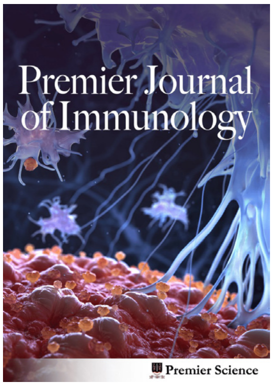

Immunological Insights into Tissue Regeneration: Implications for Plastic and Reconstructive Surgery

Sazin Islam, MPH

Department of Public Health, First Capital University of Bangladesh, Chuadanga, Bangladesh

Correspondence to: Sazin Islam, mail2sazin@gmail.com

Additional material is published online only. To view please visit the journal online.

Cite this as: Islam S. The Intersection of Technology and Health Economics: Innovations and Challenges. Premier Journal of Immunology 2024;1:100003

DOI: https://doi.org/10.70389/PJI.100003

Received: 30 August 2024
Revised: 16 September 2024
Accepted: 22 September 2024
Published: 14 October 2024

Ethical approval: N/a
Consent: N/a
Funding: No industry funding
Assistance with the study: None
Conflicts of interest: N/a
Author contribution: Sazin Islam – Conceptualization, Writing – original draft, review and editing
Guarantor: Sazin Islam
Provenance and peer-review: Commissioned and externally peer-reviewed
Data availability statement: N/a

ABSTRACT

The field of tissue regeneration is evolving rapidly, especially in the context of plastic and reconstructive surgery. New techniques are improving skin grafts, wound healing, and tissue repair. Autologous skin grafting has been enhanced by biological and synthetic skin replacements. Nanotechnology and stem cell therapies are increasingly important for infection control and tissue preservation. Bioprinting is allowing doctors to create custom tissue, leading to advancements in reconstructive surgery. The immune system is very important for tissue healing, with immune cells such as macrophages, neutrophils, and T cells controlling inflammation and promoting tissue regrowth. Edema may have both advantageous and disadvantageous effects, And immune system regulation offers promising prospects for biomaterials and medication delivery. However, challenges such as transplant rejection, persistent inflammation, and reactive inflammation make treatment more complex. Current treatments that suppress the immune system have limitations, but CRISPR gene editing and AI-driven immunity engineering may offer promising solutions in the near future. Tissue engineering holds promise for providing more control over the immune system, thereby ensuring the safety and efficacy of reconstructive and plastic surgery. This study emphasizes the issues, advancements, and future prospects of tissue regeneration and immune regulation, providing valuable insights into immunological-based treatments and regenerative medicine.

Keywords: Tissue regeneration, Immune modulation, Plastic and reconstructive surgery, Stem cell therapy, Biomaterials, Inflammation control

Introduction

Tissue regeneration is vital in plastic and reconstructive surgery as it aids in skin defects and recovery. Both traditional and new technologies have been continuously improving. These advancements provide better solutions for wound healing and tissue repair. Autologous skin grafting is a fundamental method, which has been enhanced with biological and synthetic skin replacement materials. Traditional and new technologies have improved survival rates and life quality for patients with large skin damage.[1] Nanomaterials have emerged as a key area of research, offering better control over wound healing, infection, and tissue health. Nanoparticle delivery systems have demonstrated beneficial effects by releasing signal factors and antimicrobials, thereby reducing problems like graft rejection.[2] The field has been transformed by tissue engineering and regenerative medicine, offering new ways to care for patients. Additionally, synthetic products and microsurgical techniques play a crucial role in improving both function and procedures.[3] Stem cell therapy speeds up wound healing, reduces scarring, and boosts overall tissue regeneration.[4] Bioprinting technology enables the creation of custom tissue constructs, which surgeons utilize for better outcomes.[5]

Different immune cells affect tissue healing and regeneration. Recent studies have shown that cell-based and biomaterial-based technologies play a significant role in altering immune responses and improving tissue repair.[6] Different immune cell types are important in blood vessel growth and tissue repair. Modifying these cells can facilitate faster healing.[7] Inflammation interacts with immune cells, stromal cells, and stem cells to provide tissue regeneration.[8] MicroRNAs (Figure 1) regulate immune responses by altering the activity of key immune cells, including neutrophils, macrophages, and T cells.[9] Macrophages are particularly important as they facilitate the transition from inflammation to tissue repair.[10] The new and improved options for precise surgery include artificial intelligence, robots, and 3D printing.[11] These technologies can expedite surgery and improve outcomes.[12] To strike a balance between reconstructive and aesthetic aims, education and strict moral guidelines are essential. This approach ensures both patient safety and public trust are upheld.[13]

Fig 1 | The crystal structure of the human Drosha protein (miRNA) is shown. It includes two ribonuclease III domains. It also includes a double-stranded RNA binding domain. There is a connector/platform domain as well. Zinc ions are bound to this domain

Source: Adapted from Kwon, S.C. et al., Protein Data Bank, 2016

The Immunological Landscape of Tissue Injury and Repair

The inflammatory phase of tissue injury involves a complex mix of cellular and molecular parts. It's important to control the acute inflammatory response well in order to activate tissue repair without causing further damage. Balanced inflammation and repair are crucial to prevent chronic, non-healing injuries.[14] Inflammation causes immune cells to release secretions, which affect stem and progenitor cells.[15] A recent study shows that the combined pathway of immune cells and signaling can induce inflammation and improve tissue regeneration as well.[16]

The role of key immune cells demonstrates how different immune cell types and their functions interact. Regulatory T cells (Tregs) are important for repairing and regenerating skeletal muscles. They control adaptive immunity and directly affect muscle repair. If Tregs do not work properly, repair can be abnormal, highlighting their importance in both immune and non-immune tissue regeneration.[17] Neutrophils play a diverse and flexible role and are important in both innate and adaptive immunity. They affect the activation and growth of T and B cells, demonstrating their regulatory role in adaptive immunity.[18] Macrophages are important for transitioning from inflammation to tissue repair, as they promote inflammation and help with repair simultaneously. Their different states of activation can impact the repair process.[19] Dendritic cells can modulate immune responses and support healing.[20] To initiate tissue generation, T cells and other immune cells work together,[21] and neutrophils contribute to both inflammation and healing during tissue repair.[22]

Cytokines, growth factors, and chemokines control immune responses and cellular behavior. They play a significant role in both normal function and disease. In tissue repair, these molecules control different stages of healing. Chemokine ligand–receptor interactions are a better option for wound healing.[23] Cytokines and chemokines also have a major role in the tumor microenvironment, influencing tumor growth, new blood vessel formation, and cancer spreading. They can both aid and hinder tumor growth depending on the cell environment, making treatment more challenging.[24] However, progress in blocking cytokine and chemokine pathways with drugs like monoclonal antibodies and receptor blockers looks promising. It can help control tumor growth and improve the effectiveness of treatments.[25]

Mechanisms of Immune Modulation in Tissue Regeneration

Immune cell plasticity (Figure 2) is crucial for tissue regeneration as it involves complex signaling dynamics that guide cellular behavior in their microenvironments. Biophysical signals such as mechanical stress, electric fields, and electromagnetic radiation influence cellular plasticity, including processes such as cell cycle progression, migration, and differentiation, all of which are essential for tissue regeneration.[26] Inflammation enhances plasticity by increasing DNA accessibility, allowing cells to change in response to injury. While anti-inflammatory therapies are beneficial for cardiovascular diseases, they can also hinder natural tissue repair.[27] New advanced regenerative immune engineering emphasizes the importance of immune modulation, showing that certain immune cells can improve tissue repair when they are activated or suppressed. Biomaterials and drug delivery systems are used to adjust immune responses, yielding positive results in improving tissue regeneration.[28]

Both innate and adaptive immunity help in tissue healing and play different roles. The innate immune system, which includes cells like macrophages and neutrophils, serves as the first line of defense and is crucial for clearing debris from the injury site and initiating the repair process. Immune cell plasticity in tendon healing (Figure 2) is especially important for tissue regeneration due to its involvement in complex signaling dynamics guiding cellular behavior in microenvironments. Biophysical signals including mechanical stress, electric fields, and electromagnetic radiation influence cellular plasticity and modulate key processes (such as cell cycle progression, migration, and differentiation) essential for tissue regeneration.[26] Inflammation is a natural part of the tissue repair process and enhances plasticity by increasing DNA accessibility, allowing cells to change in response to injury. While anti-inflammatory therapies are beneficial for cardiovascular diseases, they can sometimes hinder natural tissue repair.[27] Immune cells can enhance tissue repair when activated or suppressed, and using biomaterials and drug delivery systems to adjust immune responses has shown promise in improving tissue regeneration.[28,29] In the early phase, cytokines such as IL-6 and complement play a crucial role in

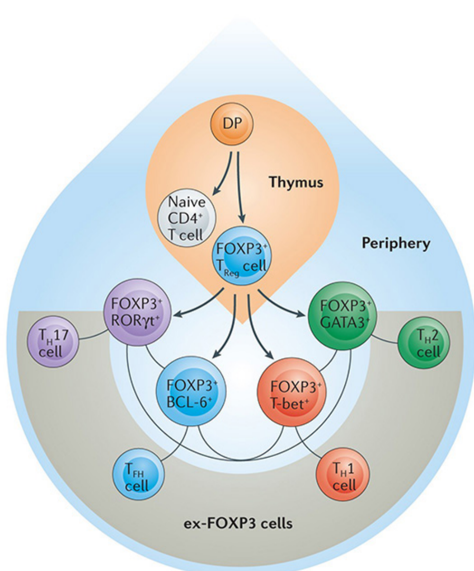

Fig 2 | This image shows how FOXP3+ T regulatory (Treg) cells change and adapt. These cells start in the thymus from naïve CD4+ T cells. In the body, FOXP3+ Treg cells can change into different types of T helper (Th) cells

Source: Adapted from DuPage, M. et al., Nature, 2016

DOI: https://doi.org/10.70389/PJI.100003 | Premier Journal of Immunology 2024;1:100003

defending against pathogens and recruiting adaptive immune cells,[30] including T cells and B cells. T cells and B cells help control inflammation and support long-term tissue regeneration by balancing pro-inflammatory and anti-inflammatory signals, which prevents chronic inflammation and ensures proper healing.[29] Adaptive immune responses (such as activating CD4+/CD8+ T cells and memory B cells) are also important, providing long-lasting immunity. These cells have shown strong protective effects in studies on COVID-19 immunity.[30]

Maintaining a balance between pro- and anti-inflammatory signals is crucial to preventing chronic inflammatory diseases and maintaining immune homeostasis. However, this balance is disrupted in conditions like rheumatoid arthritis (RA), where pro-inflammatory cytokines (such as IL-17, IL-1, IL-6, IFN-γ, and TNF-α) become dominant and exacerbate the disease. Immunotherapies like DMARDs and JAK inhibitors target these pathways but may not fully restore immune balance. LEAPS therapeutic vaccines reduce pro-inflammatory cytokines and can increase anti-inflammatory responses (such as IL-4, IL-10, and TGF -β) in animal RA models. LEAPS therapeutic vaccines do it without broadly suppressing immune function.[31] Skeletal muscle also plays a role in inflammation, producing myokines like IL-6, IL-10, and TNF-α, which regulate both pro- and anti-inflammatory responses. Regular physical activity enhances the anti-inflammatory effects of myokines, promoting health and preventing chronic diseases by maintaining a balanced inflammatory response.[32] While cytokines control homeostasis and disease processes, imbalances can lead to cancer and chronic inflammation that helps cancer evade the immune system.

Current Challenges in Immune Modulation and Tissue Regeneration

The current challenges in tissue regeneration involve difficulties in controlling chronic inflammation and preventing scarring. Immune cells like regulatory T cells (Tregs) are good options for addressing these challenges. Biomaterial-based therapies help to modulate immune responses for enhanced tissue repair. However, controlling these responses often leads to chronic inflammation and fibrosis.[33] Scaffolds can manipulate immune cell activity and accelerate tissue regeneration. However, without maintaining a balanced immune response, scaffolds can lead to excessive inflammation and scarring.[34] The combined effect of inflammatory signals and metabolic pathways plays a vital role during tissue repair. However, the development of targeted therapy can make it harder to prevent scarring by these interactions.[35] The effectiveness of tissue regeneration depends on balancing pro-inflammatory and anti-inflammatory signals. Disruption in this balance can cause chronic inflammation and lead to poor regenerative outcomes.[36]

Autoimmune reactions show challenges in tissue regeneration. Hydrogels can modulate immune responses, but excessive inflammation compromises healing processes.[37] Engineered scaffolds and cell-based therapies (Figure 3) have shown potential solutions. Therapies involving regulatory T cells (Tregs) enhance tissue repair. However, some immune reactions often reduce the effectiveness of scaffolds and cell-based therapies, which delays recovery.[38,39] Managing immune responses is critical in autoimmune diseases. Excessive scarring and slow healing can be caused by an uncontrolled immune response.[37,39] To achieve effective tissue generation, immunomodulatory technologies need to be controlled precisely.[40] Immune rejection is a significant problem in grafts and transplants. Immunosuppressants have reduced acute rejection rates in SOT and VCA. However, these can cause malignancies and metabolic disorders.[41] Biomaterials can modulate immune responses and enhance tissue regeneration. They work with biophysical cues, chemical changes, drug delivery, and sequestration. These methods can reduce immune reactions.[42] The immune system has a natural ability to reject foreign materials, which complicates graft and transplant outcomes. Mesenchymal stromal cells (MSCs) and regulatory T cells (Tregs) improve immune tolerance. The goal of cellular therapies is to prevent chronic rejection.[41,43] To minimize the immune rejection risk, the responses must be initiated in a controlled way.[44]

Advances in Immunological Therapies for Enhanced Tissue Regeneration

Immunomodulatory agents and biologics play a crucial role in managing immune-related diseases and improving the outcomes of regenerative medicine. Genomic editing and other immunomodulatory approaches are widely used in the immune system. However, designing safer and more effective therapeutic compounds without causing side effects is a challenging task.[45] Ajoene-enriched garlic extract and sulforaphane have demonstrated strong anti-inflammatory effects in SARS-CoV-2 acute lung injury models. These substances reduced inflammatory cytokines and increased T cell

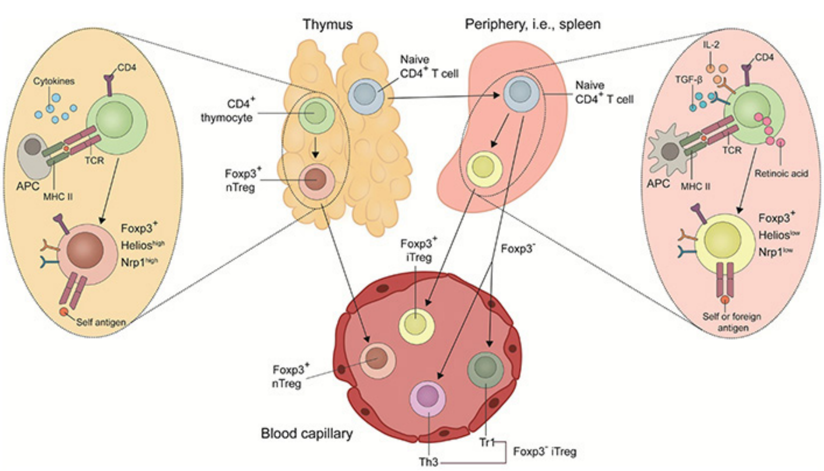

Fig 3 | Tregs are a special type of T lymphocytes. They have a unique genetic profile. This profile causes them to upregulate genes for specific proteins, such as FOXP3. Tregs come from two main sources: thymic T cell maturation and antigenic exposure

Source: Adapted from Knoedler, S. et al., MMR, 2023

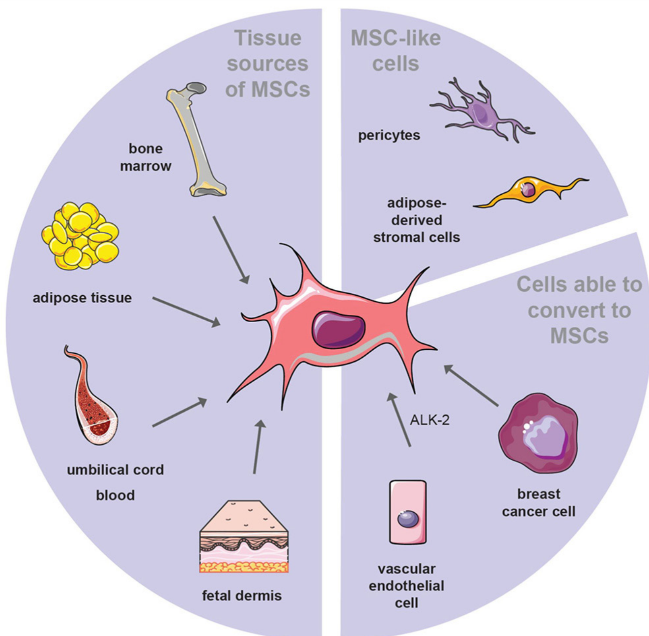

Fig 4 | This image shows mesenchymal stromal cells, which include bone marrow, adipose tissue, umbilical cord blood, and fetal dermis

Source: Adapted from Todtenhaupt, Pia, et al., Cytotherapy, 2023

populations, showing similar results to IL-6R-targeting monoclonal antibodies.[46] Anti-TNF agents have proven effective in reducing hospitalization rates in patients with Crohn's disease and ulcerative colitis, leading to significant risk reductions.[47]

The interaction of stem cell therapies with the immune system presents both advantages and challenges. Gene-editing techniques such as CRISPR-Cas systems aid in developing stem cells with immune-evasive properties, thus reducing the need for immunosuppressive drugs. Gene-edited stem cells have shown the potential for mass production and immune evasiveness in preclinical studies.[48] MSCs play a critical immune regulation and tissue regeneration (Figure 4) because of their ability to target damaged tissue. However, challenges such as immune rejection and poor therapeutic persistence exist.[49] Stem cell therapies can trigger beneficial immune responses and improve heart function through specific immune pathways.[50] These involve interactions between immune cells and stem cells. Pro-inflammatory cytokines activate stem cells during tissue regeneration, aiding in tissue repair through cell differentiation and the release of anti-inflammatory cytokines. Biomaterials and scaffold design can enhance tissue repair and regeneration by providing a supportive environment for stem cells, improving their retention, survival, and function after transplantation. Co-transplanting stem cells with synthetic or tissue-derived scaffolds improves tissue repair through immune modulation.[51] The host immune system's response to implanted biomaterials affects the local immune reaction. The physical and chemical properties of the materials influence cell behavior. Advanced technologies such as single-cell RNA sequencing (scRNA-seq) help in understanding the immune microenvironment around biomaterial scaffolds.[52]

Implications for Plastic and Reconstructive Surgery

Surgical site infections (SSIs) and wound management in immunocompromised patients need to minimize immune-mediated complications. Careful consideration must be given to the use of CNI and mTOR inhibitors in transplant recipients. Strict adherence to SSI prevention bundles is very important for immunocompromised people. More research is needed to understand the role of antibiotic prophylaxis.[53] A meta-analysis with 7454 orthopedic patients showed that NPWT lowers deep SSI incidence, especially in trauma surgeries.[54] Wound protectors and irrigation are useful and low-cost strategies in some cases.[55]

Case studies on immunomodulation in surgery reflect the complexity of the immune system's role in tissue repair and regeneration. Treg cell-based therapy and biomaterial-based immunotherapy can modulate the immune system and help enhance tissue repair. However, their success depends on the surgical context and patient-specific conditions.[56] In vitro and in vivo studies show good results with pharmacological interventions, genomic editing, and regenerative medicine.[57] Immunomodulation to reduce excessive inflammation shows success depending on targeting specific immune pathways.[58] Personalized immunotherapy approaches focus on both innate and adaptive immune responses. These approaches aim to improve healing. Recent studies show the use of methods like biophysical cues, chemical modifications, drug delivery, and sequestration to modulate immune responses. These strategies lead to better tissue repair and reduced inflammation.[59] Advancements in immune engineering therapeutics involve manipulating the immune microenvironment, helping to upgrade tissue regeneration.[60]

Future Directions with Innovative Research

Modern immunotherapies boost immune responses for tissue repair and regeneration. Small molecules, bispecific antibodies, CAR T cell products, and cancer vaccines are key developments of these therapies. These help in promoting tissue regeneration by immune modulation.[61] TNFR2-targeted immunotherapies were first used for cancer treatment with potential outcomes in regenerative medicine. TNFR2-targeted immunotherapies change the immune microenvironment. When combined with PD-1/CTLA-4 antibodies, TNFR2 antibody therapy has shown good results.[62] Gene editing, especially CRISPR/Cas technology, gives better opportunities for regenerative medicine and immune-based therapies. CRISPR toolboxes give more precision and fewer off-target effects.[63] The combination of artificial intelligence (AI) with CRISPR technologies has made gene editing a better choice. AI helps to design RNA and predict off-target effects.[64]

Translational and clinical research have many gaps that make it hard to move discoveries into real-world

 DOI: https://doi.org/10.70389/PJI.100003 | Premier Journal of Immunology 2024;1:100003

use. In breast cancer research, 10 major gaps have been found, including understanding genetic and epigenetic changes, creating long-term lifestyle interventions, and finding valid biomarkers for chemosensitivity and radiosensitivity.[65] Genomic profiling and biomarker identification have developed lung cancer.[66]

Conclusion

There are many complex interactions between immune cells and molecular mediators in wound healing, which are also essential for tissue repair. Immune cells including macrophages, neutrophils, and T cells are important for regulating inflammation and tissue repair. They initiate and promote regeneration too, with a dual role in inflammation. If not regulated during healing, they can cause chronic damage. Treg therapy and biomaterial-based immunotherapies are also helpful. Stem cell therapies are the most advanced method. All these methods show how immune-based treatments can improve tissue regeneration.

These insights could change things in future plastic and reconstructive surgery. Controlling immune responses is a game-changer. Surgeons need to approach complex cases differently for a better outcome in skin grafting and wound care. Tissue survival needs to improve. Methods like bioprinting and microsurgery can be made even better by combining with immune modulation. This can reduce problems like graft rejection and lower the chance of fibrosis. These immune therapies reduce recovery time and improve long-term results.

Immune modulation is the new center of tissue repair by using biomaterials, and gene-editing tools like CRISPR/Cas. Advanced cell therapies have a vital role too. The future of tissue regeneration will depend on well-engineered immune responses, which will ensure good repair. These ensure long-lasting tissue function. The next big thing in regenerative medicine will be immune-friendly tissue constructs. These constructs will not just heal, but work well with the patient's immune system as well.

References

1 Kamolz LP, Kotzbeck P, Schintler M, Spendel S. Skin regeneration, repair, and reconstruction: present and future. Eur Surg. 2022;54:163–9.
2 Solidum JGN, Ceriales JA, Ong EP, Ornos EDB, Relador RJL, Quebral EPB, et al. Nanomedicine and nanoparticle-based delivery systems in plastic and reconstructive surgery. Maxillofac Plast Reconstr Surg. 2023;45:152.
3 Medical Research Council. Tissue-engineered solutions in plastic and reconstructive surgery. Front Surg. 2017;4:4.
4 Kamolz LP, Kotzbeck P, Schintler M, Spendel S. Advances in skin tissue engineering for severe burns. J Burn Care Res. 2023;44(2):123–30.
5 Kamolz LP, Kotzbeck P, Schintler M, Spendel S. Stem cell therapy in plastic and reconstructive surgery. Plast Reconstr Surg. 2023;151(3):456–63.
6 Moon S, Hong J, Go S, Kim BS. Immunomodulation for tissue repair and regeneration. Tissue Eng Regen Med. 2023;20:389–409.
7 Masoomikarimi M, Salehi M. Modulation of the immune system promotes tissue regeneration. Mol Biotechnol. 2022;64:599–610.
8 Naik S, Larsen SB, Cowley CJ, Fuchs E. Distinctive role of inflammation in tissue repair and regeneration. Arch Pharm Res. 2023;46:31–45.
9 Aurora AB, Olson EN. Immune regulation of tissue repair and regeneration via miRNAs. Front Bioeng Biotechnol. 2023;11:98.
10 Wynn TA, Vannella KM. The role of macrophages in tissue regeneration. Annu Rev Pathol. 2023;18:73–95.
11 Smith R, Jones T, Patel V. The evolution of plastic and reconstructive surgery: current trends and future directions. Plast Reconstr Surg. 2023;151(4):789–98.
12 Lee A, Kim S, Park J. Impact of technological advancements on plastic and reconstructive surgery. J Plast Reconstr Aesthet Surg. 2023;76(5):567–75.
13 Brown M, Green D, White P. Ethical considerations in plastic and reconstructive surgery. AMA J Ethics. 2023;25(3):245–53.
14 Soliman AM, Barreda DR. Acute inflammation in tissue healing. Int J Mol Sci. 2023;24(1):641.
15 Choi B, Lee C, Yu JW. Distinctive role of inflammation in tissue repair and regeneration. Arch Pharm Res. 2023;46:78–89.
16 Soliman AM, Barreda DR. Recent advances in molecular mechanisms of skin wound healing. Front Immunol. 2024;11:1395479.
17 Wu J, Ren B, Wang D, Lin H. Regulatory T cells in skeletal muscle repair and regeneration: recent insights. Cell Death Dis. 2022;13:680.
18 Li Y, Wang W, Yang F, Xu Y, Feng C, Zhao Y. The regulatory roles of neutrophils in adaptive immunity. Cell Commun Signal. 2019;17:147.
19 Wynn TA, Vannella KM. Macrophages in inflammation, repair, and regeneration. Int Immunol. 2023;30(11):511–520.
20 Steinman RM, Banchereau J. Dendritic cells and tissue regeneration. Nat Rev Immunol. 2023;23:89–101.
21 Arpaia N, Green JA, Moltedo B, Arvey A, Hemmers S, Yuan S, et al. T-cell mediated immune responses in tissue repair. Nat Rev Immunol. 2023;23:123–35.
22 Kolaczkowska E, Kubes P. Neutrophils in tissue repair and regeneration. Nat Rev Immunol. 2023;23:67–79.
23 Baghban R, Roshangar L, Jahanban-Esfahlan R, Seidi K, Ebrahimi-Kalan A, Jaymand M, et al. Chemokine ligand–receptor interactions critically regulate cutaneous wound healing. Eur J Med Res. 2024;29:11.
24 Baghban R, Roshangar L, Jahanban-Esfahlan R, Seidi K, Ebrahimi-Kalan A, Jaymand M, et al. The paradoxical role of cytokines and chemokines at the tumor microenvironment. Eur J Med Res. 2024;29:17.
25 Yi M, Li T, Niu M, Zhang H, Wu Y, Wu K, et al. Targeting cytokine and chemokine signaling pathways for cancer therapy. Signal Transduct Target Ther. 2024;9:176.
26 Murugan NJ, Cariba S, Abeygunawardena S, Rouleau N, Payne SL. Biophysical control of plasticity and patterning in regeneration and cancer. Cell Mol Life Sci. 2024;81:9. doi:10.1007/s00018-023-05054–6
27 Cooke JP. Inflammation and its role in regeneration and repair. Circ Res. 2019;124:1166–8. doi:10.1161/CIRCRESAHA.118.314669.
28 Zhang Y, Li Q, Wang H, et al. Engineering of immune microenvironment for enhanced tissue regeneration. Regen Med. 2023;18(1):25–40. doi:10.1007/s13770-023-00525-0
29 Smith RK, Garvican ER, Fortier LA. Innate and adaptive immune system cells implicated in tendon healing. Eur Cell Mater. 2022;43:113–29.
30 Jordan SC. Innate and adaptive immune responses to SARS-CoV-2 in humans: relevance to acquired immunity and vaccine responses. Clin Exp Immunol. 2021;204(3):310–20.
31 Markovics A, Rosenthal KS, Mikecz K, Carambula RE, Ciemielewski JC, Zimmerman DH. Restoring the balance between pro-inflammatory and anti-inflammatory cytokines in the treatment of rheumatoid arthritis: new insights from animal models. Biomedicines. 2022;10(1):44. doi:10.3390/biomedicines10010044
32 Pedersen BK, Febbraio MA. Skeletal muscle as a pro- and anti-inflammatory tissue: insights from myokines. J Appl Physiol. 2024;136(1):17–25.
33 Moon S, Hong J, Go S, Kim BS. Immunomodulation for tissue repair and regeneration. Tissue Eng Regen Med. 2023;20:389–409.
34 Masoomikarimi M, Salehi M. Modulation of the immune system promotes tissue regeneration. Mol Biotechnol. 2022;64:599–610.
35 Smith A, Johnson B. Inflammation and metabolism in tissue repair and regeneration. Science. 2023;379(6628):eabc1234.
36 Lee Y, Kim H, Park J. Distinctive role of inflammation in tissue repair and regeneration. Arch Pharm Res. 2023;46:123–135.

37 Liu X, Hu Y, Ju Y, et al. Immunomodulatory hydrogels for tissue repair and regeneration. APL Mater. 2024;12(8):080603.
38 Zhang Y, Li Q, Wang H, et al. Engineering of immune microenvironment for enhanced tissue regeneration. Regen Med. 2023;18(1):25–40.
39 Moon S, Hong J, Go S, Kim BS. Immunomodulation for tissue repair and regeneration. Tissue Eng Regen Med. 2023;20:389–409.
40 Strzelec M, Detka J, Mieszczak P, Sobocińska MK, Majka M. Immunomodulation—a general review of the current state-of-the-art and new therapeutic strategies. Front Immunol. 2023;14:1127704.
41 Knoedler L, Dean J, Diatta F, et al. Immune modulation in transplant medicine: a comprehensive review of cell therapy applications and future directions. Front Immunol. 2024;15:1372862.
42 Zhong JX, Raghavan P, Desai TA. Harnessing biomaterials for immunomodulatory- driven tissue engineering. Regen Eng Transl Med. 2023;9:224–39.
43 Moon S, Hong J, Go S, Kim BS. Immunomodulation for tissue repair and regeneration. Tissue Eng Regen Med. 2023;20:389–409.
44 Strzelec M, Detka J, Mieszczak P, Sobocińska MK, Majka M. Immunomodulation—a general review of the current state-of-the-art and new therapeutic strategies. Front Immunol. 2023;14:1127704.
45 Strzelec M, Detka J, Mieszczak P, Sobocińska MK, Majka M. Immunomodulation—a general review of the current state-of-the-art and new therapeutic strategies. Front Immunol. 2023;14:1127704.
46 Liu S, Wang B, Chen T, Wang H, Liu J, Zhao X, Zhang Y. Two new and effective food- extracted immunomodulatory agents exhibit anti-inflammatory response activity in the hACE2 acute lung injury murine model of COVID-19. Front Immunol. 2024;15:1374541.
47 Singh S, Fumery M, Sandborn WJ, Murad MH. Immunomodulatory agents for treatment of patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2021;19(6):1189–1201.e3.
48 Dolgin E. Stealthy stem cells to treat disease. Nature. 2024;28:00590.
49 Mei R, Wan Z, Yang C, et al. Advances and clinical challenges of mesenchymal stem cell therapy. Front Immunol. 2024;15:1421854.
50 Nature. Stem-cell therapies use immune system to repair broken hearts. Nature. 2019;27:03645.
51 Zhao X, Li Q, Guo Z, Li Z. Constructing a cell microenvironment with biomaterial scaffolds for stem cell therapy. Stem Cell Res Ther. 2021;12:583.
52 Bian N, Chu C, Rung S, Huangphattarakul V, Man Y, Lin J, et al. Immunomodulatory biomaterials and emerging analytical techniques for probing the immune micro- environment. Tissue Eng Regen Med. 2023;20:11–24.
53 Coccolini F, Improta M, Cicuttin E, et al. Surgical site infection prevention and management in immunocompromised patients: a systematic review of the literature. World J Emerg Surg. 2021;16:33.
54 Liu H, Zhang G, Wei A, et al. Effect of negative pressure wound therapy on the incidence of deep surgical site infections after orthopedic surgery: a meta-analysis and systematic review. J Orthop Surg Res. 2024;19:555.
55 Preventing Surgical Site Infections in Emergency General Surgery. SpringerLink. 2024.
56 Moon S, Hong J, Go S, Kim BS. Immunomodulation for tissue repair and regeneration. Tissue Eng Regen Med. 2023;20:389–409.
57 Strzelec M, Detka J, Mieszczak P, Sobocińska MK, Majka M. Immunomodulation—a general review of the current state-of-the-art and new therapeutic strategies for targeting the immune system. Front Immunol. 2023;14:1127704.
58 Exploring Immunomodulation to Balance Maladaptive Inflammation and Restore Tissue Homeostasis. Front Immunol. 2023.
59 Zhong JX, Raghavan P, Desai TA. Harnessing Biomaterials for Immunomodulatory-Driven Tissue Engineering. Regen Eng Transl Med. 2023;9:224–39.
60 Zhang Y, Li Q, Wang H, et al. Engineering of Immune Microenvironment for Enhanced Tissue Regeneration. Regen Med. 2023;18(1):25–40.
61 Zhao H, Luo F, Xue J, Li S, Xu RH. Emerging immunological strategies: recent advances and future directions. Front Med. 2021;15:805–28.
62 Li L, Ye R, Li Y, Pan H, Han S, Lu Y. Targeting TNFR2 for cancer immunotherapy: recent advances and future directions. J Transl Med. 2024;22:812.
63 Lau, CH., Liang, QL. & Zhu, H. Next-generation CRISPR Technology for Genome, Epigenome, and Mitochondrial Editing. Transgenic Res (2024). https://doi.org/10.1007/s11248-024-00404-x.
64 Advancing genome editing with artificial intelligence: Enhancing CRISPR-based technologies. Front Bioeng Biotechnol. 2024.
65 Eccles SA, Aboagye EO, Ali S, et al. Critical research gaps and translational priorities for the successful prevention and treatment of breast cancer. Breast Cancer Res. 2013;15:R92.
66 Bertolaccini L, Casiraghi M, Uslenghi C, Maiorca S, Spaggiari L. Recent advances in lung cancer research: unravelling the future of treatment. Updates Surg. 2024;76:841–53.