending on the receptor profile of the stem cells. Through VEGFR2, VEGF stimulates the migration and survival of EPCs, promoting neovascularization and tissue regeneration [99]. VEGF has also been shown to work synergistically with Notch signaling to enhance MSC proliferation and recruitment. [55]. G-CSF, on the other hand, reduces SDF-1 expression in the bone marrow and downregulates CXCR4 on HSCs, facilitating their mobilization [76]. The interplay of these growth factors with other signalling pathways underscores the complexity of the recruitment process.

After mobilization and homing, the recruited stem cells adhere to the vascular endothelium through interactions mediated by selectins (e.g., P-selectin, E-selectin) and integrins (e.g., VCAM-1/VLA-4, ICAM-1/β2 integrin) [52, 85]. This is followed by endothelial transmigration, driven by chemokines such as CXCL9 and CXCL16, and finally, migration through the extracellular matrix, facilitated by matrix metalloproteinases (MMPs) like MMP-2 and MMP-9 (Stier et al., 2005). These coordinated steps ensure that stem cells are effectively delivered to the injury site, where they can exert their regenerative functions through direct differentiation, secretion of paracrine factors, and modulation of the immune response [94].

Despite advances in understanding the mechanisms of stem cell recruitment, the clinical application of these insights remains challenging. The limited endogenous stem cell response observed after major injuries, along with variable clinical outcomes in stem cell therapies, suggests that further refinements are needed. Enhancing stem cell retention, optimizing cell dosages, and improving the characterization and purification of stem cell populations are critical areas of ongoing research [66, 94]. By addressing these challenges, the therapeutic potential of stem cell recruitment in regenerative medicine may be fully realized.

Activation and proliferation of Stem cells

Upon reaching the injury site, stem cells transition from a quiescent state to an active state, where they must proliferate and, at times, remain undifferentiated until specific signals direct their differentiation. This activation and proliferation are critical early steps in tissue repair and regeneration, ensuring a sufficient number of cells to replace those lost or damaged and restore tissue function. These processes are tightly regulated by a complex interplay of intracellular signalling pathways, growth factors, cytokines, and interactions with the extracellular matrix (ECM), all influenced by local environmental factors such as oxygen tension, nutrients, and cellular interactions. Additionally, stem cells may be activated either as resident cells within the tissue or as recruits from distant sources like the bone marrow, further emphasizing the complexity of their regulation during tissue repair[20, 31, 68].

As previously discussed, one of the primary signals that initiates stem cell activation is the release of DAMPs from injured or necrotic cells, which bind to PRRs and initiate inflammatory signalling cascades that contribute to stem cell activation [19].

In addition to DAMPs, the hypoxic environment often created by tissue injury plays a significant role in stem cell activation. HIFs, particularly HIF-1α, are stabilized under low oxygen conditions and drive the expression of genes that promote stem cell survival, activation, and migration.

Once activated, stem cells are primed to proliferate in response to various growth factors and cytokines present in the wound microenvironment. The fibroblast growth factor (FGF) family, particularly FGF-2 (also known as basic FGF), is a potent mitogen for many types of stem cells, including MSCs and neural stem cells (NSCs). FGF-2 binds to its receptors (FGFRs) on the surface of stem cells, activating the MAPK/ERK1/2 signalling pathway, which promotes cell cycle entry and proliferation [22]. The ERK pathway, in particular, is critical for driving the expression of cyclins and cyclin-dependent kinases (CDKs), which are essential for the progression of the cell cycle from the G1 to the S phase, where DNA replication occurs.

Another key signalling pathway involved in stem cell proliferation is the Wnt/β-catenin pathway. Wnt proteins bind to Frizzled receptors and co-receptors such as LRP5/6 on the surface of stem cells, leading to the stabilization and accumulation of β-catenin in the cytoplasm. β-catenin then translocases to the nucleus, where it interacts with transcription factors to activate the expression of genes that promote cell proliferation, such as c-Myc and Cyclin D1. The Wnt/β-catenin pathway is particularly important in the regulation of stem cell populations in tissues such as the intestine, where it maintains the balance between stem cell proliferation and differentiation [49]. To that end, Hoffman et al. (2015) reported that treatment with a Wnt/β catenin pathway activator could significantly increase human MSCs proliferation.

The Notch signaling pathway also plays a crucial role in regulating stem cell activation and proliferation. Notch receptors on the surface of stem cells interact with ligands such as Jagged and Delta on neighbouring cells. Upon ligand binding, the Notch receptor undergoes proteolytic cleavage, releasing the Notch intracellular domain (NICD), which trans locates to the nucleus and activates the transcription of target genes involved in stem cell maintenance and proliferation. In the context of tissue repair, Notch signaling helps maintain a pool

of undifferentiated stem cells while also promoting their proliferation in response to injury [74].

In addition to these pathways, the PI3K/Akt signaling pathway plays a central role in promoting stem cell survival and proliferation. Activation of PI3K/Akt can be triggered by various growth factors, including insulin-like growth factor (IGF) and epidermal growth factor (EGF), which bind to their respective receptors on stem cells. The PI3K/Akt pathway promotes cell survival by inhibiting apoptotic pathways and supports proliferation by upregulating the expression of cell cycle regulators [22] [114]. Moreover, Akt signaling enhances the metabolic activity of stem cells, ensuring that they have the necessary energy and biosynthetic precursors to support rapid cell division.

Differentiation to Functional Lineages

Stem cell differentiation is a pivotal process in the transition from injury to tissue repair and regeneration. Once stem cells are recruited to the site of injury, they must differentiate into the specific cell types required to restore the damaged tissue's structure and function (Fig. 3.) This differentiation process is tightly regulated by signaling pathways, transcription factors, epigenetic modifications, and cues from the local microenvironment. [30]. In the context of wound repair, stem cell differentiation is tightly linked to the sequential phases of the wound healing process: inflammation, proliferation, and remodelling. During the initial inflammatory phase, pro-inflammatory molecules such as cytokines, chemokines, and growth factors are released by damaged and immune cells, stem cell activation, and recruitment. Among these, the Wnt/β-catenin pathway plays a crucial role in directing MSCs toward osteoblast differentiation, especially in the context of bone repair. Activation of this signaling promotes the expression of osteogenic markers, driving MSCs to differentiate into osteoblasts, which are essential for the formation of new bone tissue [118].

Simultaneously, the TGF-β and bone morphogenetic protein (BMP) pathways are integral to controlling MSC differentiation during wound repair [107]. Recent data show that TGF-β in secretome derived from dental pulp stem cells significantly enhances osteogenesis and wound healing, emphasizing its potency in lineage specification [86]. TGF-β is particularly important in chondrogenesis, where it promotes the differentiation of MSCs into chondrocytes by inducing cartilage-specific matrix proteins. This is crucial for repairing cartilage in joints or other tissues requiring cartilage regeneration. BMPs, on the other hand, are key regulators of both osteogenesis and

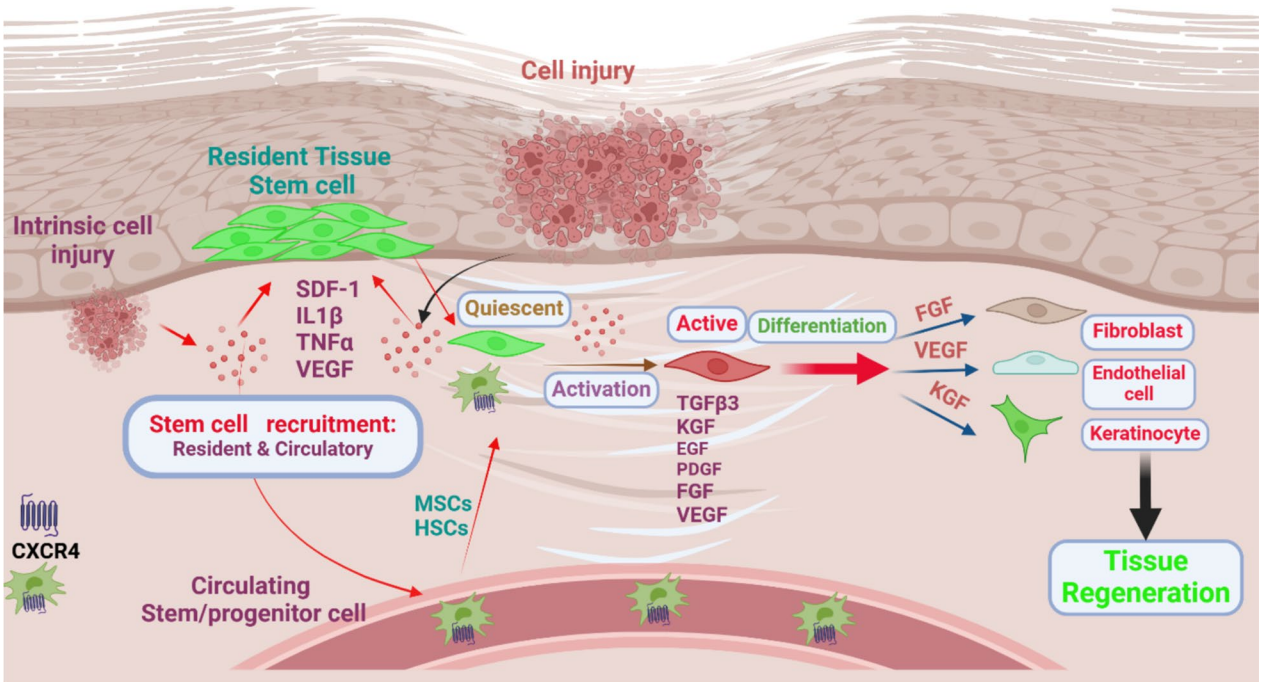

Fig. 3 Stem Cell Recruitment, Activation, and Differentiation in Tissue Injury and Regeneration. This diagram depicts the stem cell–driven process of tissue regeneration following injury. Injury-induced release of cytokines and growth factors (e.g., SDF-1, IL-1β, TNFα, VEGF) activates resident stem cells and recruits circulating MSCs and HSCs via CXCR4. Quiescent stem cells are activated and differentiate under the influence of factors such as TGFβ3, KGF, EGF, PDGF, FGF, and VEGF, forming fibroblasts (FGF-mediated), endothelial cells (VEGF-mediated), and keratinocytes (KGF-mediated), which collectively restore tissue structure and function

chondrogenesis, promoting the expression of transcription factors such as Runx2, which drives osteoblast differentiation, and Sox9, which is critical for chondrocyte formation [10].

During the proliferation phase of wound repair, HSCs are also actively differentiating. Cytokines such as erythropoietin (EPO) and interleukins direct the differentiation of HSCs into various blood cell lineages, including red blood cells, white blood cells, and platelets. This process is crucial for replenishing blood cells lost during injury and supporting the immune response necessary for clearing debris and preventing infection [14]. The EPO-driven differentiation of HSCs is largely controlled by JAK2/STAT5 signaling pathways [50].

EPCs differentiate into endothelial cells, which are vital for angiogenesis, the formation of new blood vessels. This process is critical during the proliferation phase of wound repair, as the newly formed blood vessels supply the regenerating tissue with oxygen and nutrients essential for the survival and function of newly differentiated cells. VEGF, a key factor in angiogenesis, activates the PI3K/Akt and MAPK/ERK pathways in EPCs, promoting their differentiation into endothelial cells [8]. The differentiation of EPCs into functional endothelial cells contributes to the restoration of the vascular network, which is vital for the overall repair process. The Notch signaling pathway also interacts with VEGF signaling to refine and direct the differentiation process, ensuring effective wound healing [91].

As the wound enters the remodeling phase, the focus shifts to restoring the tissue's structural integrity and function. In this phase, the differentiation of MSCs into fibroblasts and myofibroblasts is critical. These cells are responsible for producing collagen and other extracellular matrix components that form the scaffold for tissue regeneration. The TGF-β pathway is again crucial here, as it promotes the differentiation of MSCs into myofibroblasts, which are essential for wound contraction and the closure of the wound [36]. A study using a full-thickness rat wound model demonstrated that topically applied MSCs significantly increased TGF-β levels and α-SMA expression in myofibroblasts during the early healing phase, leading to enhanced wound closure [77].

Epigenetic modifications play a crucial role in regulating stem cell differentiation during wound repair by modulating the transcription of lineage-specific genes involved in differentiation by their activation or repression. For instance, methylation of promoters for differentiation-related genes can silence their expression, maintaining stem cells in a pluripotent state. Conversely, demethylation of these promoters or acetylation of histones can activate gene expression, promoting differentiation. [72].

MSCs can differentiate into various cell types: osteoblasts, chondrocytes, myocytes, and adipocytes, depending on the signals they receive, which has a significant impact on tissue repair. For instance, in bone repair, MSCs differentiate into osteoblasts, which are responsible for producing new bone matrix and facilitating the regeneration of bone tissue. In cartilage repair, MSCs differentiate into chondrocytes, the cells that produce the extracellular matrix of cartilage, thereby helping to restore the structural integrity and functionality of the cartilage [100].

Similarly, hematopoietic stem cells (HSCs) differentiate into various blood cell lineages, including red blood cells, white blood cells, and platelets. This differentiation is crucial not only for replenishing the blood supply but also for supporting the immune response during tissue repair [14]Differentiated HSCs contribute to the immune system's ability to clear debris, fight infection, and secrete cytokines and growth factors that further promote tissue regeneration [84].

In conclusion, the differentiation of stem cells is essential for tissue regeneration and is precisely regulated by signaling, transcriptional, and epigenetic mechanisms in response to repair demands.

Integration and tissue remodelling

Following the differentiation of stem cells into the specific cell types required for tissue repair, the next crucial phase in the healing process is the integration of these cells into the existing tissue and the remodelling of tissue to restore its structure and function [30].

Once differentiated, the newly formed cells, such as fibroblasts, myofibroblasts, endothelial cells, osteoblasts, or chondrocytes, must integrate into the surrounding tissue to contribute effectively to repair [26, 89]. This integration process is highly dependent on cell–cell and cell-ECM interactions. For example, Integrins, a family of cell surface receptors, interact with ECM components such as fibronectin, collagen, and laminin, anchoring the newly differentiated cells in place and facilitating communication between the cells and their microenvironment. This interaction is critical for ensuring that the cells are correctly positioned and can function as part of the tissue [29, 42]. Myofibroblasts play a central role in wound repair, particularly during the remodelling phase. These cells, which are differentiated from fibroblasts under the influence of TGF-β, produce and organize the collagen-rich ECM that forms the structural framework of the healed tissue. Myofibroblasts are also responsible for wound contraction, a process that reduces the wound size by pulling the edges of the wound together [89]. This contraction is facilitated by the formation of actin-myosin contractile fibres within the myofibroblasts, which are

anchored to the ECM through integrin-mediated adhesions. The contraction of these fibers generates tension within the ECM, drawing the wound margins inward and promoting faster closure [41]. Tissue remodelling is a dynamic process that involves the continuous deposition and degradation of ECM components. During the early stages of wound healing, the ECM is primarily composed of a provisional matrix rich in fibrin and fibronectin, which provides a scaffold for cell migration and proliferation. As healing progresses, this provisional matrix is replaced by a more permanent collagen-based matrix, which gives the tissue its strength and resilience [111]. The balance between ECM synthesis and degradation is tightly regulated by MMPs and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs). MMPs, a family of proteolytic enzymes, degrade various components of the ECM, including collagen and elastin, allowing for the removal of the provisional matrix and the restructuring of the new matrix. TIMPs regulate MMP activity to ensure that ECM degradation does not outpace synthesis, maintaining the integrity of the newly formed tissue [60, 67].

The signaling pathways that regulate integration and tissue remodelling are complex and involve multiple factors. TGF-β is one of the most important regulators of ECM production and myofibroblast differentiation. It promotes the synthesis of collagen and other ECM components, and also upregulates the expression of integrins and MMPs, facilitating both the assembly and remodelling of the ECM [110]. In addition to TGF-β, the Wnt/β-catenin pathway also plays a role in tissue remodelling, particularly in bone repair, where it regulates the differentiation of osteoblasts and the synthesis of bone matrix [46]. The interaction between these signaling pathways ensures that the remodelling process is coordinated with the integration of new cells, leading to the restoration of tissue architecture and function.

As previously discussed, vascularization of the newly formed tissue is essential for regeneration; during tissue remodelling, VEGF and Notch signaling promote the maturation and integration of new blood vessels, ensuring stable and functional tissue repair [13] [65].Tissue remodelling also involves the resolution of inflammation and the removal of excess cells and ECM components by macrophages [69]. Once the tissue has been sufficiently repaired, myofibroblasts undergo apoptosis, reducing their numbers and preventing excessive scar formation. The remaining ECM is remodelled to resemble the native tissue as closely as possible, restoring its original architecture and function [24]. However, in cases where remodelling is dysregulated, such as in fibrosis, excessive ECM deposition can lead to the formation of scar tissue, which may impair tissue function [88].

In conclusion, Integration and remodelling are critical for restoring functional tissue, guided by cell–ECM interactions, signaling pathways, and balanced matrix turnover. Understanding these processes is key to promoting regeneration and preventing fibrosis.

Comparative overview of stem cell types in regeneration and clinical application

Although our review emphasizes the generalized regenerative journey of stem cells, it is important to recognize the fundamental differences among various stem cell types MSCs, HSCs, embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs), in terms of their biological roles, therapeutic potential, and clinical applicability. To contextualize the role of these different stem cell types in regenerative medicine, it is essential to recognize the distinct biological properties, risks, and clinical implications of each of them. MSCs and HSCs are adult stem cells naturally involved in injury detection and physiological repair. MSCs are multipotent, playing a crucial role in regenerating bone, cartilage, and soft tissues through paracrine effects and immune modulation, but they face challenges in differentiation efficiency and engraftment [37]; Liu et al., 2006). HSCs, on the other hand, are essential for hematopoietic regeneration and have been widely used in hematopoietic stem cell transplants for blood disorders and immune system regeneration [23], although they are limited to blood-related therapies and pose risks such as graft-versus-host disease (GVHD) [37] [37, 63]. In contrast, ESCs and iPSCs are pluripotent cells capable of differentiating into all three germ layers, offering unparalleled regenerative potential for complex tissues such as the heart, liver, and neural tissues. However, their clinical use is limited by tumorigenicity, genomic instability, and, in the case of ESCs, ethical concerns regarding their derivation (Clevers, 2006,Eilken et al., 2009. While iPSCs overcome some ethical issues, they still present challenges related to reprogramming fidelity and safety (Takahashi et al., 2007; Yamanaka, 2012. Thus, while ESCs and iPSCs are highly valuable in disease modelling, drug screening, and regenerative engineering, MSCs and HSCs are more clinically translatable for tissue-specific repair, owing to their lower risk profile, immunomodulatory effects, and direct involvement in natural injury detection and regeneration responses.

Although our review emphasizes the generalized regenerative journey of stem cells, it is important to recognize the fundamental differences among various stem cell types, MSCs, HSCs, embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs) in terms of their biological roles, therapeutic potential, and clinical applicability. To contextualize the role of these different

stem cell types in regenerative medicine, it is essential to recognize the distinct biological properties, risks, and clinical implications of each of them. MSCs and HSCs are adult stem cells naturally involved in injury detection and physiological repair. They possess well-characterized immunomodulatory functions and have been widely used in clinical trials for inflammatory, cardiovascular, and musculoskeletal diseases [102, 105]. HSCs, in particular, are the cornerstone of hematopoietic transplantation and regenerative treatments in oncology and hematology [23]. In contrast, ESCs and iPSCs are pluripotent cells capable of giving rise to all three germ layers, but they do not participate in endogenous tissue repair. Their clinical use is limited by concerns such as tumorigenicity, genomic instability, and in the case of ESCs, ethical controversies surrounding their embryonic origin (Knoepfler, 2009). iPSCs circumvent some ethical concerns but still pose challenges in reprogramming fidelity and safety [32]. Thus, while ESCs and iPSCs are highly valuable in disease modeling, drug screening, and regenerative engineering, MSCs and HSCs are more clinically translatable for tissue-specific repair owing to their lower risk profile, immunomodulatory effects, and participation in natural injury and regeneration responses.

clinical translation of regenerative signalling pathways

A comprehensive understanding of the cellular and molecular pathways involved in tissue repair, from damage recognition to stem cell mobilization, homing, proliferation, and differentiation, is essential for designing effective regenerative therapies and improving clinical outcomes. By elucidating how DAMPs initiate inflammatory signaling through PRRs and how this influences subsequent repair processes, clinicians and researchers can identify precise targets to modulate inflammation without impairing healing [73, 82]. For instance, controlling the HIF-1α/VEGF/SDF-1 axis enables enhancement of vascularization and recruitment of reparative cells in ischemic or non-healing wounds (Liu et al., 2006; [16]. An alternative approach involves pharmacological conditioning of MSCs using deferoxamine, which enhances HIF-1α expression and targets CXCR4, resulting in more effective wound healing in diabetic wounds [61].

Furthermore, leveraging knowledge of CXCR4-mediated homing and niche-specific retention allows for better localization of stem cells at injury sites, increasing therapeutic efficacy [1, 113]. This mechanistic insight also informs the development of preconditioning protocols, gene-modified stem cells, or bioengineered scaffolds that replicate or enhance endogenous healing signals [79, 80]. Clinically, these approaches are being applied in the treatment of diabetic ulcers, myocardial infarction, stroke, and chronic inflammatory diseases, etc., demonstrating how an integrated understanding of the underlying biology translates into targeted, personalized, and more effective regenerative interventions [37, 63]. Ultimately, this systems-level knowledge bridges basic science and clinical practice, leading to therapies that not only repair tissue but also restore function with improved precision and durability.

Coordinated biological networks in tissue regeneration

Tissue regeneration is not an isolated cellular event but a highly coordinated, systems-level process involving the interplay of multiple biological networks [95]. The immune system serves as the initial responder, detecting injury and guiding the inflammatory phase that primes tissue for repair. Stem cell niches, activated by these immune signals, mobilize regenerative cells directed to the injury site [2]. This process requires a balanced immune response, as excessive inflammation can inhibit regeneration (Prasad Abnave & E. Ghigo, 2019). The vascular system plays a critical role in supporting this process by enabling immune cell trafficking, delivering oxygen and nutrients, and initiating angiogenesis to restore perfusion [96]. Concurrently, the extracellular matrix provides both the physical scaffold and biochemical cues necessary for stem cell adhesion, migration, and differentiation [35]. The nervous system adds another layer of regulation by sensing injury and modulating immune and regenerative responses through neuropeptides [90]. Additionally, the endocrine system exerts a systemic influence by modulating stem cell activity and metabolic demands during repair [34]. Together, these interdependent systems form an integrated network that drives the regenerative journey from injury detection to functional tissue restoration. Understanding this orchestration provides a powerful foundation for developing therapies that harness or enhance endogenous regenerative capacities.

Challenges and future directions

The exploration of stem cell roles in the regenerative journey, from injury detection to tissue repair, represents one of the most promising yet challenging areas of biomedical research. The potential of stem cells to detect injury, mobilize, differentiate, and ultimately repair damaged tissues offers significant therapeutic opportunities. However, the journey from understanding these processes in the lab to applying them in clinical practice is troubled with challenges that must be addressed to fully harness the power of stem cells in regenerative medicine.

This section will elaborate on these challenges and propose future directions for advancing this field.

Challenges

1. **Complexity of Injury Detection and Response:** The process by which stem cells detect injury and initiate a regenerative response is complex and not yet fully understood. This process involves a finely tuned interplay of signalling molecules, the microenvironment, and the intrinsic properties of the stem cells themselves. [39]. Variations in the severity, location, and type of injury can lead to different cellular responses, making it difficult to predict and control the regenerative outcome [38]. Moreover, the ability of stem cells to correctly interpret and respond to these signals can be impaired in aged or diseased tissues, which adds another layer of complexity.
2. **Heterogeneity and Source of Stem Cells**: Stem cell heterogeneity poses a significant challenge in the regenerative journey. Different types of stem cells (e.g., MSCs, HSCs, and neural stem cells) have distinct regenerative potentials and responses to injury. Additionally, the source of stem cells, whether they are derived from bone marrow, adipose tissue, or other tissues, can significantly influence their behaviour and effectiveness in tissue repair [70]. For example, unlike HSCs, MSCs often express low levels of key homing receptors and, when administered systemically, tend to become trapped in organs like the lungs and liver due to their size and poor responsiveness to chemotactic signals, leading to reduced engraftment [25]. Standardizing stem cell therapies to account for this variability remains a major hurdle.
3. **Regulation of Stem Cell Behaviour:** Effectively controlling stem cell behaviour is critical for successful regeneration. However, the signalling pathways that regulate these processes are complex and context-dependent. Small perturbations in the microenvironment or the signalling cascades can lead to undesirable outcomes, such as fibrosis instead of regeneration, or uncontrolled cell proliferation leading to tumorigenesis [21]. Furthermore, some studies highlight the risk of stem cells spontaneously differentiating into undesired cell types in response to host microenvironmental cues post-transplantation. For instance, in earlier studies, unfractionated bone marrow cells were occasionally found to differentiate into osteoblasts, leading to undesired ossification within heart tissue [15]. The challenge lies in developing precise and reliable methods to guide stem cell behaviour towards desired therapeutic outcomes.
4. **Immune Response and Compatibility:** The immune system's response to stem cell therapies can be a double-edged sword. While immune cells play a vital role in injury detection and the initial phases of tissue repair, they can also contribute to the rejection of transplanted stem cells, especially in allogeneic (donor-derived) settings. Even in autologous (self-derived) therapies, immune responses can be triggered by the manipulation of cells outside the body or by changes in the microenvironment [75]. A major source of rejection is HLA mismatch, which activates host immune responses [3].
5. **Long-Term Safety and Efficacy:** Ensuring the long-term safety and efficacy of stem cell-based therapies is a major concern. The potential for tumorigenesis, immune rejection, or the development of fibrotic tissue instead of functional tissue are significant risks that need to be carefully managed. Additionally, the long-term behaviour of transplanted stem cells within the host tissue remains poorly understood, with concerns about the stability of their therapeutic effects and the risk of adverse outcomes over time [62].

Future directions

1. **Advancing Single-Cell and Omics technologies:** Comprehensive lineage tracing of stem cells is essential for guiding differentiation and ensuring therapeutic specificity. In recent years, single-cell RNA sequencing (scRNA-seq), proteomics, and metabolomics have played a pivotal role in understanding the heterogeneity of stem cell populations and their responses to injury. These technologies allow researchers to explore the behaviour of individual cells within a complex tissue environment. Future research should focus on integrating these omics approaches to develop a comprehensive map of the regenerative journey at the single-cell level [78].
2. **Gene editing and Synthetic Biology:** The development of gene editing tools, such as CRISPR-Cas9, and synthetic biology approaches opens new avenues for engineering stem cells with enhanced regenerative capabilities. By precisely editing genes involved in injury detection, immune modulation, or differentiation, scientists can create "designer" stem cells tailored for specific therapeutic applications. Furthermore, these technologies can be leveraged for Cas9-based genetic barcoding, allowing labeling of single progenitor cells, making it possible to reconstruct detailed lineage trajectories [17].
3. **Development of Biomimetic Scaffolds and Microenvironments:** The creation of biomimetic scaffolds that mimic the natural ECM of tissues can provide a supportive environment for stem cell proliferation, differentiation, and integration. These scaffolds

can be engineered to deliver growth factors, modulate the immune response, and guide tissue remodelling. Future research should focus on developing advanced biomaterials that can dynamically interact with stem cells and the host tissue to optimize regeneration [117]. In recent years, scaffold materials such as graphene and its derivatives [115], along with natural polymers like chitosan [45] and collagen [87], have gained growing attention for their ability to support stem cell growth and guide differentiation.

4. **Harnessing the Immune System for Regeneration:** Modulating the immune response to support tissue repair and regeneration is a promising strategy. Research should focus on understanding the crosstalk between stem cells and immune cells during the regenerative journey. By manipulating immune cells or engineering stem cells to produce immune-modulatory factors, it may be possible to create a more favourable environment for regeneration while minimizing the risk of immune rejection [5]. For example, HLA engineering through gene editing is a promising solution to create immune-evasive stem cells for broader clinical use [18].
5. **Personalized or patient-specific Regenerative Medicine:** The future of regenerative medicine lies in personalized approaches that take into account the unique genetic, epigenetic, and environmental factors of each patient. Personalized stem cell therapies could be tailored to the specific needs of the individual, using their own cells or genetically matched donor cells to reduce the risk of rejection and improve therapeutic outcomes. Advances in genomics, bioinformatics, and personalized medicine will be key to realizing this vision [6].

Conclusion

The regenerative journey of stem cells, from injury detection to tissue repair, is an intricate and finely tuned process essential for effective healing and recovery. Stem cells, through their remarkable ability to sense injury and respond to physiological and pathological cues, are central to tissue regeneration. However, the therapeutic application of stem cells presents various challenges, including the complexity of injury detection, stem cell recruitment, differentiation, and integration into the tissue matrix. The biological differences between stem cell types, MSCs, HSCs, ESCs, and iPSCs, each offers distinct advantages and limitations, especially in terms of their regenerative capacity, tissue specificity, and safety profiles. MSCs and HSCs are particularly promising for tissue-specific repair, with robust clinical applications in musculoskeletal, hematopoietic, and cardiovascular regeneration. Meanwhile, ESCs and iPSCs hold great potential for regenerating complex organs, but tumorigenicity, ethical concerns, and genomic instability hinder their clinical implementation. Advancements in gene editing technologies, biomaterial engineering, and immune modulation are paving the way for safer and more effective stem cell-based therapies. Future research will be crucial in optimizing stem cell applications, improving the efficiency of stem cell recruitment and integration, and minimizing potential risks such as fibrosis or tumor formation. By harnessing the intricate biology of stem cells and integrating advanced therapeutic strategies, regenerative medicine will continue to evolve, offering new possibilities for treating degenerative diseases, injuries, and age-related conditions, ultimately restoring tissue function with improved precision and durability.

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