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The Role of the Immune System in Tissue Repair and Regeneration: A Comprehensive Review

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ABSTRACT

Tissue repair and regeneration are essential processes that restore tissue structure and function after injury. The immune system plays a critical role in orchestrating these processes, regulating inflammation, clearing debris, and promoting tissue regeneration through complex interactions with tissue-specific stem cells and resident immune cells. Key immune players, such as neutrophils, macrophages, and T cells, coordinate the early inflammatory phase, while macrophages, particularly M2-polarized macrophages, facilitate tissue repair by secreting growth factors like **VEGF** and **TGF-β**. The balance between pro-inflammatory and anti-inflammatory responses is crucial for proper healing; dysregulated immune activity can lead to chronic wounds, fibrosis, or autoimmune-related tissue damage. In conditions like chronic wounds or liver fibrosis, prolonged inflammation hinders the repair process, emphasizing the need for controlled immune responses. Therapeutic strategies aimed at modulating immune activity, including the use of stem cells, immune-modulatory drugs, and biomaterials, hold promise in enhancing tissue repair and regeneration. This review highlights the key roles of immune cells in tissue repair, the impact of immune dysregulation on healing, and the therapeutic potential of targeting immune pathways to improve regenerative outcomes. Understanding the immune mechanisms behind tissue repair opens new avenues for treating chronic diseases and promoting tissue regeneration in clinical settings.

Keywords: Immune system, Tissue repair, Regeneration, Macrophages, Immune modulation

INTRODUCTION

Tissue repair and regeneration are vital processes that restore tissue integrity and function following injury [1]. While traditionally the immune system is seen as primarily defending against infections, it also plays a central role in promoting tissue healing and regeneration. Immune cells like neutrophils, macrophages, and T cells are critical at various stages of the repair process, from clearing debris and pathogens to promoting tissue proliferation and remodeling [2]. Immune cells secrete cytokines and growth factors that drive these processes, while dysregulation of immune responses can lead to chronic inflammation, impaired healing, or fibrosis. Recent advances highlight the interplay between the immune system and tissue-specific stem cells, revealing therapeutic opportunities to enhance tissue repair by modulating immune responses [3]. This review discusses the phases of tissue repair, the role of key immune cells, and the potential of immune-modulating therapies to improve regenerative outcomes in chronic and degenerative diseases.

Phases of Tissue Repair

Tissue repair after injury follows a well-defined sequence of events, which can be broken down into four overlapping phases:

Hemostasis

The initial response to tissue injury is the formation of a clot to stop bleeding and prevent further damage. Platelets are the key players in this phase, releasing clotting factors and signaling molecules such as **platelet-**

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derived growth factor (PDGF) and **transforming growth factor-beta (TGF-β)**. These molecules activate immune cells, initiating the subsequent inflammatory phase [4].

Inflammation

Inflammation is a crucial stage that begins minutes after injury and can last for several days. The immune system, particularly innate immune cells such as macrophages and neutrophils, is activated to clear dead cells, pathogens, and debris [5]. This process is essential to create a clean environment conducive to repair.

Neutrophils

Neutrophils are among the first immune cells to arrive at the site of injury. These cells are rapidly recruited by chemokines and cytokines such as **IL-1β**, **TNF-α**, and **CXCL8** (IL-8) [6]. Neutrophils engulf bacteria and dead cells through phagocytosis and release reactive oxygen species (ROS) and proteases that help break down damaged tissue.

Macrophages

Macrophages are key players in orchestrating the repair process. They exhibit remarkable plasticity, and their role depends on their polarization state, which can be broadly categorized into pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages.**M1 macrophages** dominate the early stages of inflammation. They release pro-inflammatory cytokines such as **TNF-α**, **IL-6**, and **IL-1β**, and produce ROS and nitric oxide (NO) to destroy pathogens and clear damaged cells [7].**M2 macrophages**, which emerge as inflammation resolves, promote tissue repair by secreting anti-inflammatory cytokines such as **IL-10** and **TGF-β**. They also produce growth factors like **vascular endothelial growth factor (VEGF)** and **fibroblast growth factor (FGF)** that stimulate angiogenesis and tissue repair [8]. The balance between M1 and M2 macrophages is critical for proper tissue repair. Excessive M1 activity can lead to chronic inflammation and tissue damage, whereas insufficient M1 activation can result in poor debris clearance and incomplete healing.

Dendritic Cells

Dendritic cells (DCs), although less studied in the context of tissue repair, play an essential role in sensing damage and orchestrating immune responses. They present antigens from dead cells to T cells, helping to modulate adaptive immunity and influence the long-term outcome of repair and regeneration [9].

Proliferation

The proliferative phase is characterized by the migration and proliferation of cells involved in rebuilding the tissue, such as fibroblasts, endothelial cells, and tissue-specific progenitor or stem cells. Immune cells contribute to this phase by releasing growth factors that promote tissue regeneration. **Fibroblasts** are activated during this phase, producing collagen and other extracellular matrix (ECM) proteins that form the scaffolding for new tissue [10]. **Endothelial cells** are involved in angiogenesis, the formation of new blood vessels, which is crucial for providing oxygen and nutrients to the regenerating tissue[11].Macrophages continue to play a key role during this phase. M2 macrophages, in particular, secrete **TGF-β**, **VEGF**, and **FGF** to stimulate fibroblast activity, ECM production, and angiogenesis. **T cells** also modulate the proliferation phase by releasing **IL-4** and **IL-13**, which encourage macrophage polarization towards the M2 phenotype, promoting tissue repair and resolution of inflammation [12].

Remodeling

In the remodeling phase, the newly formed tissue undergoes maturation and strengthening, which can last for weeks or even months. The ECM is continuously remodeled to restore tissue architecture and function. Immune cells, particularly macrophages, continue to play a role by secreting matrix metalloproteinases (MMPs) and other enzymes that regulate ECM turnover [13]. Dysregulation of the immune response during this phase can lead to fibrosis, characterized by excessive deposition of ECM components, which can impair tissue function.

IMMUNE CELL TYPES IN TISSUE REPAIR AND REGENERATION

Different immune cell populations play distinct roles in tissue repair and regeneration, from initiating the inflammatory response to promoting resolution and regeneration. Below, we review the contributions of key immune cell types to the repair process.

Macrophages

Macrophages are central to the repair process due to their ability to adopt different functional states (M1 vs. M2). The early M1 phase is critical for clearing debris and pathogens, while the M2 phase promotes repair and tissue regeneration by secreting anti-inflammatory and pro-regenerative factors.**M1 macrophages**: These cells are pro-inflammatory and are necessary for the initial clearance of debris and pathogens. Their persistence, however, can lead to chronic inflammation.**M2 macrophages**: These cells promote tissue repair and regeneration by secreting **VEGF**, **FGF**, and **TGF-β**. They support angiogenesis, fibroblast activation, and the resolution of inflammation,

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facilitating tissue repair [14]. Impaired macrophage function can lead to either chronic wounds or excessive fibrosis, highlighting the importance of their balanced regulation.

Neutrophils

Neutrophils are the first responders to injury and are essential for pathogen clearance and tissue debridement. While they are beneficial in the early stages of repair, excessive neutrophil activity can cause tissue damage due to the release of proteases and ROS. Neutrophils also interact with macrophages, promoting their recruitment and polarization to the M2 phenotype, thereby influencing the resolution of inflammation and tissue healing.

T Cells

T cells play a dual role in tissue repair, participating in both immune regulation and the promotion of tissue regeneration. Different T-cell subsets have distinct effects: **Regulatory T cells (Tregs)**: These cells are essential for suppressing excessive inflammation and promoting tissue repair. They produce **IL-10** and **TGF-β**, which help to modulate the activity of macrophages and fibroblasts, ensuring proper tissue remodeling [15]. **Effector T cells**: Cytotoxic T cells (CTLs) and helper T cells (Th1 and Th2) can either promote inflammation or facilitate repair depending on the context [16]. Th2 cells are particularly important in promoting M2 macrophage polarization, while Th1 cells can exacerbate inflammation if not properly regulated.

Innate Lymphoid Cells (ILCs)

Innate lymphoid cells (ILCs) are a relatively new class of immune cells that have emerged as key regulators of tissue repair and regeneration. These cells do not express antigen-specific receptors like T and B cells but respond rapidly to cytokine signals from damaged tissues. ILC2s, in particular, have been implicated in tissue repair due to their production of **IL-13** and **IL-4**, which promote epithelial regeneration and M2 macrophage polarization [17].

Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs) are multipotent stem cells that can differentiate into various cell types, including fibroblasts, osteoblasts, and chondrocytes [18]. They also exhibit immunomodulatory properties, secreting factors such as **TGF-β**, **IL-10**, and **prostaglandin E2 (PGE2)**, which regulate immune cell activity and promote tissue repair [19]. MSCs can modulate the immune response, suppressing excessive inflammation and enhancing the regenerative potential of injured tissues.

IMMUNE SYSTEM-MEDIATED REGENERATION IN SPECIFIC TISSUES

Skin

The skin provides an excellent model for understanding immune-mediated tissue repair. After skin injury, immune cells such as neutrophils, macrophages, and T cells are recruited to the wound site to clear debris and promote healing. Macrophages, particularly M2-polarized macrophages, play a key role in promoting the proliferation of keratinocytes and fibroblasts during the proliferative phase [20]. In cases of chronic wounds, dysregulated immune responses can lead to delayed healing or excessive fibrosis, as seen in hypertrophic scars or keloids.

Liver

The liver has a remarkable ability to regenerate, even after significant tissue loss. Macrophages, specifically liver-resident **Kupffer cells**, are critical in sensing liver damage and initiating the repair process. Upon injury, Kupffer cells release pro-inflammatory cytokines and recruit monocyte-derived macrophages to the liver. These recruited macrophages polarize towards the M2 phenotype, producing **TGF-β** and **VEGF** to promote hepatocyte proliferation and tissue repair. Chronic liver injury, however, can lead to the persistence of M1 macrophages, contributing to fibrosis and cirrhosis [21, 22].

Muscle

Muscle regeneration following injury involves a coordinated response between immune cells and muscle stem cells, known as satellite cells. After muscle injury, macrophages are rapidly recruited to the injury site, where they clear necrotic debris and promote satellite cell activation. M2 macrophages, in particular, secrete **IL-10** and **TGF-β**, which support satellite cell proliferation and differentiation into new muscle fibers [23]. Dysregulation of immune responses in muscle repair can result in impaired regeneration or chronic inflammatory conditions such as muscular dystrophy.

Central Nervous System (CNS)

The CNS has limited regenerative capacity compared to other tissues, but immune cells still play a critical role in CNS repair. After CNS injury, **microglia**, the resident macrophages of the brain, become activated and contribute to debris clearance [24]. However, excessive microglial activation can lead to neuroinflammation, impeding regeneration and contributing to neurodegenerative diseases. Emerging research is exploring how modulating microglial activity can promote CNS repair and limit inflammation.

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Immune Dysfunction in Tissue Repair and Disease

While the immune system is essential for tissue repair, dysregulation of immune responses can lead to impaired healing, chronic inflammation, or fibrosis. Below are key examples of how immune dysfunction impacts tissue repair in different diseases.

Chronic Wounds

Chronic wounds, such as diabetic ulcers or pressure sores, are characterized by prolonged inflammation and impaired healing [25]. In these conditions, the persistent activation of M1 macrophages and neutrophils results in the release of proteases and ROS that cause tissue damage and prevent the transition to the proliferative phase. Strategies to modulate immune responses, such as promoting M2 macrophage polarization or reducing neutrophil activity, are being explored as potential therapies for chronic wounds [26].

Fibrosis

Fibrosis occurs when excessive ECM deposition impairs tissue function. It is a common feature of chronic inflammatory diseases such as liver cirrhosis, pulmonary fibrosis, and cardiac fibrosis. Immune cells, particularly M2 macrophages, play a dual role in fibrosis [27]. While they are essential for tissue repair, their persistent activation can promote the excessive production of collagen and other ECM components, leading to fibrosis. Targeting immune pathways that regulate macrophage activation and fibroblast function holds promise for reducing fibrosis and improving tissue repair.

Autoimmune Diseases

In autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, the immune system mistakenly attacks healthy tissues, leading to chronic inflammation and tissue damage [28]. The imbalance between pro-inflammatory and anti-inflammatory immune responses impairs the tissue repair process. Therapeutic strategies that modulate immune responses, such as immunosuppressive drugs or biologics targeting specific cytokines, are used to reduce inflammation and promote tissue repair in these diseases [29].

THERAPEUTIC APPROACHES TO MODULATING IMMUNE RESPONSES IN TISSUE REPAIR

Given the critical role of the immune system in tissue repair, there is growing interest in developing therapeutic strategies that modulate immune responses to enhance tissue regeneration. Below are some promising approaches:

Immune Modulatory Drugs

Drugs that modulate immune cell activity, such as **macrophage polarization inhibitors** and **TGF-β blockers**, are being explored for their potential to enhance tissue repair and reduce fibrosis [30]. **Biologics**, such as **anti-TNF** or **anti-IL-6** antibodies, have already shown efficacy in reducing inflammation and improving healing in autoimmune diseases [31].

Stem Cell Therapy

Mesenchymal stem cells (MSCs) have shown promise in promoting tissue repair due to their immunomodulatory properties [32]. MSCs secrete a range of cytokines and growth factors that modulate immune cell activity and promote tissue regeneration. Clinical trials are underway to explore the potential of MSCs in treating chronic wounds, liver fibrosis, and other conditions characterized by impaired tissue repair [33].

Biomaterials and Scaffolds

Biomaterials and tissue-engineered scaffolds that deliver immune-modulating agents or stem cells are being developed to promote tissue repair [34, 35]. These scaffolds can be designed to release cytokines or growth factors that enhance immune cell function and support tissue regeneration. **Hydrogels** loaded with **VEGF** or **FGF** are one example of how biomaterials can be used to promote angiogenesis and tissue repair in skin wounds [36].

Immunotherapy for Regeneration

Immunotherapy, traditionally used to treat cancer and autoimmune diseases, is being explored for its potential in tissue regeneration. **Immune checkpoint inhibitors**, such as **anti-PD-1** and **anti-CTLA-4**, are being investigated for their ability to enhance immune responses that promote tissue repair [37]. **T-regulatory cell** (Treg) therapy is also being studied for its potential to suppress excessive inflammation and promote tissue healing in conditions such as myocardial infarction and neurodegenerative diseases [38, 39].

CONCLUSION

The immune system plays a central role in tissue repair and regeneration, coordinating the removal of debris, modulating inflammation, and promoting the proliferation and differentiation of tissue-resident stem cells. While immune cells such as macrophages, neutrophils, and T cells are essential for proper healing, their dysregulation can lead to impaired repair, chronic wounds, or fibrosis. Understanding the complex interactions between immune cells and tissue-specific progenitor cells offers new opportunities for developing therapies that enhance tissue repair and regeneration. Approaches such as immune modulation, stem cell therapy, and biomaterial scaffolds hold promise for improving outcomes in patients with impaired tissue healing. As research in this field continues to

advance, novel therapeutic strategies targeting the immune system are likely to play a critical role in regenerative medicine and the treatment of chronic diseases.

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